1370 abstracts were received in March 2012 and were evaluated by the SIOP scientific committee. The accepted abstracts are printed here in order of:

- 217 Oral presentations (O + number), this includes Nurses sessions x 26 (N + number), Radiation Oncology Free Paper sessions x 10 (RO + number), 32 IPSO Oral presentations (IPSO + number), 17 ICCPO Oral presentations (ICCPO + number) and all Free Paper sessions (FP + number).
- 475 Poster presentations (P + letter discipline + number)
- 542 Publications (Pub + number)
- 136 Abstracts were rejected and will not be included in the Journal.

Symposia presentations will be provided under separate cover.

**ABSTRACT CONTENTS:**

**SYMPOSIA ABSTRACTS**

**SYMPOSIUM 1–SYMPOSIUM 10**

**Oral presentations (O + number)**

| O001 | O004 | FP 1 | Renal Tumours |
| O005 | O008 | FP 2 | Acute Lymphoblastic Leukemia |
| O009 | O012 | FP 3 | Late Effects 1 |
| O013 | O016 | RO1/PROS | Radiation Oncology PROS |
| O017 | O020 | N 1 | Nurses 1 |
| O021 | O026 | FP 4 | Bone Prize |
| O027 | O032 | FP 5 | Lymphomas |
| O033 | O038 | FP 6 | Brain Session |
| O039 | O044 | RO2/PROS | Radiation Oncology PROS |
| O045 | O048 | N2 | Nurses 2 |
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| O073 | O077 | N 3 | Nurses 3 |
| O078 | O081 | FP 10 | Bone Tumours |
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| O094 | O099 | FP 13 | Neuroblastoma |
| O100 | O105 | FP 14 | Germ Cell Tumours |
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| O148 | O150 | N 6 | Nurses 6 |
| O151 | O156 | FP 22 | Renal Tumours |
| O157 | O162 | FP 23 | Rare Tumours |
| O163 | O168 | FP 24 | Neuroblastoma |

**IPSO Oral presentations (IPSO + number)**

| IPSO001 | IPSO004 | IPSO 1 | Renal Tumours |
| IPSO005 | IPSO010 | IPSO 2 | Soft Tissue Tumours |
| IPSO011 | IPSO016 | IPSO 3 | Neuroblastoma |
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| IPSO021 | IPSO023 | IPSO 6 | Germ Cell Tumours |
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| IPSO030 | IPSO032 | IPSO 8 | Liver Tumours |

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966    SIOP ABSTRACTS

ICCCPO Oral presentations (ICCCPO + number)

ICCCPO001    ICCCPO0017 Parents and Survivors

Poster presentations (P + letter discipline + number)

PA001    PA050   Acute Lymphoblastic Leukaemia
PB001    PB013   Other Leukaemia + MDS
PC001    PC021   Lymphoma + Histiocytosis
PD001    PD023   Bone Tumours
PF001    PF047   Neuroblastoma + Renal Tumours
PH001    PH008   Retinoblastoma
PI001    PI012   Soft Tissue Sarcomas
PK001    PK006   Liver Tumours
PL001    PL019   Rare Tumours
PM001    PM059   Brain Tumours
PM060    PM073   Germ Cell Tumours
PN001    PN013   New Drugs/Experimental Therapeutics
PP001    PP031   Epidemiology
PQ001    PQ042   Late Effects
PR001    PR016   Supportive Care – Fever/Neutropenia/Infectious
PR017    PR029   Supportive Care - Miscellaneous
PR030    PR032   Supportive Care - Nutrition
PR033    PR033   Supportive Care – Palliative/Psychosocial
PS001    PS034   Psychosocial
PU001    PU017   Nursing
PW001    PW016   IPSO
PX001    PX010   PROS
PERSONALIZED TREATMENT APPROACHES IN NEUROBLASTOMA

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Purpose: The Neuroblastoma and Medulloblastoma Translational Research Consortium (NMTRC) opened the first FDA-approved study using molecular guided therapy in pediatric oncology focused in relapsed neuroblastoma. Recent efforts to systematically characterize the molecular basis of neuroblastoma confirm the biologic heterogeneity of the disease and reveal major molecular sub-types with varying prognoses, suggesting that different sub-types of neuroblastoma may respond to different therapeutic strategies. If we properly select patients and match them to appropriate therapies based on their individual genomic signature, a high proportion may benefit.

Methods: We hypothesize that transcriptome analysis of individual tumor samples can be combined with data concerning molecular pathways and knowledge of drug targets to allow for more rational and individualized selection of potentially active drugs. Specifically, the strategy is to analyze tumor biopsies for genetic biomarkers or signatures using RNA expression profiles, and RNA/DNA sequencing. The unique genetic fingerprint of each patient’s cancer is screened against a drug database from which a unique set of cancer therapies are predicted in a report. Utilizing this report through a molecular tumor board will lead to the creation of individual treatment plans.

Results: All biopsies show adequate pathology evaluation (> 75% viable tumor) and RNA quality (> 6 u RIN). Gene chips are completed in 3–7 days, report generation in 1–5 days with tumor board in 1–3 days and medical monitor sign off in 1 day. The total time to create the individual treatment plan is 10–12 days for all patients. The molecular tumor board consists of pediatric oncologists from sites across the US, bioinformaticians, pathologists and pediatric oncology pharmacists.

Conclusion: It is feasible to obtain real-time genomic profiling for molecularly guided therapy and informed treatment decision making in children with cancer. This method may provide improved ways to make therapeutic decisions for patients with resistant pediatric diseases.

ROLE OF SYSTEMS BIOLOGY IN PERSONALIZED MEDICINE

Walter Kolch

Systems Biology Ireland, University College, Dublin, Ireland

Purpose: In the postgenomic age our ability to generate biological and biomedical data has outpaced our capacity to understand them. This data revolution has highlighted an urgent need for understanding the functional organisation of living systems rather than just mapping the components. This is a grand challenge for biology and biomecine alike. Systems biology is applying mathematical and computational methods to biomedical data to accomplish this task. In this talk I briefly will review the contributions systems biology approaches can make to medicine, especially personalised medicine and give some examples from our own work including the EU FP7 Project ASSET on Embryonal Tumours.

Methods: Overview of systems biology approaches and examples for application of systems biology approaches to the analysis of aberrant signal transduction in cancer and mechanisms of drug resistance.

Results: Emergent properties arising from signaling network structures can encode pathogenetic behaviour that may be used for diagnostic and therapeutic stratification, e.g. to predict individualised disease progression and drug responses.

Conclusion: Mathematical and computational modelling can reveal new functional rules that can be used to analyse and predict physiological and pathological behaviour. In combination with patient specific data such functional modelling approaches are likely to become key for personalised medicine.

PERSONALISED MEDICINE: THE PARENTS’ PERSPECTIVE

Danielle Horton Taylor1,2

1Children’s Cancer and Leukaemia Clinical Study Group, NCRI, Leeds; 2Pediatric Oncology Reference Team (PORT), London, UK

Purpose: How are parents and users involved in clinical research? What are some of the issues they face? How can they contribute in a meaningful way?

Methods: Parents have many concerns at diagnosis with reference to taking part in clinical trials, including: consent issues, timing of information, access to results from trials, late effects, etc. Critical input from parents to clinical research staff is welcomed through consumer or public and patient involvement (PPI). PPI members are allocated to Clinical Study Groups, with the specific brief of: assessing relevance of trial question to families, risk
or burden for child; burden for families; timing of hospital visits/sampling times etc. N.B. Our role is not to review the Science of the study.

**Results:**

The role of a PPI member of a clinical study group is to be practical, unbiased and unaffiliated, and to ensure accountability. The aim is to not present one’s own view, but rather be as representative as possible. This wider view can be achieved by including other consumers to comment, and ever weaving a larger web of users to contribute their views.

**Conclusion:**

Parents can have a strong input into clinical trials, right from the conception of a trial, and their involvement (through PPI) is now an accepted practice.

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**SYMPOSIUM 2**

**TARGETING AML BY NOVEL CARS: NEW INSIGHTS BY IN VIVO MODELS**

**Ettore Biagi, Andrea Biondi**

Pediatric Hematology/Oncology, University of Milano Bicocca, Monza, Italy

**Purpose:**

Chimeric-antigen-receptor T-cells (CAR-Ts) have recently emerged as a powerful tool to redirect T-cell activity against tumors. AML is a potential optimal target for a CAR strategy due to the over-expression of CD33 and CD123. In particular, the IL-3Rα (CD123) is selectively expressed at higher levels on AML-leukemia stem cells (LSCs) and is associated with poor prognosis.

**Methods:**

We initially evaluated the anti-leukemic activity of anti-CD33.CAR+ cytokines-induced-killer (CIK) cells in NSG mice reconstituted with KG-1 cell expressing firefly-luciferase. Secondarily, we developed a novel CAR with an anti-CD123-scFV-based targeting domain. CIK cells were transduced with SFG-retroviral vectors encoding scFvCD123.CAR. Moreover, the ex vivo use of the latest generation Sleeping Beauty (SB) transposon-mediated gene transfer combined with nucleofection allows for the generation of CIK cells genetically modified to express CD123-specific third generation CARs.

**Results:**

Firstly, in untreated mice almost all (95%) bone-marrow was infiltrated by leukemia, whilst in mice treated with unmanipulated, anti-CD33- or anti-CD33-CD123- OX40+ T-cells, CIK-cells the levels of AML engraftment was 59, 5.67 and 0.04%, respectively. Secondly, transduced CIK cells potently kill THP-1 and TF-1 cell-lines (up to 70%), as well as primary AML blasts (up to 70%). We then evaluated the safety profile of the anti-CD123 CARs towards low CD123-expressing HSCs. Secondary colonies experiments showed that the classical scFvCD123.CAR model is safer than CD33.CAR in recovering complete haematopoietic reconstitution. Thirdly, transposed CIK cells displayed stable expression of γδ CAR+CD123.CAR (39.4% ± 8.6), efficient lysis of AML target cells, and CAR-specific cytokine secretion. Finally, long-term expansion (day 40) upon stimulation with AML cells in vitro promoted efficient selection of CAR+ CIK cells with potent cytotoxic activity towards AML target (up to 100% lysis).

**Conclusion:**

Efficient transfection of CARs together with a feasible manufacturing practice strategy to select and propagate CAR-expressing CIK cells will be instrumental in defining novel therapeutic approaches to treat AML, either by selective CAR-mediated targeting of CD33 or CD123.

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**T-CELL ENGINEERING FOR CANCER APPLICATIONS**

**Martin Pule**

Cancer Institute, University College London, London, UK

**Summary:**

Harnessing the human immune system against cancer has long been a long medical goal. Adoptive immunotherapy, administration of cancer-specific T-cells expanded ex vivo can result in dramatic clinical responses. However, until recently, the difficulty in generating T-cells against a wide range of cancer antigens has limited adoptive immunotherapy to only a few cancers, most of which are vitally driven. Recently, genetic engineering techniques have afforded us a means of generating T-cells with arbitrary specificities and new properties, for instance, by introduction of genes coding for chimeric antigen receptors (CARs). CARs combine the antigen recognition domain of a monoclonal antibody (mAb) with a T-cell signaling domains. A T-cell expressing a CAR will recognize and kill a cell bearing the cognate antigen of the parental mAb. In addition, the T-cell retains its native function of homing to sites of disease, extravasation and release of inflammatory cytokines at sites of disease. Other engineering components can be introduced into T-cells with CARs – for instance suicide genes which allow us to trigger selective destruction of T-cells in the face of unacceptable toxicity. Resistance genes which render T-cells resistant to immunosuppressive drugs. More advanced genomic and protein engineering techniques also allowing us to efficiently disrupt expression of arbitrary genes. I will review the field including recent clinical studies with some of our clinical data and describe our plans for clinical studies in ALL and neuroblastoma. In addition I will discuss advancements in the field of T-cell engineering and hope to show how this area is rapidly developing to allow us to re-engineer T-cells into highly complex new therapies.

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**SYMPOSIUM 3**

**OVERVIEW OF ALL DRUGS AND INNOVATIVE APPROACHES FOR PRIMARY OR RECURRENT EПEПDYMOMA**

**Didier Frappaz**

Institut d’Hématologie HématoLOGie Pédiatrique, Lyon, France

**Pediatr Blood Cancer DOI 10.1002/pbc**

**Purpose:**

Ependymoma is a heterogeneous disease. Pathology (classic vs anaplastic, molecular biology, age, location (supra vs infratentorial)) may all represent specific challenges for chemotherapy trial strategies.

**Methods:**

Ependymoma is not among the most chemo-sensitive tumor with a response rate that usually does not exceed 20%. Even high dose chemotherapy has failed to overcome resistance. In vitro experiments have pointed out unexpectedly SPU as one of the candidates that may be explored in future trials. However, clinical trials in babies have raised the possibility that postoperative polychemotherapies, especially when intensive and using high dose Methotrexate, may obtain cure without further treatment. Moreover, cooperative groups are currently engaged in randomising chemotherapy post radiation therapy to explore its role in older children.

**Results:**

Despite in vitro demonstration of the presence of the target, targeted therapy have failed today to demonstrate striking activity. Innovative approaches will include either combination of drugs with chemotherapy, such as for instance instore dacarbazine/ paclitaxel or, antiangiogenics. Several biological agents are currently under development.

**Conclusion:**

Ependymoma treatment remains in need of addition research of new compounds and combinations, and justifies the efforts of collaborative groups to launch international trials.

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**MULTIMODAL MANAGEMENT OF EПEПDYMOMA: EFFICACY, TOXICITY AND FUTURE PLANS USING RADIATION THERAPY**

**Thomas Edward Merchant**

Radiation Oncology, St. Jude Children’s Research Hospital, Memphis, TN, USA

**Purpose:**

The evolution in multimodality therapy for children with ependymoma during the past 20 years is an excellent story that highlights the benefit of pediatric clinical trials and data-driven research. There is strong evidence that the primary role of surgery has been secured and that the adjuvant use of radiation therapy is pivotal in achieving high rates of disease control.

**Methods:**

Disease control and late effects after radiation therapy have been reviewed from prospective and retrospective clinical trials to document the progress that has been made using radiation therapy during the past 20 years and the potential benefit of newer methods of irradiation.

**Results:**

The rates of treatment complications have been acceptable leading to the use of aggressive surgery and irradiation even in the very young. The current level of success has invited reappraisal of the use of chemotherapy, consideration of observation in lieu of irradiation for selected patients and biological stratification of therapy. The attribution of timing of surgery and irradiation has been documented for the first time in the way we treat ependymoma. The progression of knowledge of which the targeted volume for radiotherapy may be dramatically reduced without affecting the rate or pattern of failure. Reducing the targeted volume of irradiation is important for radiation dose and volume have been found to correlate with functional outcomes.

**Conclusion:**

Investigators are now able to estimate the risk of a wide variety of neurological, endocrine and cognitive effects in these patients and this information is being used to further optimize therapy or compare different treatments regimes or treatment modalities. Recent clinical trials have been designed with the combined goal of improving disease control and eliminating side effects; future trials will take advantage of tumor biology to improve risk-stratification for radiation therapy and test the role of conventional chemotherapy or novel agents.

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**SYMPOSIUM 5**

**BREAST CANCER FOLLOWING TREATMENT FOR WILMS TUMOR**

**Jane Lange1, Susan M. Peterson2, Daniel M. Green3, Norman E. Breslow4,5**

1Biosciences, University of Washington; 2Biosciences and Bioinformatic, Fred Hutchinson Cancer Research Center, Seattle, WA; 3Epidemiology and Cancer Control, St. Jude Children’s Research Hospital, Memphis, TN, USA

**Purpose:**

To estimate breast cancer (BC) risk in female survivors of Wilms tumor

**Methods:**

A cohort of 2,488 female participants in National Wilms Tumor Studies 1–4 (1969–1995) known to be alive at age 15 was followed through 2010 for incident BC. Cumulative risks at age 40 (CR40), hazard ratios (HR) estimated by Cox regression and standardized incidence ratios (SIR) relative to US population rates were calculated together with 95% confidence intervals (CI).

**Results:**

Among 371 women who received any pulmonary radiation therapy (RT) for metastatic Wilms tumor (WT), 13 developed BC (CR40 = 3.9; CI = 5.1–21.5%); among 2,117 women without lung RT, 10 developed BC (CR40 = 2.9%; CI = 0.2–5.7%). The SIRs for these two groups were 29.7 (CI = 15.7–50.8) based on 4,497 person-years (PY) of follow-up and 5.2 (CI = 2.5–9.6) based on 25,542 PY, respectively, and the HR comparing them was 6.5 (CI = 2.8–15.3). The median age at diagnosis of all 23 BC cases was 33 years (range 16–48) and the median time between WT diagnosis and BC was 27 years (range 8–35). Accounting for some missing dose information using multiple imputation, there was no evidence that BC incidence for an estimated 86 women who received bilateral whole lung RT in excess of 12 Gy was any greater than for that an estimated 268 women who received 10–12 Gy of whole lung RT (HR < 1). However, treatment with doxorubicin increased the BC incidence by a factor of HR = 3.0 (CI = 1.2–7.9) after adjustment for pulmonary RT.
Conclusion: Girls who receive chest RT for metastatic WT are at high risk for BC, nearly 30 times background, with an estimated 13% developing the secondary cancer by age 40. Parents acknowledged the benefits of communicating openly with children, but had experienced difficulties in accessing separate consultations. About whether it was considered legitimate to ask to see doctors separately from their child or had experienced difficulties in accessing separate consultations.

Conclusion: The difficulties parents described could potentially be addressed by extending, beyond the diagnosis period, the practice of sequencing ‘significant’ information so that it is communicated to parents in separate consultations before being communicated to the child, and by periodically exploring the views of parents about how best to manage communication with their child. Parents’ difficulties in seeking separate consultations may be linked to the moral emphasis on open communication with children.

**SYMPOSIUM 7**

COMMUNICATION AND DECISION MAKING WITH CHILDREN AND FAMILIES – A PARENT’S PERSPECTIVE

Renate Pfeifer

Parents Organization, Bonn, Germany

**Purpose:** This is the perspective of a mother of a cancer-sick child. Parents’ difficulties in seeking separate consultations may be linked to the moral emphasis on open communication with children. Parents’ difficulties in seeking separate consultations may be linked to the moral emphasis on open communication with children.

**Methods:** A review of the literature was conducted investigating three specific topics within supportive care: genetics variation influencing the risk of infection; genetic variation influencing nausea control; and genetic variation influencing end-organ toxicity.

**Results:** Numerous studies have been identified and will be presented at the meeting.

**Conclusion:** Genetic variation between individuals appears to play a significant role in influencing outcomes for children being treated for cancer. In the future, genetic testing may be able to be used in order to risk stratify children, such that specific supportive care measures can be delivered to those at highest risk. Further studies and collaborative efforts are needed to investigate this further in pediatric oncology.

**SYMPOSIUM 8**

USING MICE TO UNDERSTAND GERM CELL TUMORS: LESSONS FROM DMRT1

David Zarkower

**Genetics, Cell Biology, and Development, University of Minnesota, Minneapolis, MN, USA**

**Purpose:** Dmrt1 is a conserved transcriptional regulator with varied functions in the mammalian gonad. It is required for spermatogonial differentiation, regulating the mitosis versus meiosis decision, and maintaining male germ cell fate commitment in somatic cells of the testis. In addition, Dmrt1 mutant mice develop testicular teratomas at very high incidence, but only in mice of the 129Sv strain. GWAS studies have implicated DMRT1 in human testicular germ cell tumor (TGCT) formation, so a hope is that insights gained from mice may inform studies of the human disease.

**Methods:** To help learn how loss of Dmrt1 contributes to TGCT formation we have combined mRNA profiling, ChIP-seq, and genetics to compare genes regulated by Dmrt1 in a tumor-prone strain (129Sv) and a tumor-resistant strain (B6). We also have begun to ask which of these genes play a significant role in TGCT formation.

**Results:** Loss of Dmrt1 in the fetals tests disrupts developmental progression in both B6 and 129Sv mice, but causes misregulation of distinct sets of genes in each strain. In 129Sv mutant testes many pluripotency genes are upregulated, and several signaling pathways, including Wnt, Gdnf, and Nodal, are misregulated. Conditional gene target demonstrated that the Gdnf receptor Gfyc is required to suppress tumors in 129Sv mice and identified a genetic interaction between Dmrt1 and the germ cell regulator Nano3.

**Conclusion:** DMRT1 transcriptionally regulates overlapping but distinct sets of genes in the fetals testis of TGCT sensitive and resistant mouse strains. The genes specifically misregulated in the TGCT-sensitive strain are prime candidates for a role in TGCT formation. The relationship of DMRT1 expression to expression of target genes is similar in mice and in human TGCTs, suggesting that DMRT1 acts similarly in human TGCTs. The genes and pathways implicated in mouse TGCT formation may therefore be relevant to the human disease.

DEVELOPMENTAL SIGNALING PATHWAYS IN GERM CELL DIFFERENTIATION AND GERM CELL TUMORGENESIS

James Amatruda 1,2, Keneth S. Chen 2,3, Dinesh Rakheja 4

1Pediatrics, Molecular Biology and Internal Medicine, University of Texas Southwestern Medical Center; 2Center for Cancer and Blood Disorders, Children’s Medical Center; 3Pediatrics; Pathology, University of Texas Southwestern Medical Center, Dallas, TX, USA

**Purpose:** Germ cell tumors (GCTs) affect infants, children and young adults, and testicular germ cell tumor is the most common cancer in young men. While cisplatin treatment has been successful for GCTs, patients suffer long-term side effects including hearing loss, kidney damage and increased secondary malignancies. The genes and pathways that contribute to the development of GCTs are incompletely understood, which is a serious impediment to the development of targeted therapy for this disease.

**Methods:** We have taken a genetic approach to understand the etiology of GCTs, using zebrafish as a model system. We carried out a forward genetic screen in zebrafish to discover novel cancer genes, and identified a zebrafish mutant line with a high incidence of spontaneous testicular GCTs consisting of undifferentiated germ cells. We also carried out gene expression profiling and immunohistochemistry on a series of clinically annotated human GCTs.

**Results:** Positional cloning of the mutant zebrafish locus revealed an inactivating mutation in the Type I BMP receptor Alk6b (activin receptor-like kinase 6b) (1). BMP (bone morphogenetic protein) signaling has diverse roles including regulation of cell proliferation, cell differentiation, embryonic development, germ cell specification and gonadogenesis. We find evidence of impaired BMP signaling in the zebrafish GCTs, and altered expression level of BMP target genes. In humans, tumors in agreement with the zebrafish model, we find that undifferentiated GCTs such as seminomas lack BMP signaling activity, whereas signaling is maintained in differentiated GCTs such as yolk sac tumors (2). We are now conducting a genome wide interrogation of childhood germ cell tumors, including copy number analysis and deep sequencing, to discover other aberrant pathways that contribute to human germ cell tumorigenesis.

**Conclusion:** These results emphasize impaired differentiation as a possible oncogenic pathway and may foster the development of improved, targeted therapy of human GCTs.

MICRORNAS IN MALIGNANT GERM CELL TUMOURS: NOVEL APPROACHES TO DIAGNOSIS AND TREATMENT

Pediatr Blood Cancer DOI 10.1002/pbc
**SYMPOSIUM 9**

**CLONAL ARCHITECTURE IN ACUTE LYMPHOBLASTIC LEUKAEMIA**

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1Division of Molecular Pathology, Institute of Cancer Research, London, 2Cancer Genome Project, Wellcome Trust Sanger Institute, Cambridge, UK

**Purpose:** Cancer clone development is regarded as an evolutionary or Darwinian process of genetic diversification and natural (or therapeutic) selection within tissue ecosystems. Dynamic and complex branching sub-clonal genetic architectures are proving to be a common feature of cancer and this complexity may underpin the intransigence of advanced cancer to therapeutic control. Studies of clonal diversity have adopted various technologies from fluoroscent in situ hybridisation to whole-genome sequencing of micro-dissected foci or single cells. However, a methodology is needed that allows unbiased single cell sampling, high throughput analysis of many cells and simultaneous detection of multiple genetic alterations in a single cell, e.g. fusion genes, DNA copy number alterations (CNAs) and sequence-based mutations. We have developed a novel multiplex microfluidic Q-PCR approach to accomplish this.

**Methods:** As a proof of principle investigation we interrogated ~300 single cells from two ETv6-RUNX1 positive acute lymphoblastic leukaemia cases with point mutations and CNAs (determined by whole-genome sequencing). Briefly, single cells were flow sorted and lysed prior to multiplex DNA specific target amplification and Q-PCR using the BioMark HD (Fluidigm, UK).

**Results:** Evolutionary and clonal diversity analysis of these data demonstrated that both CNAs and mutations define complex branching sub-clonal architectures. The sub-clonal architecture of case A showed that the leukemic cells harbored the ETv6-RUNX1 fusion in conjunction with additional mutations but only sub-clones had further CNAs. In contrast, case B showed that whilst the ETv6-RUNX1 fusion was the earliest (or universal) genomic event, CNAs were early events preceding the acquisition of point mutations. In both cases, the major clone harbored the ETv6-RUNX1 fusion, point mutations and CNAs.

**Conclusion:** This proof of principle study validates multiplex Q-PCR coupled with a microfluidic platform as an appropriate technology to interrogate clonal architectures in cancer. Such studies may facilitate the identification of initiating lesions and appropriate molecular targets for therapy.

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**SYMPOSIUM 10**

**TWO BIRDS WITH ONE STONE**: MORAL AWARENESS SKILLS TRAINING TO IMPROVE BOTH PATIENT CARE AND PROFESSIONAL GROWTH

Myra C.B. van Zwieten

Dept. of General Practice, Academic Medical Center, University, Amsterdam, The Netherlands

**Purpose:** A major task for health care professionals is to integrate ethical expertise in their own everyday practice. With the steady increase in so called preference-based treatments (in distinction to evidence-based treatments) and diagnostic options, forcing patients to make morally charged decisions more and more frequently, it is desirable for doctors to be able to offer ethical guidance to their patients in a day-to-day basis. For all patients – and their parents – are becoming increasingly well-informed, but they still rely on their doctor for immediate action. Therefore, whenever an ethical issue arises in medical practice, there will always be the need to make the issue discussible in some way or another. In these cases, health care professionals can draw on expertise from the discipline of medical ethics, which promotes structural reflection on responsible conduct.

**Result:** In this plenary session on bioethics we will present three ethical methods that help physicians deal with ethical issues in a practical manner: discussing ethical issues with patients (moral counseling), discussing ethical issues with colleagues (moral deliberation), and ‘discussing’ ethical issues with yourself (moral reflection).

**Conclusion:** All these methods integrate ethical skills training with skills training in another domain of competence, i.e. communication, collaboration and professionalism. Common element of these three methods is the focus on moral awareness skills. This common focus kills two birds with one stone. Training moral awareness throughout the conversations with patients and colleagues directly enhances patient care. At the same time, moral awareness in the form of self-examination allows professionals to develop their own sense of ethical integrity.

**MORAL REFLECTION: ‘DISCUSSING’ ETHICAL ISSUES IN MEDICAL PRACTICE WITH YOURSELF**

Myra C.B. van Zwieten

Dept. of General Practice, Academic Medical Center, University, Amsterdam, The Netherlands

**Purpose:** The modern doctor needs to be a well-rounded professional. Patients – and their parents – are becoming increasingly well-informed, but they still rely on their doctor for council, when it comes to morally sensitive issues. In such cases, instead of a medical expert who makes the decision, the role of the doctor is more like that of a guide who helps the patient to disentangle the mass of information they are faced with and evaluate it.

**Methods:** In order to be able to discuss ethical questions with their patients – and parents – medical professionals first of all need to know their own moral viewpoint. The website Moralmap.com helps medical professionals to open moral issues up for discussion in an accessible way.

**Results:** Moralmap.com is a modern educational tool that invites the user to reflect on questions like ‘Should you always discuss everything with your patients?’, ‘How assertive should your patients be?‘, or ‘How do you deal with the pressures of time in your work?’ Visually appealing assignments encourage users to think about moral issues in a playful way. Personal views are made explicit step by step, based on individual case histories. Print-outs of the assignments form the basis for further classroom discussions. Medical professionals are regularly faced with ethical issues and questions, but generally, day-to-day practice offers little time for reflection. Moralmap has been designed to meet this need for reflection: the guest lecturers in the development of the website, all the necessary expertise is already incorporated in the assignments themselves as it were.

**MORAL COUNSELING: DISCUSSING ETHICAL ISSUES IN PEDIATRIC PRACTICE WITH YOUR PATIENTS AND FAMILIES**

Elizabeth Rider1,2

Dept. of General Practice, Academic Medical Center, University, Amsterdam, The Netherlands

**Purpose:** The modern doctor needs to be a well-rounded professional. Patients – and their parents – are becoming increasingly well-informed, but they still rely on their doctor for council, when it comes to morally sensitive issues. In such cases, instead of a medical expert who makes the decision, the role of the doctor is more like that of a guide who helps the patient to disentangle the mass of information they are faced with and evaluate it.

**Methods:** In order to be able to discuss ethical questions with their patients – and parents – medical professionals first of all need to know their own moral viewpoint. The website Moralmap.com helps medical professionals to open moral issues up for discussion in an accessible way.

**Results:** Moralmap.com is a modern educational tool that invites the user to reflect on questions like ‘Should you always discuss everything with your patients?’, ‘How assertive should your patients be?‘, or ‘How do you deal with the pressures of time in your work?’ Visually appealing assignments encourage users to think about moral issues in a playful way. Personal views are made explicit step by step, based on individual case histories. Print-outs of the assignments form the basis for further classroom discussions. Medical professionals are regularly faced with ethical issues and questions, but generally, day-to-day practice offers little time for reflection. Moralmap has been designed to meet this need for reflection: the guest lecturers in the development of the website, all the necessary expertise is already incorporated in the assignments themselves as it were.
Purpose: Skilful communication, relationship-centered care, and attention to everyday ethics are indispensable to the practice of high quality pediatric medicine. The ability to form deeper relationships and connections with patients and families goes beyond acquiring a set of communication behaviors. Reflection can strengthen the moral aspects of practice by helping physicians and other clinicians contemplate their actions, hold themselves responsible for their influence on patients, family members and colleagues, choose to act altruistically by supporting patients’ and families’ perspectives, and consider the underlying ethical meaning of their work.

Objectives: (1) To discuss concepts for relational competency, everyday ethics, and the role of reflection in enhancing practice; (2) to describe an interprofessional international faculty development program. “Difficult Conversations in Healthcare,” and model for relationship-centered learning used to enhance communication with patients and families.

Methods: The Institute for Professionalism and Ethical Practice (IPEP) at Boston Children’s Hospital, Harvard Medical School, promotes relationship-centered, interprofessional learning by integrating patient and family perspectives and the moral and relational aspects of care, creating safety for learning, honing multiple perspectives, and valuing reflection and self discovery. IPEP’s programs are designed to prepare clinicians to engage in challenging conversations, such as conveying a bad diagnosis, making difficult end of life decisions, or addressing adverse medical outcomes.

Results: Approximately 2500 professionals have participated in IPEP programs, including 254 in the Difficult Conversations faculty course. Participants report a greater sense of preparation, confidence, improved communication and relational skills, and decreased anxiety when holding challenging healthcare conversations.

Conclusion: The program strives to help professionals enhance their relational competence in the healthcare world, including qualities of compassion, trust and respect between clinicians and patients, improve interprofessional collaboration, and increase the capacity to relate to patients and families in the moral domain. Participants in IPEP programs report enhanced communication and relational skills.

MORAL DELIBERATION: DISCUSSING ETHICAL ISSUES IN PEDIATRIC ONCOLOGY PRACTICE WITH THE INTER-PROFESSIONAL TEAM

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Purpose: To enable healthcare staff to carry through morally correct actions they need and understanding during the MCD.

Methods: Results show that healthcare staff are clarifying perspectives as they are sharing arguments during the MCD and interviews are performed. Data is analyzed using grounded theory. Preliminary results indicate that healthcare staff are moving from the expert role, giving recommendations on actions, to the role of facilitator often following a model of analysis and several models are available including the dilemma method, the Norwegian procedure for case discussions, and the Karolinska University Hospital model for ethics analysis. In 2008 a joint working group on ethics were reviewed. Analyses were carried out with special regard to patients’ data, tumor characteristics, local treatment, and outcome. Follow-up was 63.5 months (range 6–175 months).

Results: Median age of patients was 58 months (3–193 months). Primary lung metastases had been present in 38/91 children. In 58 children pulmonary relapses occurred as singular recurrence (<2 weeks since diagnosis) or toxic (>2 weeks after diagnosis).

Conclusion: Multicenter protocol-driven therapy tailored to fit local needs is feasible in patients with WT in this setting. Abandonment of the challenge as do early and toxic deaths due to advanced presentations in fragile children. Local control in stage II patients needs to be further optimized.

PULMONARY RELAPSES IN CHILDREN WITH NEPHROBLASTOMA – DATA FROM SIOP 93-01/GPOH AND SIOP 2001/GPOH

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Purpose: To analyze patients’ data, treatment results, and outcome of patients with nephroblastoma, in whom pulmonary relapses occurred.

Methods: Data of 91 patients with Wilms tumor and pulmonary relapses, registered within the collaborative multicenter trials SIOP 93-01/GPOH and SIOP 2001/GPOH of the Society of Pediatric Oncology and Hematology, were reviewed. Analyses were carried out with special regard to patients’ data, tumor characteristics, local treatment, and outcome. Follow-up was 63.5 months (range 6–175 months).

Results: Median age of patients was 58 months (3–193 months). Primary lung metastases had been present in 38/91 children. In 58 children pulmonary relapses occurred as singular recurrence (<6 lesions per side). Mostly, pulmonary relapses occurred in nephroblastoma of intermediate risk histology (n = 65, low risk n = 1, high risk n = 25). The tumors with high risk histology (n = 25, 6 contained anaplasia, 15 were predominantly blastemal, and 4 had both, blastemal predominance with anaplasia. Local treatment of pulmonary relapses consisted of irradiation in 4 children, surgery in 35 children, and combined surgery plus irradiation in 33 children. 15 children did not undergo local treatment for pulmonary relapses (no data for 4 patients). 5 year overall survival (OS) was 60.44% for all children. A second pulmonary relapse occurred in 18 children (15 died of disease, 1 in progressive disease, 2 survived without evidence for disease).

Conclusion: Pulmonary relapses in nephroblastoma patients are associated with a significantly impaired prognosis. Further prospective studies are necessary to identify risk factors for the patients. Especially the role of treatment of primary lung metastases will have to be thoroughly evaluated.

LONG TERM OUTCOME OF CLEAR CELL SARCOMA OF THE KIDNEY (CCSK) PATIENTS TREATED ACCORDING TO SIOP93-01/GPOH PROTOCOL

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Purpose: Earlier we had reported an excellent outcome of CCSK patients treated according to the SIOP93-01/GPOH hup-risk protocol, however showing a new tendency to metastasize to the CNS when recurring. Whether the intensification treatment remains unclear due to short follow up.

Methods: We therefore re-analyzed all 50 patients having had a CCSK registered and treated in the SIOP 93-01/GPOH nephroblastoma trial from 1993 to 2001 in Switzerland, Germany and Austria.
Results: The median follow up time in March 2012 is 9.9 y (1.7–16 y). Event free survival rate (EFS) 5 y and 11 y after diagnosis is 85 ± 5% and 77 ± 7% respectively. 5 and 11 y overall survival rate is 92 ± 4% and 89 ± 5% respectively 8 patients suffered from recurrence. 5 patients relapsed within two years after diagnosis four of whom had CNS metastasis and died from progressive disease. Two CNS-relapses which occurred 2.6 and 4.1 y after diagnosis were successfully salvaged. One patient with an extra-renal CCKS suffered from local recurrence 10.5 y after diagnosis and despite intensive treatment deceased 2.8 y later. None of the three stage IV patients developed a late relapse. 1 patient died from congestive heart failure after megatherapy and thoracic irradiation as her first line treatment suffered from local recurrence 10.5 y after diagnosis and despite intensive treatment deceased 4.1 y after diagnosis were successfully salvaged. One patient with an extra-renal CCKS the only independent risk factor for event in cox-regression analysis (ExpB 6.4; 95%-CI: 1.2–33).

Conclusion: CCKS patients treated according to the SIOP high risk regimen have an excellent prognosis also after long term follow up. Contrary to the changed predominantly cerebral localization of relapses, late relapses still occur and must be taken into account when following these patients.

References

0004
WILMS TUMOR: CARDIAC FINDINGS IN 11P GERM LINE MUTATIONS
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Purpose: Gern line alterations of 11p in the WT-1 region are associated with Wilms tumor development. We sought to describe cardiac findings in this population.
Methods: Utilizing oncology and genetic data bases, medical records, and presence of germ line mutations, we matched Wilms patients with eochocardogram, EKGs and cardiac histories.
Results: We identified 14 patients with Wilms tumor with germ line mutations of 11 p. Of two patients with features of WAGR and genetic concordance, 1 had insufficient cardiac information, the other normal findings. 5 of the remaining 12 pts had cardiac findings of note. 1. 25 mo., Stage 1; FH with rest; Exon 8 mutation; VA discordance, VSD, PDA, Truncal Vein Septum. 2. 55 mo., Stage 1; FH (Rhabdomyomatous); (XX) intron 9; Moderate Perimembranous VSD. 3. 12 mo., Stage 3; FH (Rhabdomyomatous), Exon 7 mutation; Ostium Secundum ASD as Fossa Ovalis. 4. 12 mo., Stage 5; FH (Rhabdomyomatous), Exon 2 mutation; Parasyssymal Atrial Tachycardia. 5. 24 mo., Stage 1; FH (Rhabdomyomatous), Deletion distal to intact WT and PAS6 genes; Rt-sided Aortic Arch, aberrant left subclavian.
Conclusion: Wilms Tumor has well known associations with hemihypertrophy, genito-urinary anomalies, BWS and Drash syndromes. Authors have described an excess of congenital heart findings associated with Wilms tumor. In this limited series 38% of Wilms tumor patients with recognized 11p anomalies have structural heart findings. Animal models demonstrate the role of WT-1 in cardiac morphogenesis. With advances in genome analysis, improved mutation/deletion detection techniques and attention to structural cardiac findings in Wilms, may lead to an understanding of cardiac late effects in this population.

References

0005
ACUTE LYMPHOCYTIC LEUKAEMIA 1
METHOTREXATE-INDUCED NEUROTOXICITY AND LEUKENCEPHALOPATHY DURING TREATMENT OF CHILDHOOD ACUTE LYMPHOCYTIC LEUKAEMIA (ALL)
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Purpose: Methotrexate (MTX) is an essential drug in the treatment of childhood ALL. Sub-acute MTX neurotoxicity typically occurs 2–14 days after intrathecal (IT) or high-dose (HD) IV. Leukencephalopathy (LE) evidenced by white matter hypointensities on T2-weighted magnetic resonance imaging (MRI) can be associated with clinical symptoms. Though the majority of patients can be re-challenged with MTX, some patients have recurrences of neurotoxicity. Subsequent MTX is sometimes omitted from the treatment plan, thus compromising therapy.

Methods: Between 2000 and 2007, 411 patients with newly diagnosed ALL were enrolled in the Total XV study at our institution1. Therapy included 4–5 doses of HDMTX and 13–25 doses of IMTMX.
Results: Fourteen patients (3.4%) aged 2–18 years developed sub-acute MTX neurotoxicity. Eight patients presented with seizures, 4 with stroke-like symptoms/hemiparesis, 1 with ataxia and 1 with acute behavioral changes 3–11 days after MTX. Neurotoxicity occurred in 8 patients following the simultaneous administration of HDMTX and IMTMX and in 6 patients after IMTMX. Thirteen patients were subsequently re-challenged with HDMTX (N = 5) and/or IMTMX (N = 13). One patient was due for only one more IMTMX and was not re-challenged. Two patients received amnionophylly prophylaxis prior to subsequent HDMTX and 5 patients received leucovorin rescue after IMTMX. MTX-related neurotoxicity recurred in one patient who had received amnionophylly. The other 12 patients tolerated MTX re-challenge well. MRI with diffusion-weighted imaging was available at the time of the event for 12 patients. Ten patients had evidence of LE (6 grade-1, 4 grade-2). At a median follow up of 24 months, LE persisted in 8 patients while abnormalities resolved in 2 patients.
Conclusion: MTX can be safely re-challenged in the majority of patients who develop a transient MTX-related neurotoxic event. MRI changes of LE are found in most but not all patients with clinical neurotoxicity. LE changes likely resolve over time, but longer follow up is needed.

References

0006
Dexamethasone Exposure and Memory Function in Adult Survivors of Childhood Acute Lymphoblastic Leukemia
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Purpose: Dexamethasone is commonly used in acute lymphoblastic leukaemia (ALL) treatment, although the long-term impact of prolonged exposure on central nervous system (CNS) function is unclear. As glucocorticoids influence hippocampal function, we investigated whether survivors who received dexamethasone versus prednisone during continuation therapy were at a higher risk for memory dysfunction.
Methods: CNS function was investigated in 38 adult survivors of childhood ALL treated on one of two standard protocols, which differed primarily in type of glucocorticoid given during continuation therapy (dexamethasone [n = 18] vs. prednisone [n = 20]). Mean (SD) age of diagnosis was 10.2 (3.80) years and age at evaluation was 25.1 (3.44) years, with no significant differences between survivors treated with dexamethasone vs. prednisone. Groups did not differ in cumulative methotrexate exposure, and no survivors were treated with cranial radiation. Group comparisons of memory function were conducted using paired-samples T-tests and Mann–Whitney U tests for neurocognitive and functional magnetic resonance imaging (fMRI) during word and facial recognition tasks.
Results: Survivors treated with dexamethasone (mean = 2,240 mg/m²) demonstrated lower performance on multiple memory-based measures, including memory for stories (p = 0.007), reading (p = 0.033), and mathematics (p = 0.017) compared to survivors treated with prednisone (mean = 10,616 mg/m²). Story memory performance correlated with word recognition during fMRI (p = 0.028, r = 0.36) and was associated with altered activation in left inferior fronto-temporal brain regions. Between group fMRI analyses also demonstrated survivors treated with dexamethasone had decreased activation in retrosplenial regions, which have dense reciprocal projections with the hippocampus, are involved in memory function, and are associated with integrity of multiple neural networks.
Conclusion: These results suggest adult survivors of ALL treated with dexamethasone are at increased risk for memory deficits and altered neural activity associated with hippocampal circuitry. Since dexamethasone is more potent and has higher CNS penetration than prednisone, results may be due to relative differences in CNS exposure to glucocorticoids.

0007
CEREBRAL SINUS-VENOUS THROMBOSSIS IN CHILDREN RECEIVING ANTILEUKEMIC THERAPY
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Purpose: To describe the epidemiology and outcome of cerebral sinus-venous thrombosis (CSVT) in children receiving antileukemic therapy.
Methods: Data were extracted from medical records of 23 (14 males) patients consecutively diagnosed with CSVT at McMaster Children’s Hospital (MAC) and The Hospital for Sick Children (HSC) between 2000–2012.
Results: Average age was 9.3 years (range 2–18). Primary diagnosis was precursor-B cell acute lymphoblastic leukemia (ALL) (n = 17), T-cell ALL (n = 4) and T cell lymphoblastic lymphoma (treated according to ALL chemotherapy) (n = 2). Only two children with precursor-B ALL had leptomeningeal disease at diagnosis. Chemotherapy was according to Dana-Farber Cancer Institute protocols (00-01, 05-01) in 9 patients, Children’s Oncology
Group protocols (AALL0232, 0331) in 8 and other in 5. One patient was asymptomatic. Headache (n = 17), seizure (n = 13) and focal neurological deficit (n = 7) were common symptoms. All but one patient received recent therapy either with E.coli (n = 13) or pegylated (n = 9) asparaginase along with dexamethasone (n = 17) or prednisone (n = 6). Involved vessels included superior sagittal sinus (78%), transverse sinus (52%) and cortical veins (52%). Seven (30%) patients had cortical bleeding at diagnosis. Elevated factor VIII level was seen in 65% of patients. Only 2 of 17 patients had elevated D-dimer (>500 ng/ml) (both patients with asymptomatic therapy) re-instated in 16 patients usually with asparaginase therapy; none developed thrombosis. Mortality of patients who had favorable outcome without any neurologic sequela or thrombosis-related mortality with complete and near complete radiological resolution in 77% patients.

Conclusion: LMWH is safe and effective therapy for CSVT in children receiving antileukemic therapy. Asparaginase therapy can be safely re-instated with concurrent antileukemic therapy.

O008
LOW EFFICACY OF ROUTINE CSF SURVEILLANCE IN DETECTING ASYMPTOMATIC CNS RELAPSE IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKAEMIA

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Purpose: The incidence of CNS relapse in childhood ALL is < 5%. Depending on NCI risk status, patients received between 20–28 doses of intrathecal methotrexate to prevent CNS relapse. Cerebrospinal fluid (CSF) was collected with each lumbar puncture and examined for the presence of blasts. A retrospective analysis was conducted to determine efficacy and cost effectiveness of surveillance CSF cytospins.

Methods: The records of children enrolled on UKALL2003 who had completed treatment by May 2011 at Great Ormond Street Hospital and University College Hospital, London were reviewed. Exclusion criteria were CNS disease at diagnosis, refractory ALL & Pb + ALL CNS relapse was diagnosed if blasts were detectable on CSF cytocentrifuge (>5/ml) and/or clinical signs of CNS leukaemia. Relapses were classified as symptomatic if they had headache, diplopia, cranial nerve palsies or asymptomatic if absent. To determine the detection rate of positive cytospins, the number of asymptomatic children with positive cytospins were divided by total number of cytospins in the whole cohort.

Results: 331 children were eligible for analysis (male = 170). Median age 4.8 years (range 1–20); pre B-cell 87%, T-cell 12%, WBC < 50 × 10³/μL, 77% WBC > 50 × 10³/μL. Regimens A: 54%, B: 27%, C: 19%. Of the twenty-seven patients who relapsed on treatment (8.1%), 12 had CNS relapse (3.6%). Six patients had combined CNS and BM relapse while six had isolated CNS relapse. Five were symptomatic leading to a diagnostic LP whilst 7 asymptomatic patients were diagnosed via surveillance CSF cytospin. The detection rate of asymptomatic positive CSF cytospin was 0.99%. Three patients with asymptomatic CNS relapse died; all had an early relapse (OR1 < 18 months). The total cost of cytospins was £67,000.

Conclusion: The efficacy of detecting asymptomatic CNS relapse by routine CSF cytospin surveillance is low, cost ineffective and may be safely discontinued.

LATE EFFECTS 1

O009
CHARACTERISTICS OF HIGH HEALTH CARE USERS AMONG CHILDHOOD, ADOLESCENT AND YOUNG ADULT CANCER SURVIVORS IN BRITISH COLUMBIA, CANADA

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Purpose: The CAYACS (Childhood, Adolescent and Young Adult Cancer Survivors) program examines survivorship issues though linkage of population-based registries, clinical data and administrative databases. This study describes patterns of outpatient health care utilization and costs, and factors associated with high (top 10%) or low (bottom 25%) users, among a population-based cohort of 5-year survivors of cancer diagnosed before age 25 years between 1970 and 1994 in British Columbia, and followed to 2001.

Methods: We linked provincial cancer registry and health care records of 1154 childhood (diagnosed aged 0–14) and 1392 adolescent and young adult (AYA – diagnosed aged 15–24) survivors. Comparison subjects were frequency-matched from the provincial health insurance plan registry by birth year and gender. We estimated the odds of being a high or low user (compared to medium use) of total physician-ordered outpatient services, including prescription drugs. Cost distributions and mean costs were compared between cases and comparators.

Results: Within the childhood survivor group, those with a brain tumour (OR 2.9, 95% CI 1.5–5.6), with cranial radiation (OR 95% CI 1.1–3.3) or a relapse (OR 2.1, 95% CI 1.2–3.7) were more likely to be high users. Females were more likely high users in the AYA cohort (OR 1.7, 95% CI 1.1–2.6). Childhood survivors had 9 times the odds of being high users compared to controls; AYA survivors were no more likely to be high users than their peers. Survivors (compared to medium use) had higher annual health care costs than their peers, driven largely by greater prescription drug costs.

Conclusion: Childhood cancer survivors are more likely to be high users of health care compared to their peers, most likely due to late effects of their cancer or its treatment. The same result was not found in AYA survivors, although annual costs were significantly greater for AYA survivors compared to the comparison group.

O010
TREATMENT FACTORS AND NOT GENETIC VARIATION PREDOMINANTLY DETERMINE METABOLIC SYNDROME IN CHILDHOOD CANCER SURVIVORS

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Purpose: Genetic variation that regulates insulin resistance, blood pressure and adiposity in the normal population might determine differential vulnerability for metabolic syndrome after treatment for childhood cancer. Aim of the study was to evaluate the contribution of candidate single nucleotide polymorphisms (SNPs) relevant for metabolic syndrome in our single centre cohort of adult long-term childhood cancer survivors.

Methods: In this retrospective study 352 adult long-term survivors of childhood cancer were analyzed. JAZF1 gene rs864745, THADA gene rs758798, IR5 gene rs2943641 TPAP2 gene rs987237, MSRA gene rs7826222, ATP2B1 gene rs2681472 and rs2681492 were genotyped. The association of genotypes with total cholesterol levels, blood pressure, body mass index, waist circumference and frequency of diabetes were assessed.

Results: Median age at diagnosis was 5.7 years (range 0.0–17.8 years), median follow-up time was 17.9 years (range 5.0–48.8) months and median age at follow-up was 25.6 years (range 18.0–50.8). Metabolic syndrome was more frequent in cranially (23.3%, P = 0.002) and 18.0%–50.8). Metabolic syndrome was more frequent in cranially (23.3%, P = 0.002) and abdominally (23.3%, P = 0.009) irradiated survivors as compared with non-irradiated survivors (10.0%). Association of allelic variants in rs2681472 and rs2681492 were not significant. None of the SNPs was associated with the metabolic syndrome. Adjusting for age, sex, follow-up time, cranial irradiation and abdominal irradiation did not change these results.

Conclusion: Treatment factors but not genetic variation determine hypertension, waist circumference, diabetes and metabolic syndrome in adult long-term survivors of childhood cancer.

O011
ACCELERATED AGING, DECREASED WHITE MATTER INTEGRITY AND ASSOCIATED COGNITIVE DYSFUNCTION 25 YEARS AFTER CHILDHOOD ACUTE LYMPHOBLASTIC LEUKAEMIA

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Purpose: To determine metabolic syndrome in childhood acute lymphoblastic leukemia (ALL) have neurotoxic properties. The aim of this study is to find the underlying mechanisms of neurocognitive sequelae in adult long-term survivors 25 years after diagnosis.

Methods: Twenty-four patients treated with standard dose CT only, 29 patients treated with high dose CT and 49 patients treated with standard dose CT + CRT (1800–2500 Gy), 2 patients treated with high dose CT and 49 patients treated with standard dose CT only, 20 patients treated with high dose CT and 49 children treated with the Amsterdam Neuropsychological Tasks Program (ANT) and MR Diffusion Tensor Imaging (DTI). Differences in Fractional Anisotropy (FA) – a DTI measure describing white matter (WM) integrity – were analysed using whole brain

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VALIDITY OF SELF-REPORTED DATA ON PREGNANCY OUTCOMES—COMPARING SELF-REPORTED DATA OF CHILDHOOD CANCER SURVIVORS WITH DATA FROM A NATIONWIDE POPULATION-BASED REGISTRY

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Purpose: To assess the accuracy of self-reported pregnancy outcomes among female childhood cancer survivors (CCS) and sister controls.

Methods: This study is part of a nationwide study in which CCS and sister controls are asked (amongst others) to fill out a questionnaire regarding socio-demographic characteristics, fertility and pregnancy outcomes. Data on self-reported pregnancy outcomes were compared with reference data from the Netherlands Perinatal Registry (PRN), which contains data on all births between 1985 to 2009. Data on each self-reported pregnancy were linked to the PRN based on the mother’s and child’s date of birth.

Results: 589 pregnancies were reported in 289 CCS, whereas 300 pregnancies were reported in 123 controls. Linkage to the PRN yielded 524 unique hits (357 pregnancies in 218 CCS; 167 pregnancies in 105 controls). A high intra-class correlation coefficient (ICC) was found for birth weight (0.94 (95% CI 0.91–0.96) and 0.96 (95% CI 0.83–0.96) for CCS and controls, respectively). For gestational age, the ICC was 0.88 for CCS (95% CI 0.85–0.91), but only 0.49 for controls (95% CI 0.32–0.62). The kappa value for method of conception was moderate to good, but varied largely per method (0.55 to 1.0). The kappa values for different methods of delivery were good for CCS and controls (0.76 to 0.92). Kappa for pregnancy-induced hypertension was 0.59 for CCS and 0.61 for controls. Multilevel analyses showed no differences in accuracy associated with time since pregnancy or educational level.

Conclusion: Overall, self-reported pregnancy outcomes of CCS agreed better with the registry data than that of controls. This might be due to increased awareness of late effects and a higher frequency of medical follow-up. In conclusion, although self-reported data regarding fertility and pregnancy by CCS seem consistent with registry parameters, there is a need for follow-up to further investigate the accuracy of self-reported data.

RADIATION ONCOLOGY PROS 1

THE EFFECT OF RADIATION TIMING ON PATIENTS WITH INTERMEDIATE-RISK PARAMENINGEAL RHABDOMYOSARCOMA: AN ANALYSIS OF IRS-IV AND D9803

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Purpose: Radiation therapy remains an essential component of treatment for patients with intermediate risk parameningeal rhabdomyosarcoma (PM RMS). The proportion of patients with intermediate risk parameningeal rhabdomyosarcoma (PM RMS) had decreased from 81% to 59% over the last forty years and hence questions the importance of timing of radiation therapy.

Methods: Patients treated on IRS-IV without ICE were treated immediately at day 0 whereas those on D9803 had delayed XRT at week 12. Therefore, we investigated whether a delay in radiation therapy produced similar outcomes as those undergoing immediate radiation in PM RMS patients as those undergoing immediate radiation. The median follow up was 8.5 years for IRS-IV patients and 5.6 years for D9803 patients.

Results: Compared with 198 patients on IRS-IV, the 192 patients from D9803 had no difference (p < 0.05) in 5 year outcomes of local relapse (19% vs. 19%), failure-free-survival (70% vs 67%), or overall survival (75% vs 73%) as a cohort or when separated by the degree of intracranial extension classified as no extension (None), cranial nerve palsy (CNP) cranial base-of-skull erosion (CBBE) without intracranial extension (CNP/BBCE), or ICE. The D9803 patients were more likely to have initial MRI staging (71% vs 55%) and more likely to receive either 3 dimensional or intensity modulated radiation therapy (90% vs 33%).

Conclusion: These data support that a delay in radiation therapy for PM RMS patients does not compromise clinical outcomes when modern imaging and radiation techniques are used.

PEDIATRIC RADIATION ONCOLOGY SOCIETY (PROS) ACTIVITIES FOR LOW- AND MIDDLE-INCOME COUNTRIES

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Purpose: Pediatric Radiation Oncology Society (PROS) recognizes unique needs of low- and middle-income countries (LMICs) for building cancer therapy capacity. The PROS is dedicated to achieve empowerment of the providers practicing in nations and help them to create their own guidelines for better quality radiotherapy. Society makes long-term commitment for continuous educational activities tailored for unique needs of particular nation.

Methods: PROS is in the process of reaching out to LMICs for assessment of existing human resources and radiation oncology infrastructures, knowledge-gaps and practice challenges, as well as input on practical tools applicable for learning for that particular nation or region. PROS is evaluating additional mechanisms to facilitate representation and participation from LMICs and views partnerships with other societies and organizations as a great tool in outreach to these nations. The Society plans to develop educational materials and tools for basic radiotherapy methods and techniques that are more applicable to centers utilizing Cobalt-60 machines and 2-D treatment planning and delivery systems.

Results: PROS has low-cost membership for practitioners from LMICs who can access on-line forum for discussion of challenging cases. PROS is also providing low rates for LMICs representatives for congress registration. While the Society has members from nations in the most part of the world, there is still limited representation of LMICs for both membership and in meetings. Information dissemination is progress with initial positive feedback received from East Asian nations expressing great interest in PROS activities. The PROS has established initial contacts with International Atomic Energy Agency (IAEA) and will collaborate in educational and training.

Conclusion: In collaboration with other societies and organizations, the PROS plans to continue educational mission for LMICs to help improve the outcome of childhood cancer in resource-poor countries.

PEDIATRIC RADIATION ONCOLOGY SOCIETY (PROS) ACTIVITIES FOR LOW- AND MIDDLE-INCOME COUNTRIES

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Purpose: To correlate dose distribution and MRI information related to neurocognitive outcome in paediatric patients focally irradiated to the brain. The first challenge was to register MRI acquired 3 to 10 years after radiotherapy (RT) to original planning CT. We present the registration process and its validation in a multi-step process made of rigid and non-rigid registration. The so registered images were further matched with MRI, using a similar approach enhanced by the use of an affine registration to model the growth of the patient. This allowed us to superimpose the dose distribution to DWI and DTI maps, and to produce a list of VOIs of interest that could be compared with standard MRI. We conclude that the registration process works and can be used for quantitative analysis of the neurocognitive outcome in paediatric patients treated with RT for brain tumours.
Results: We observed an increase of normalised mutual information (NSMI) for the rigid and affine registration of average 4% enhanced by the non-rigid registration which added a further 3% (max final NMI 1.30). Statistical evaluation on defined ROIs confirmed reproducibility and accuracy and was assessed by the qualitative analysis of an experienced radiologist.

Conclusion: This multi-step registration process was able to account for different positions during the examinations and the growth of the patients. We can now use this method to correlate dose distribution to morphological and functional damage pointed out by DLI, DTI maps and neurocognitive tests.

O016

MODELING THE RISK OF SECONDARY SOLID CANCERS AFTER RADIOTHERAPY IN CHILDREN AND YOUNG ADULTS: A COMPARISON OF INTENSITY MODULATED PROTON THERAPY AND PHOTON THERAPY

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Purpose: To quantify the secondary cancer risk in paediatric and young adult patients after radiation therapy for both intensity modulated proton radiation therapy (IMPT) and photon therapy.

Methods: IMPT plans were created for 28 patients (11 brain tumors, 11 mediastinal Hodgkin lymphoma, 1 neuroblastoma, 1 pelvic rhabdomyosarcoma, and 4 medulloblastomas), aged 1–29, previously treated with IMRT or 3D-CRT using the Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA) using a proton dose calculation algorithm with an IMPT scanned beam model. IMPT and photon plans were compared for volumes of tissue receiving low doses, integral dose, and second cancer risk. Second cancer risk was determined using two methods. The first (integral dose) model, applied a linear relationship between the relative risk (RR) of second cancer and the integral dose to determine the relative risk. The second (OED) model, applied the organ equivalent dose concept to describe the body dose followed by a derived excess absolute risk (EAR) and cumulative risk for solid cancers.

Results: The RR, EAR and cumulative risk for second cancers was lower for all IMPT plans. Using the integral dose model the RR was reduced by 14%, 18%, 12%, 23% and 31% for brain tumors, mediastinal Hodgkin lymphoma, neuroblastoma, pelvic rhabdomyosarcoma and medulloblastoma patients respectively. In the OED model, the mean reduction in cumulative risk of secondary cancer was 47% for brain patients, 48% for Hodgkin lymphoma, 43% for neuroblastoma, 56% for the rhabdomyosarcoma and 55% for patients who received craniospinal irradiation. IMPT plans had also reduced integral dose and smaller body volume exposure to low radiation doses.

Conclusion: Across a variety of clinical scenarios, IMPT resulted in an overall reduction of secondary malignancy risk of 18% for the integral dose model and 49% OED model respectively.

O017

DEVELOPING AN ONLINE INFORMATION INTERVENTION FOR PARENTS SHARING INFORMATION ABOUT ACUTE LYMPHOBlastic LEUKAEMIA WITH THEIR CHILD

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Purpose: Our previous research identified that parents of children with ALL felt that they received minimal support to facilitate the acquisition of knowledge about the disease, especially in the period immediately after diagnosis. We therefore developed an online intervention named HELP (Harmonising Education about Leukaemia for Parents) to facilitate easy access to information about leukaemia. This resource was aimed at parents of children with ALL up to 6-months post diagnosis. At SIOP 2011, we presented an early feasibility testing with a group of parents, before being evaluated in a randomised controlled study. We anticipate HELP will increase parents’ knowledge, confidence and competence, and make communication with professionals easier.

Results: HELP is a web-based interactive educational intervention that aims to both inform and facilitate communication between family members. It is comprised of short summaries, videos made by parents and health and social care professionals, printable discussion guides, age-appropriate diagrams, a discussion board and ‘ask a question’ section; and links to external resources, which have been checked for accuracy by a health professional.

Conclusion: In the next stage of the development process, HELP will undergo feasibility testing with a group of parents, before being evaluated in a randomised controlled study. We anticipate HELP will increase parents’ knowledge, confidence and competence, and make communication with professionals easier.

O018

ADOLESCENT CANCER PATIENTS’ USE OF A MOBILE PHONE-BASED ELECTRONIC SYMPTOM DIARY

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Purpose: The delivery of optimal supportive care depends on accurate communication between patients and clinicians regarding disease or treatment-related symptoms. Documentation of patients’ symptom experiences necessitates reliance on patient recall, which may be vague and imprecise. Our team developed an electronic diary (eDiary) for adolescent cancer patients to record symptoms. The objectives of this project were to: 1) determine the reliability of the application, the reasons for any missing data, and participants’ adherence rates to daily symptom queries; and 2) determine participants’ perceptions of the usefulness and acceptability of data collection via mobile phones.

Methods: Our team developed an electronic symptom diary based on interviews conducted with adolescent and young adult cancer patients and oncology clinicians. This diary included daily severity ratings of five cancer-related sequelae (i.e., pain, nausea, vomiting, fatigue, sleep). The occurrence of selected physical sequelae (i.e., diarrhea, constipation, fever, numbness/tingling, mouth sores, dizziness, headache) was assessed daily. In addition, participants selected descriptors of their current mood. After the application was beta-tested by clinicians and researchers, 10 adolescent cancer patients participated in a 3 week trial of the eDiary’s feasibility and usability. Mobile phones with accessories and monthly service plans were loaned to participants who were instructed to report their symptoms daily. Participants completed a brief usability questionnaire and were interviewed to elicit their perceptions of the eDiary and any technical difficulties encountered.

Results: Overall adherence to daily symptom reports ranged from 91%–97%. The participants experienced few technical difficulties during the study. They reported that recording their symptoms daily was beneficial. Symptom occurrence rates were high and considerable inter-patient and intra-patient variability was noted in the symptom and mood reports. This variability cannot be appreciated when symptoms are assessed using longer week recall periods.

Conclusion: eDiaries are feasible to use and may stimulate valuable insight in patients’ symptom patterns to promote effective symptom management.

O019

USABILITY TESTING OF A COMPUTERIZED COMMUNICATION TOOL IN A DIVERSE URBAN PEDIATRIC POPULATION WITH CANCER

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Purpose: SiSom is an interactive, computerized communication tool designed to help children express their perceived symptoms, and social-emotional problems that has shown to significantly improve communication in patient consultations. Children travel virtually from island to island assessing their symptoms or problems. Despite completed rigorous testing in Norway, usability testing is warranted with children from the US.

Methods: A mixed methods usability study was conducted with a purposive sample of children treated for cancer at an urban tertiary care medical center. Children completed 8 tasks using a “think aloud” protocol. These tasks included the ability to build an avatar, select the first island, visit each of the 5 islands, and generate a symptom report. Other features such as voice and screen activity were also captured with the Morae 3.3 usability software. During a scheduled clinic visit, children were offered the choice to complete SiSom in English or Spanish using the interactive web-based module for online access. The data was downloaded and analyzed using NVivo

Results: Five children, aged 6 to 12 years, diagnosed with leukemia (n = 3) or brain tumor (n = 2) participated in the study. Four children completed all tasks and 1 child missed 3 island-related tasks due to fatigue. All children navigated successfully from one island to the next, ranking their symptom severity, clicking the magnifying glass for help, or asking the researcher for assistance. Children spent an average of 4.04 minutes (SD 1.46) to complete each task. All Spanish-speaking children (n = 3) requested to complete the English-version SiSom. All children were satisfied with the aesthetics and expressed an interest in using SiSom to communicate their symptoms.
6/65 patients, first recurrence treatment included radiotherapy, in 22/63 chemotherapy. 63/66 metastases operated, a diameter of metastases: 2.5 cm (range: 0.6–16 cm; $\bar{x}$ = 5.6); 7/41 pleural disruption; 44/57) or through symptoms

- Conclusion: Children may feel uncomfortable discussing certain concerns with clinicians or their parents and may be reticent to report these issues via interview. The interactive cartoons and computerized reporting in Sisom may promote children to acknowledge issues and may lead to an improved understanding of pediatric oncology patients’ emotional and physical concerns.

**BONE PRIZE**

**O021**

**PREDICTING DISEASE FREE SURVIVAL USING PHARMACOGENETICS IN PATIENTS WITH OSTEOSARCOMA**

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Purpose: Osteosarcoma comprises 5% of all pediatric malignancies and only 50% of patients will survive. A poor response to chemotherapy is the dominant risk factor for poor survival. Pharmacogenomics research can help to understand the mechanism of drug response and offers the possibility to optimize treatment and improve outcome. Therefore, we investigated the cumulative effect of genes involved in the transport and metabolism of cisplatin, doxorubicin and the possibility to optimize treatment and improve outcome. Therefore, we investigated the cumulative effect of genes involved in the transport and metabolism of cisplatin, doxorubicin, and the possibility to optimize treatment and improve outcome.

Methods: Pediatric oncology patients between the ages of 7 to 12 years (English or Spanish speaking, on or off-therapy) reported their symptoms using two methods: the MSAS administered verbally by the researchers and Sisom completed by children on touch-pad computers. One of the children’s parents simultaneously completed the same two instruments. The order of symptom completion was assigned randomly. The children’s responses for 22 symptoms that were included on both instruments were compared.

Results: Over a 20 month period 100 child-parent dyads were enrolled. Weighted Kappa statistics were generally fair to moderate (i.e., 0.2–0.6). McNemar tests were used to evaluate differences in symptom reporting. Significant differences were noted for 13 of the 22 comparisons. For all such comparisons, the children were more likely report the symptom using Sisom than the on the MSAS.

Conclusion: Children may feel uncomfortable discussing certain concerns with clinicians or their parents and may be reticent to report these issues via interview. The interactive cartoons and computerized reporting in Sisom may promote children to acknowledge issues and may lead to an improved understanding of pediatric oncology patients’ emotional and physical concerns.

**THE USE OF CHEMOTHERAPY DOES NOT IMPROVE OUTCOME OF PATIENTS WITH A LATE SOLITARY LUNG METASTASIS AS FIRST RECURRENCE OF OSTEOSARCOMA**

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Purpose: Late, solitary pulmonary osteosarcoma metastases are believed to carry a rather favorable prognosis with surgery only. We investigated this hypothesis and analyzed factors that might correlate with prognosis.

Methods: The Cooperative Osteosarcoma Study Group (COSS) and the Italian Sarcoma Group (ISG) jointly investigated characteristics, treatment, outcome and prognostic factors for patients with high-grade central osteosarcoma of the extremities who developed a late (≥3 years from initial diagnosis) solitary lung metastasis as first recurrence. Results: 66 evaluable patients (44 male, 22 female; median age at initial diagnosis: 13 years). Metastases detected via a routine follow-up imaging (N = 44/57) or through symptoms (N = 13/57) after a median of 4.4 years (range: 3.0–19.0) from initial diagnosis. Median diameter of metastases: 2.5 cm (range: 0.6–16 cm; N = 56); 7/41 pleural disruption; 18/45 adjacent to pleura and 6/40 documented pleural effusions. 63/66 metastases operated, a support system for patient-centered care in pediatric oncology. A previous study showed that the master regulator of ES pathogenesis, EWS-FLI1, modulates basal p53 levels via suppression of cell autonomous NOTCH signaling. Here, we report NOTCH signaling-dependent suppression of the NAD dependent deacetylase sirtuin 1 (SIRT1) and its effect on p53 in ES.

Methods: Regulation of SIRT1 expression downstream of EWS-FLI1 and NOTCH was discovered using comparative genomics, and was validated in reporter gene assays upon experimental modulation of EWS-FLI1 and HEY1, and upon co-cultivation of ES cells with NOTCH ligand expressing fibroblasts. Expression of SIRT1 and of acetylated p53 in cell lines was monitored by immunoblotting. SIRT1 expression in primary tumors was analysed by immunohistochemistry. The effect of a small molecule SIRT1 inhibitor, Tenovin 6, on p53 activation and ES cell survival was tested in in-vitro growth assays. Results: 108/310 primary tumors expressed high to moderate SIRT1 levels. Co-cultivation of ES cell lines with NOTCH ligand expressing cells lead to activation of the NOTCH transcriptional effector HEY1. Mimicking NOTCH activation by ectopic HEY1 expression suppressed SIRT1 in ES cells leading to acetylation and functional activation of p53. A similar HEY1 induced SIRT1 suppression-dependent mechanism of p53 activation was observed in cell lines from B-cell malignancies and in primary keratinocytes. The small molecule SIRT1 inhibitor Tenovin 6 efficiently killed SIRT1 expressing ES cells in vitro. While only 25% (50/228) primary tumors from patients with localized disease expressed high to moderate levels of SIRT1, this percentage increased to 42% (11/26) in patients with metastatic disease. Strikingly, 75% (12/16) of metastases were found highly positive for SIRT1.

Conclusion: SIRT1 suppression connects tumor suppressive NOTCH to p53 activation in Ewing sarcoma and B-cell malignancies. Our preliminary data suggest that SIRT1 inhibitors represent promising drugs to specifically target metastases in ES patients.
After a median follow up from first recurrence of 4.7 years (range: 0.1–20), actuarial overall and even free survival (EFS) at 5/10/15 years were 65.1%/57.5%/52.9% and 41.9%/ 39.1%/39.1%, respectively. The interval from first to second recurrence was shorter (median: 12 years; range: 0.6–6.9) than the interval from initial diagnosis to first recurrence in 26/28 patients suffering a second recurrence. Positive prognostic factors (p < 0.05) for EFS were: Detection of first recurrence by imaging rather than symptoms, diameter of metastasis <5 cm, no pleural disruption, no macroscopic or microscopic tumor residuals after surgery. Patients not receiving chemotherapy or radiotherapy had better EFS than those who did, but the groups were positively selected.

**Conclusion:** Approximately one half of our patients with late solitary pulmonary metastases became long term survivors with appropriate therapy. Our results do not support the use of chemotherapy for this indication.

**References**

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**O024 IMPROVED RADILOC ASSESSMENT OF CHILDREN WITH SOFT TISSUE SARCOCM IN THE FRAMEWORK OF THE COOPERATIVE WEICHTEILSARKOM STUDIENGRUPPE (CWG)**

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**Purpose:** Pediatric soft tissue sarcoma (PSTS) mainly occur in young children and are frequently located in complex anatomic sites such as the base of the skull. The exact imaging of the primary tumor, lymph nodes and metastases is a crucial step in the diagnosis/treatment with major therapeutic/prognostic relevance. But imaging quality and interpretation in PSTS patients has rarely been investigated in larger series.

**Methods:** The CWG-Guidance recommends imaging standards, but reference review is not mandatory and was only performed if imaging was submitted for the purpose of diagnostic/ therapeutic consultations. The imaging submitted 1/2009–1/2012 was reviewed by the CWG-reference radiologists and oncologists. Compliance with the recommendations and the therapeutic relevance of shortcomings were evaluated. The proportion of divergent interpretations of local and reference radiologist was assessed.

**Results:** 6/23 imaging studies from Germany (n = 577) and Sweden/Switzerland (n = 46) were reviewed. Most studies were MRI- investigations (n = 558), followed by CT-scans (n = 62). The imaging encompassed 293 children studied at primary diagnosis (n = 253), response assessment (n = 123), end of therapy (n = 42), relapse or occurrence of a 2nd cancer (n = 54) or other time points (n = 121). Merely 171 investigations were CWG-guidance compliant and the proportion of incomplete studies was largest in the MRIs (448/ 554 evaluable); 158/448 incompleiances were categorized as therapeutically relevant. The proportion of incomplete MRIs with a therapeutic impact was improved in the more recent half of the study (since 7/2010 compared with 97/155; p < 0.1). In 31/554 evaluable MRIs the interpretations of local/reference radiologist diverged significantly.

**Conclusion:** In this study, approximately every fourth PSTS-imaging was performed incomplete with the recommendations with a potentially relevant impact on treatment. Compliance with the imaging guidance and reference review of PSTS-imaging are important methods to avoid inadequate treatment, to assure the quality of the diagnosis/therapy and may aid to improve outcome of PSTS-patients. Obligatory reference review should be required in future protocols.

**O025 DELAYED RESECTION CAN AVOID IRRADIATION IN LOCALIZED EMBRYONAL RHABDOMYOSARCOMA**

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**Purpose:** Pediatric soft tissue sarcoma (PSTS) mainly occur in young children and are treated with sR0 + XRT and in sR0-XRT. Even though the risk profile of the sR0 + XRT group was unfavorable compared to the sR0-XRT cohort, sR0 + XRT patients had a longer 5-year EFS (79 ± 65 ± 10, p = 0.03). However, some OS was however similar (87 ± 7 vs 87 ± 7). 155 individuals were IRS-I, treated without adjuvant radiation in n = 149 [IRSG-I-XRT]. 5-year EFS was inferior in -XRT-compared with IRS-GIR-XRT compared (65 ± 10 vs 82 ± 6, p = 0.05); but OS was similar (87 ± 7 vs 92 ± 4) despite the unfavorable risk-profile of sR0-XRT.

**Conclusion:** Event-free, but not overall survival is improved with radiation in addition to sR0. The event-free survival of non-irradiated patients with primary complete resection is superior compared with sR0, but overall survival is not compromised. In the framework of an adequate risk-stratification, sR0 can thus avoid radical therapy and/or radical surgery without compromising survival. This strategy may be especially beneficial for young children with favorable tumor characteristics.

**O026 ALVEOLAR SOFT PART SARCOMA IN CHILDREN: A LARGE SERIES WITH LONG FOLLOW-UP BASED ON THE EUROPEAN EXPERIENCE**

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**Purpose:** Alveolar Soft Part Sarcoma (ASPS) is a highly malignant, chemio- and radio-resistant mesenchymal tumor, characterized by an unbalanced recurrent translocation t(X;17)(p12;p132). No standardized treatment guidelines have been yet been defined.

**Methods:** 46 children and adolescents with ASPS, prospectively enrolled in 7 European trials with histological panel comparison, or with tumors harboring t(X;17) transcript were analyzed.

**Results:** Median age was 13 years (Range: 4–21). Primary site included limbs (61%), trunk (20%), head and neck (15%) or orbit (4%). 43% of patients had a tumor larger than 5 cm. IRS postoperative staging was: IRS-I 35%, II 20%, III 20% and IV 25%. Only 3 out of the 16 evaluable patients had a response to conventional chemotherapy. After a median follow-up of 10.5 years (0.5–20), 15/16 patients with IRS I tumor survived (with chemotherapy 7 pts and radiotherapy 5 pts), 7/9 IRS II (with chemotherapy 9 pts and radiotherapy 5 pts); 7/9 IRS III (with chemotherapy 9 pts and radiotherapy 5 pts) and only 2/12 IRS IV are alive without disease. Sunitinib lead to 2 VGP in 4 patients. 57 IRSIII-IV pts locally treated only with radiotherapy had at least a local progression. No local relapse was seen after surgery ± radiotherapy. Ten year overall survival (10-OS) was 82% ± 6% and Event free survival 66% ± 7%. Stage IV patients had a poorer evolution: 10-OS is 40% vs 92%, 100% and 89% for respectively stage I to III (p < 0.002).

**Conclusion:** ASPS is a very rare tumor arising frequently in adolescents and in extremities. Local surgery is critical. Chemo-sensitivity is poor and role of chemotherapy in grossly resected tumor is controversy. For IRS-III/IV tumor, delayed radical local therapies including surgery are essential. Metastatic patients had a poor prognosis but target therapies as multiple receptor-syrosine-kinases inhibitors are promising as long term controls of metastatic disease are seen. Comparison with adult’s experience will be discussed.

**LYMPHOMAS**

**O027 A RESPONSE-BASED ABVD REGIMEN WITH OR WITHOUT RADIOTHERAPY FOR PEDIATRIC LOW AND INTERMEDIATE RISK HODGKIN LYMPHOMA IN CENTRAL AMERICA AND DOMINICAN REPUBLIC A REPORT FROM AHOPCA**

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1Pediatric Blood Cancer DOI 10.1002/pbc
Purpose: In 2004 AHOPCA designed a treatment regimen for low-risk (LR) (stage IA, IIA without bulky disease, less than 4 nodal regions) and intermediate-risk (IR) (stage IA or IIA bulky disease, IR IIA with more than 4 nodal regions, or stage IIA)). The purpose of the protocol was to provide proven effective therapy to improve survival of children with HL in Central America while decreasing the amount of radiation therapy required based on response to chemotherapy.

Methods: LR patients received 4 cycles of ABVD (adriamycin 25 mg/m², bleomycin 10 units/m², vinblastine 6 mg/m², and dacarbazine 375 mg/m² on days 1 and 14 of every 28-day cycle). Involved field radiotherapy (IFRT) (2500 cGy) was prescribed only to patients that did not achieve a complete response (CR) after the second cycle of ABVD. IR patients received 6 cycles of ABVD and IFRT (2000 or 2500 cGy) at the end of all chemotherapy, according to response status after 4 cycles of ABVD (CR = 20 Gys and PR > 50% 25 Gys).

Results: From 1/2004 to 12/2011, 242 evaluable (162 IR and 80 LR) patients with a median age of 7 years were treated with this regimen. (87%) of the LR patients were rapid early responder (RER) and 73% of IR patients were RER and only required 2000 cGy. With a median follow-up time of 3 years we had 3 relapses in LR (91% EFS and 94% OS) and 4 relapse, 2 progression with 18 patients abandoned (85% EFS and 94% OS) in IR subtypes. There were no grade 4/5 toxicities.

Conclusion: This regimen was well tolerated and produced excellent results for our setting. Abandonment among the intermediate risk group is still a problem and earlier and more aggressive interventions are needed to target this group.

Purpose: Selecting appropriate patients for involved-field radiation therapy (IFRT) is a clinical challenge in the management of Hodgkin Lymphoma (HL). The Children’s Oncology Group AHOHD0301 trial demonstrated that response-adapted therapy could identify Hodgkin lymphoma patients who did not benefit with the addition of IFRT. We conducted an exploratory analysis to evaluate the impact of IFRT among patients with chemosensitive disease on this trial.

Methods: Children with intermediate risk HL received 2 cycles of doxorubicin, bleomycin, vinblastine, etoposide, prednisone, and cyclophosphamide (ABVE-PC), followed by 4 cycles of the chemotherapy (p<0.019) to be predictive of EFS. Multivariable modeling using the CHIPS score (based on 1 point per cohort: mediastinal mass, stage 4, albumin, fever).

Results: 156 evaluable patients had MCHL. Univariate predictors of decreased EFS (p<0.019) included: albumin <3.5 g/dL (HR 5.126, p<0.0019), age >12 HR = 3.984, p = 0.0325), hemoglobin <9.5 (HR 2.98, p = 0.0078), fever (HR = 3.36, p = 0.0215), night sweats (HR = 3.34, p = 0.0215), and gender (HR 2.389, p = 0.0025): Multivariable modeling (albumin, age, hemoglobin, gender, fever) showed low albumin (HR = 7.343, p = 0.0032), age > 12 (HR = 5.441, p = 0.0119) and gender (HR = 2.869, p = 0.0615) to be predictive of EFS. Multivariable modeling using the CHIPS score showed patients with albumin <3.5 to be a robust predictor in MC HL (HR = 4.673, p = 0.0084). Albumin could be used to identify cohorts with EFS of 94.5% (N = 114) vs. 75.7% (N = 37), neither age nor gender enhanced this analysis. The CHIPS score of 0 allocated patients to cohorts with 96.7% EFS (N = 82) vs. 80.6% (N = 62).

Conclusion: Low albumin is an excellent predictor of decreased EFS in MCHL and allows identification of a cohort of intermediate risk MCHL patients who may need augmented therapy.

References
Methods: LMP-CTL were generated using dendritic cells for initial stimulations then EBV-transformed lymphoblastoid cell lines (LCL) both of which had been genetically modified to express the subdominant EBV antigens LMP1 and LMP2. Patient- and CTL-derived specific T-cells were transferred through two cycles of 4 days of culture, rest, and re-stimulation. The CTL infusion, increased numbers of LMP-specific T-cells were detected in the blood of evaluable patients. 23/24 high-risk and/or multiply relapsed patients who received LMP-CTL with CT demonstrated the highest PFS for these patients is 60%. Among CNS+ pts, pts with blasts in the CSF are at higher risk of events and should benefit from new treatment modalities.

Conclusion: Among CNS+ pts, pts with blasts in the CSF are at higher risk of events and should benefit from new treatment modalities.

O032

COMPLETE TUMOR RESPONSES IN LYMPHOMA PATIENTS WHO RECEIVE AUTOLOGOUS CYTOTOXIC T LYMPHOCYTES TARGETING EBV LATENT MEMBRANE PROTEINS

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Purpose: EBV-associated Hodgkin Lymphoma (HL) and some non-Hodgkin lymphoma (NHL) have type II viral latency expressing the subdominant EBV antigens LMP1 and LMP2 which may serve as targets for immunotherapy approaches. We hypothesized that CTL enriched for effector cells specifically targeting LMP antigens would have efficacy in patients with EBV+ lymphoma.

Methods: LMP-CTL were generated using dendritic cells for initial stimulations then EBV-transformed lymphoblastoid cell lines (LCL) both of which had been genetically modified to overexpress either LMP2 alone or inactive LMP1 and LMP2. All LMP-CTL lines were polyclonal comprising CD4+, CD8+ T-cells and CD5RA–/CD28+ T-cells. CTL lines had specificity for CD4+ + CD8+ restricted LMP2/– LMP1 epitopes per CTL line, as determined using ELISPOT assays.

Results: 44 patients with EBV+ HL and NHL have been treated on dose escalation studies; 16 with LMP2 CTLs and 28 with LMP1/2 CTLs. No immediate toxicity was observed. After CTL infusion, increased numbers of LMP-specific T-cells were detected in the blood of evaluable patients. 23/24 high-risk and/or multiply relapsed patients who received LMP-CTL as an adjuvant treatment remain in remission for a median of 2.5 years after CTL with a PFS of 80% at 3 years. 1 patient had detectable disease at the time of CTL 5 of these had progressive disease by 8 weeks and 15 had clinical responses. The median duration of the clinical responses is 1.5 years with 3 partial responses and 12 complete responses. The 3 year PFS for these patients is 60%.

Conclusion: In conclusion, immunotherapy with CTL targeting LMP antigens is well tolerated in patients with EBV+ lymphoma and infused LMP-CTL can accumulate at tumor sites and induce clinical responses in 15/20 patients. Our future directions include the development of a simpler LMP-specific CTL expansion protocol to perform a definitive efficacy study.

BRAIN TUMOURS I

O033

CHEMOTHERAPY FOR CHILDREN WITH NEUROFIBROMATOSIS TYPE 1 AND PROGRESSIVE LOW GRADE GLIOMA: PRELIMINARY OUTCOME ANALYSIS FROM THE SIOP LGG 2004 NFI STUDY

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Purpose: To describe characteristics and progression free survival (PFS) of children affected by Neurofibromatosis type 1 (NF1) and progressive Low Grade Glioma (LGG) enrolled within the SIOP-LGG2004NFI study.

Methods: The SIOP-LGG2004NFI is a prospective single-arm study of 18 months carboplatin-vincristine chemotherapy (CT) for NF1 children and LGG with clinical and/or radiological progression. PFS definition was the following: death (for all reasons), progression of a residual tumor, relapse following previous complete remission, appearance of new or progression of existing metastasis.

Results: From June 2004 to December 2011, 240 patients were enrolled in the study. Age at diagnosis was 5.9 years (2.2–9.8). Females were 57%. 70% of patients were site specific in brain metastases in 85%. 39 children resulted in partial remission (12) or biopsy only (27). Tumor histologies were Pilocytic astrocytoma (33), Fibroblastic astrocytoma (2), Ganglioglioma (2), and others (5). CT was initiated in 66% of children because of visual impairment alone or combined with other symptoms while tumor progression was present in 34% of children. Allergy to carboplatin was common (52%), requiring change to alternative CT in 33%. Treatment grade 3–4 toxicities were hematological (86%), infectious (22%) and neurological (21.5%). After a median follow-up of 25 months, 25 patients (56%) CT was 76.8%, 95% CI (66.3–83.7). Outcome after any surgery was significantly worse at univariate analysis (p < 0.0001). A trend towards a worse PFS was documented in younger children (<2 years) and Dodge III optic pathways tumors.

Conclusion: In this NF1 LGG cohort the estimated 5 years-PFS of 76% after 18 months of carboplatin-vincristine seems acceptable. Historical comparison with the 5 years-PFS of 73% (1) of the 12 months CT regimen is confounded by more stringent criteria for starting treatment and possible selection of worse cases/real progresses in SIOP-LGG2004 study. Visual outcome was not systematically considered in the PFS analysis.

References

O034

HEALTH RELATED QUALITY OF LIFE IN PEDIATRIC BRAIN TUMOR PATIENTS: A COMPARISON OF PROTON AND PHOTON TREATED COHORTS

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Purpose: The use of radiotherapy (RT) can impair Health Related Quality of Life (HRQoL) in survivors of childhood brain tumors. Proton radiotherapy (PRT) reduces normal tissue irradiation and therefore may partially mitigate negative effects on HRQoL. To compare HRQoL in PRT and XRT pediatric brain tumor survivors.

Methods: HRQoL data were prospectively collected during proton radiotherapy and annually thereafter using the PedsQL survey for patients age 2-18 treated at Massachusetts General Hospital (MGH). Mean PedsQL HRQoL scores were calculated and compared to cross-sectional data obtained from a Lucille Packard Children’s Hospital (LPCH) study by diagnosis and by treatment type.

Results: The HRQoL scores in the PRT cohort compare favorably to the XRT cohort in many groups of patients. Patients treated with RT without chemotherapy (CT) demonstrated the largest differences, with mean total summary scores of 81.2 (PRT) versus 52.6 (XRT, P < 0.001), physical health summary scores of 86.4 versus 55.2 (p < 0.001) and psychosocial summary score of 78.5 versus 50.3 (p < 0.001) respectively. There were no significant differences in HRQoL between PRT and XRT cohorts in children treated with combined RT and CT. Differences between the PRT and XRT group were correlated with diagnosis. Total summary scores were higher in the PRT cohort in patients with medulloblastoma, ependymoma/high-grade glioma and low grade glioma, but not different for patients with germ cell tumors.

Conclusion: Proton radiotherapy is correlated with higher HRQoL scores in many patients but depends upon treatment type and diagnosis.

O035

INTEGRATIVE GENOMICS IDENTIFIES ACTIONABLE TARGETS FOR THERAPY IN MEDULLOBLASTOMA SUBGROUPS

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Purpose: To describe characteristics and progression free survival (PFS) of children affected by Neurofibromatosis type 1 (NF1) and progressive Low Grade Glioma (LGG) enrolled within the SIOP-LGG2004NFI study.
SIOP ABSTRACTS

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**Purpose:** The application of genomics to the study of medulloblastoma has recently led to a significant enhancement in our understanding of its pathogenesis, implicating previously uncharacterized molecular processes and the existence of distinct biological subgroups. Despite these advances, few genomic studies have profiled sufficient cases to identify recurrent genetic events, including those restricted to a particular molecular subgroup.

**Methods:** To specifically address these issues we have performed a comprehensive copy number analysis of 1,250 medulloblastomas and summarized their genomes by molecular subgroup.

**Results:** The most prevalent oncogenic events observed in medulloblastoma included those targeting known oncogenes and tumor suppressors such as members of the MYC family (MYCN, MYC), cell cycle regulators (CDK4, CDK6), and genes involved in Hedgehog signaling (PTCH1, PTCH2, SMARM2). A subgroup of medulloblastomas further, we performed whole genome sequencing (WGS) for 28 tumor samples from our group demonstrated that SHH medulloblastomas in older children frequently have TP53 mutations and are characterized by chromotripsis through promotion of cell proliferation, survival, and differentiation in numerous human cancers, including approximately 30% of medulloblastomas. LDE225 is a potent and selective inhibitor of Smoothened, a positive regulator of Hedgehog signaling. The safety and pharmacokinetics of LDE225 in pediatric patients with advanced solid tumors potentially dependent on Hedgehog signaling are presented.

**Conclusion:** LDE225 is well tolerated in pediatric patients with advanced malignancies. Preliminary data show promising efficacy in medulloblastoma patients and support the use of the 5-gene Hedgehog signature assay as a pre-selection tool in future trials. A Phase II study in medulloblastoma is in preparation.

**0036**

**ICG PedBrain Tumor – Dissecting the Genomic Complexity Underlying Medulloblastoma**

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**Purpose:** Despite advances in treatment for medulloblastoma (MB) over the past few decades, approximately 40% of children who develop this aggressively-growing brain cancer will experience tumor recurrence, and 30% will die from their disease. Those children who do not suffer from severe tumor- or treatment-related morbidity, including neurocognitive dysfunction. Four biologically distinct subgroups are currently discriminated (WNT, SHH, Group 3 and Group 4), but the genetic events driving this distinction remain unclear.

**Methods:** In this study, part of the International Cancer Genome Consortium (ICGC) PedBrain Tumor Project (www.pedbraintumor.org), we have utilized an integrated next-generation sequencing-based approach to identify alterations at the DNA and RNA level. We have sequenced samples from a total of 125 medulloblastoma patients and matched germline material. This was supplemented with large-insert mate-pair sequencing for structural variant detection, and strand-specific RNA-sequencing (RNASeq) data, in a subset of cases.

**Results:** Strikingly, tetraploidy was found to be a common driving event in clinically challenging Group 3 & 4 tumors. For non-tetraploid tumors, a clear correlation of patients' age and mutation rate was observed. Beside alterations affecting known medulloblastoma-related genes (CTNNB1, PTCH1, MLL2, SMARM2), several novel recurrent mutations were identified (DIDXX, CTND1EP1, KDM6A), often in subgroup-specific patterns. RNA-sequencing data confirmed these alterations, and additionally revealed the expression of several novel fusion genes. Across all subgroups, genes encoding chromatin modifiers were altered in one-third of tumors, indicating a key role for this process in MB development.

**Conclusion:** Our integrative next-generation sequencing study has allowed us to provide a detailed insight into medulloblastoma tumorigenesis, and disclose novel targets for therapeutic approaches, especially for clinically challenging Group 3 & 4 patients.

**0037**

**UPDATED RESULTS FROM A PHASE I STUDY OF LDE225, A SMOOTHENED ANTAGONIST, IN PEDIATRIC PATIENTS WITH RECURRENT MEDULLOBLASTOMA OR OTHER SOLID TUMORS**

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1Pediatric Blood Cancer DOI 10.1002/pbc

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**Purpose:** Hedgehog signaling is crucial in the development and homeostasis of many human organs and tissues. About 10% of all human cancers are dependent on Hedgehog signaling. The safety and pharmacokinetics of LDE225 in pediatric patients with advanced solid tumors potentially dependent on Hedgehog signaling are presented.

**Methods:** Dose-escalation was performed according to a Bayesian design starting at 372 mg/m² of continuous once daily oral LDE225. Pharmacokinetic profiles were assessed at Day 1 and 2. Tumor samples were analyzed for Hedgehog pathway activation status using a 5-gene Hedgehog signature assay.

**Results:** Thirty-six patients (25 medulloblastoma, 3 rhabdomyosarcoma, 3 osteosarcoma, 2 neuroblastoma, and 1 each of gliomatosis, glioblastoma, and ependymocystoma) with a median age of 12 years (range, 4–17 years) have enrolled. Dose-limiting toxicity of Grade 4 was determined to be Hedgehog-non-activated.

**Conclusion:** LDE225 is well tolerated in pediatric patients with advanced malignancies. Preliminary data show promising efficacy in medulloblastoma patients and support the use of the 5-gene Hedgehog signature assay as a pre-selection tool in future trials. A Phase II study in medulloblastoma is in preparation.
average more mutations than pediatric medulloblastomas; 2. the observed correlation between mutation rate and patient age in pediatric medulloblastomas holds true in the adult cohort; 3. beside similar gene mutations affecting the SHH pathway, adult SHH medulloblastomas also harbor several recurrent mutations that were not detected in pediatric SHH medulloblastomas.

Conclusion: These data will help to better understand the biology of adult medulloblastoma and may help predicting responsiveness to targeted SHH inhibition in a clinical setting.

RADIATION ONCOLOGY PROS 2
O039
NORMAL TISSUE COMPLICATION PROBABILITY MODEL FOR LUNG TOXICITY AFTER RADIONUATHERAPY IN PEDIATRIC PATIENTS WITH HODGKIN LYMPHOMA RECEIVING BLEOMYCIN
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Purpose: To determine the tolerance doses for lung toxicity after radiotherapy in pediatric patients with Hodgkin Lymphoma receiving bleomycin-containing chemotherapy using the Lyman Kutcher Burman (LKB) model of Normal Tissue Complication Probability (NTCP). Methods: Toxicity data from patients treated between January 2005 and March 2012 were used to derive LKB parameters n, m, and TD50. Clinical and radiographic pneumonitis were assessed retrospectively using the CTCAE v 4.03 and the RTOP grading scales. Fitting was performed using maximum likelihood estimation. 68% confidence intervals for the NTCP curves were estimated using the profile likelihood method. Patient clinical data were analyzed with the SAS V 9.2 software package to generate descriptive statistics, using the proc freq and proc means procedures. Pooled-t-tests were used to look for differences in mean Heart and Lung dose volume between patients who developed pneumonitis and those who did not.

Results: Thirty patients, median age 15.5 years (range: 4–21) were identified as receiving radiotherapy as part of their treatment. Median radiation dose was 21 Gy (range: 21–60.6). 8 patients developed a clinical pneumonitis while 6 developed a radiographic pneumonitis. The LKB parameters for clinical pneumonitis were n = 0.423 (0.18–0.979), m = 0.327 (0.23–0.53) and TD50 = 19.2 Gy (14.7–26.5). The LKB parameters for radiographic pneumonitis were n = 0.428 (0.21–0.777), m = 0.226 (0.16–0.34) and TD50 = 19.2 Gy (15.8–25.4). A statistical difference was noted in the mean lung V15 and 20 between those patients who did and did not develop any pneumonitis, 44% vs. 32%, p = 0.02 and 33% vs. 24%, p = 0.04, respectively. Only one patient developed grade 3 pneumonitis.

Conclusion: Needing confirmation in an independent data set, this is the first study using a NTCP model to calculate LKB parameters in patients with pediatric Hodgkin Lymphoma receiving bleomycin-containing chemotherapy undergoing radiotherapy.

O040
DEVELOPMENT OF GOOD PRACTICE GUIDELINES FOR PAEDIATRIC RADIONUATHERAPY
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Purpose: To develop good practice guidelines for paediatric radiotherapy with the aim of improving multi-professional delivery of care in centres delivering radiotherapy to children and young people. Methods: A group of paediatric clinical oncologists, therapeutic radiographers and parents as patient advocates, was convened by the Royal College of Radiologists, the Society and College of Radiographers and the Children’s Cancer and Leukaemia Group. It reviewed existing patterns of care and guidance, and identified a set of key areas for further guidance. Consensus on more detailed guidance in each area was reached by discussion. The draft guidance has been refined following wider consultation. Results: The ten key themes are: top quality clinical outcomes; excellent patient safety; good patient experience; information and communication with families; communication and multi-professional relationships; child and family-friendly environment; radiotherapy equipment and techniques; human and financial resources; education and training; and research and development. Selected aspects of the guidance include: best treatment technique for each patient, even if it requires referral to another centre; access to a specialist paediatric anaesthetic service and paediatric resuscitation and life support teams immediately available; staff with the interpersonal skills and experience to engage with children, teenagers and their families, and have the required time and resources available; timely referral with accurate and complete information; staff facilitated to attend paediatric oncology and radiotherapy meetings and courses to maintain and improve their knowledge and skills; new radiotherapy techniques to be critically evaluated before widespread introduction. Conclusion: It is possible to bring together existing guidance from various authoritative sources, and with an experienced multi-professional group and lay input create a manual of good paediatric radiotherapy practice. These guidelines should enable paediatric radiotherapy to be consistently and safely delivered with the best possible clinical effectiveness, resulting in a good experience for patients and their families.

O041
ADAPTIVE RADIONUATHERAPY FOR PAEDIATRIC HEAD & NECK MALIGNANCIES: DOSIMETRIC IMPLICATIONS
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Purpose: Evaluate the role of adaptive radiotherapy (ART) for children receiving curative radiotherapy to the head and neck (H&N) region.

Methods: Ten children receiving definitive, conformal radiotherapy (RTs) to the H&N region were prospectively evaluated for anatomic changes during the course of RTs. Images were acquired midway during the planned course of RTs. Body contours, target volumes and OARs were re-drawn on the new set of images. Two sets of additional treatment plans were generated: i) Un-optimised plan i.e. overlay of the original plan on the new set of contours ii) Optimised plan with the new set of contours. These three sets of plans were then compared for dosimetric differences.

Results: Four had Ca Nasopharynx, while 5 had Embryonal Rhabdomyosarcoma (ERMS) of the H&N region. Average reduction in Gross Tumour Volume (GTV) was 40% (mean volume: 41.87 cc, p = 0.005). The average change in Rt & Lt Parotid volumes were 2.72 cm^3 & 1.92 cm^3 respectively. With un-optimised plans the average increase in maximum dose (Dmax) to spinal cord was 15% (97.99% to 94.99%, p = 0.013). With re-optimisation Dmax decreased from 94.99% to 85.26% (mean difference = 9.73, p = 0.02). Average D99 for PTV was 88.66% & 89.89% with the original & re-optimised plans respectively (p = 0.50). D1cc to spinal cord reduced from 64.95% to 62.44% with re-optimisation (p = 0.37). For the entire group the mean conformation number Index with non-optimised plans was reduced from 0.734 to 0.628 (p = 0.013). This improved with re-optimisation (p = 0.114). Homogeneity Index improved with re-optimisation from a mean value of 0.113 to 0.098 (p = 0.28). For non-optimised plans the average Integral Dose increased from 74.66 Lit.Gy to 76.27 Lit.Gy (p = 0.486) when compared with the original plans. Re-optimisation resulted in 5% average reduction in the ID from 76.27 Lit.Gy to 72.28 Lit.Gy (p = 0.007).

Conclusion: This study demonstrates usefulness of adaptive radiotherapy for children receiving RTs to the H&N region.

O042
EVALUATION OF A TECHNIQUE FOR POSTOPERATIVE PELVIC HIGH DOSE RATE BRACHYTHERAPY IN YOUNG CHILDREN
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Purpose: To evaluate an image-guided and intensity-modulated technique for fractionated Iridium-192 high dose-rate (HDR) brachytherapy in children with pelvic rhabdomyosarcoma.

Methods: Children with pelvic rhabdomyosarcoma were carefully selected by multidisciplinary discussion. Included were those who, after initial chemotherapy and surgery, required radiotherapy to a small volume, and who might benefit through improved sparing of normal tissues. Following bowel preparation, urinary catheterisation, and under general anaesthetic, afterloading brachytherapy catheters were inserted with ultrasound guidance percutaneously through a template on the perineum. A caudal block was used to prevent post-procedural pain. A custom made immobilisation device was used to reduce the risk of the child displacing the catheters between fractions. The positioning was confirmed on a computed tomography scan used for target volume definition. Catheter position was verified by computed tomography each day. The volume was treated twice daily under general anaesthetic to 27.5 Gy with five fractions of 5.5 Gy.

Results: Five children (3 male, 2 female) median age 33 months (range 14 to 59 months) with non-metastatic embryonal (4) or alveolar (1) rhabdomyosarcoma arising in the bladder (3), prostate (2) and perineum (1) were treated as part of initial multimodality therapy (4) or for salvage of local recurrence (1). There was no acute toxicity. All remain free of disease at a median of 22 months (range 12 to 38 months), with limited long term complications. One prostate patient required urinary diversion because of dribbling and urethral stricture formation. One bladder patient required a cystostomy to investigate haematuria, but this was self limiting.

Conclusion: This HDR brachytherapy technique is feasible and safe in young children, but requires a large specialist paediatric team including a paediatric oncologist, clinical...
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oncologists with paediatric and brachytherapy expertise, a radiologist, an anesthetist, radiographers and physicists. More patients and longer follow-up will be required to assess its effectiveness.

0043

EFFECTIVENESS OF THYROID BLOCKADE IN PATIENTS RECEIVING ¹³¹I-META IODOBENZYLGLUANIDINE MOLECULAR RADIOTHERAPY

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Purpose: Molecular radiotherapy with ¹³¹I-metaiodobenzylguanidine (mIBG) is an established therapy for advanced neuroblastosarcoma and metastatic neuroendocrine tumours. Medication is routinely given to block thyroid uptake of free radioactive iodine during therapy, to prevent the development of hypothyroidism and to reduce the risk of carcinogenesis. We have audited the effectiveness of thyroid blockade in patients receiving ¹³¹I-mIBG therapy in our practice.

Methods: Patients who had received ¹³¹I-mIBG were identified and their case notes reviewed. All had received standard pharmacological thyroid blockade prior to and after ¹³¹I-mIBG therapy according to the Administration of Radioactive Substances Advisory Committee (ARSAC) guidelines. This was most commonly potassium iodide 120 mg daily, or aqueous oral iodine solution BP 0.8 mL, for adults. Oral potassium iodate was an alternative. The administered activity of ¹³¹I-mIBG was typically 444 MBq kg⁻¹. Post ¹³¹I-mIBG therapy, whole body planar scintigraphy scans were performed at 48 to 72 hours. Scans were reviewed by at least three individuals, and a consensus about the absence or presence of a visible thyroid outline was reached. Where thyroid uptake was seen, a ratio of thyroid activity (counts per pixel) to background activity (counts per pixel) was measured.

Results: Fifty two patients (33 male, 19 female), median age 8 years (range 1.0 to 47 years), with neuroblastoma (48) or other neuroendocrine cancers (4) received 106 ¹³¹I-mIBG administrations (median 2, range 1–4) between 2006 and 2012. Thyroid blockade was effective following 78 administrations (74%). Following the 28 administrations where thyroid uptake was noted, the median thyroid to background ratio was 1.54 (range 1.10 to 3.7).

Conclusion: Standard thyroid blockade protocols are effective in the majority of cases; however, low grade iodine break through in the thyroid gland requires clinical follow-up.

0044

EARLY OUTCOMES FOR CENTRAL NERVOUS SYSTEM GERM CELL TUMORS TREATED WITH PROTON THERAPY

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Purpose: To assess early clinical outcomes for pediatric patients with central nervous system germinomas and nongerminomatous germ cell tumors treated with proton therapy.

Methods: Pediatric patients with central nervous system germ cell tumors (CNS GCTs) treated at the University of Texas at MD Anderson Cancer Center (MDACC) Proton Therapy Center between 2006 and 2009 were included. Toxicity was prospectively evaluated prospectively. The continued inclusion of a patient/case controlled analysis/medication (PCA/POM) facility was deemed essential to facilitate optimal management.¹ 'Smart pump' technology was identified as potentially able to support a superior, safer system, incorporating multi-day infusion cassettes.¹ No evidence was found of this technology being adapted for use in palliative/end of life care for the children and young people (CYP) home setting in the UK or worldwide. We aimed to develop and implement a 'ground-breaking' system.

Methods: We adopted an eclectic approach, harnessing the knowledge & expertise of a diverse multi-disciplinary team. A systematic approach was used including 'used case scenarios' to develop a comprehensive system encompassing: an extensive range of tailored drug protocols (379) with robust referencing for drugs and advisory notes, a Resource Pack including standard operating procedures (10), documentation to support ongoing audit, evaluation and modification, prescription parameter tables and proforma.

Results: Implementation began in December 2011 facilitating a range of quality outcomes. Rapid and safe titration to changing symptom intensity. Reduced costs – fewer home visits and hospital admissions. Nursing time and personnel saved by using pharmacy dispensed cassettes. Risk of medication errors reduced. Supply of controlled drugs in the home reduced. CYP and family’s control and independence increased. Family time liberated, allowing short breaks away from home. Increased body of knowledge relating to developing drug libraries – CYP and palliative care.

Conclusion: The immediate availability of PCA/POM facilitates optimal symptom control¹ in any setting. With detailed re-configuration it would seem that current smart pump technology may provide an enhanced and sustainable structure for supporting parenteral symptom management in CYP. Comparison of production and nursing costs are positive.

References


0046

THE POWER OF KNOWLEDGE

Einat Ginat

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Purpose: Hospital without Pain is one of Safra children’s hospital’s main goals. In our Pediatric Hemato Oncology department a special anesthesia room was designed to perform many procedures under general anesthesia regarding the disease and treatment for children. To sustain this goal the nursing staff initiated a quality of care program containing guidelines, protocols and a pantomime motion picture with emphasis on reduction of children and parents anxiety levels. The purpose was to reduce the level of anxiety and thereby develop an appropriate teaching protocol.

Methods: Examine the anxiety levels of children age 14 and above and their parents before and after their first general anesthesia experience. Spielberger questionnaires on anxiety levels were performed for children 14 to 18 years old and after first anesthesia, as well as for their parents. 19 children and 23 parents answered before and after questionnaires, followed by minimal oral preparative instructions by the nurses.

Results: Among the group of the parents we found a decrease of 45% in general anxiety levels and decrease of 55% in situational anxieties. Among the group of the children a decrease of 61% in situational anxiety levels was found. The participants answered the question regarding the way they would prefer receiving the information: 23.3% of the parent’s preferred written material; 41.9% of them prefer visual tools (film or presentation). Among the children group, 33% preferred visual tool and 20% written material.

Conclusion: Anxiety levels of parents and children decreased when preoperative anesthesia education was provided by nurses. Today this project, providing general anesthesia in our department, has become a routine protocol prior to anesthetizing children. Our research results validate the need for appropriate pre anesthesia information. Our Pamphlets, along with a short clown pantomime film for children who do not yet read and our non Hebrew speaking multi national population, fulfill this need.

0047

DEVELOPING A PROGRAM TO REDUCE CENTRAL LINE ASSOCIATED BLOODSTREAM INFECTIONS AT THE NATIONAL CANCER INSTITUTE IN BOGOTA, COLOMBIA

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Purpose: Our system of supporting the administration of palliative symptom control infusions at home became technically obsolete. The continued inclusion of a patient/case controlled analgesia/medication (PCA/POM) facility was deemed essential to facilitate optimal management.¹ ‘Smart pump’ technology was identified as potentially able to support a superior, safer system, incorporating multi-day infusion cassettes.¹ No evidence was found of this technology being adapted for use in palliative/end of life care for the children and young people (CYP) home setting in the UK or worldwide. We aimed to develop and implement a ‘ground-breaking’ system.

Methods: We adopted an eclectic approach, harnessing the knowledge & expertise of a diverse multi-disciplinary team. A systematic approach was used including ‘used case scenarios’ to develop a comprehensive system encompassing: an extensive range of tailored drug protocols (379) with robust referencing for drugs and advisory notes, a Resource Pack including standard operating procedures (10), documentation to support ongoing audit, evaluation and modification, prescription parameter tables and proforma.

Results: Implementation began in December 2011 facilitating a range of quality outcomes. Rapid and safe titration to changing symptom intensity. Reduced costs – fewer home visits and hospital admissions. Nursing time and personnel saved by using pharmacy dispensed cassettes. Risk of medication errors reduced. Supply of controlled drugs in the home reduced. CYP and family’s control and independence increased. Family time liberated, allowing short breaks away from home. Increased body of knowledge relating to developing drug libraries – CYP and palliative care.

Conclusion: The immediate availability of PCA/POM facilitates optimal symptom control¹ in any setting. With detailed re-configuration it would seem that current smart pump technology may provide an enhanced and sustainable structure for supporting parenteral symptom management in CYP. Comparison of production and nursing costs are positive.

References


0046
Purpose: Central venous catheters ensure reliable venous access for children with cancer, yet are associated with increased morbidity and mortality related to infection. Nurses play an important role in minimizing the risk of catheter associated bloodstream infections (CLABSI). In 2009, a swimming program was formed between Dana-Farber/Children's Hospital Cancer Center and Instituto Nacional de Cancerologia (INC), where approximately 300 children are diagnosed with cancer annually in a resource limited setting. The INC pediatric utilization rate for central venous catheters is currently 20–25%, and steadily rising. An infection reduction program, led by the INC nurse educator, has been established.

Methods: In October 2011, the twinning program leaders reviewed the Center for Disease Control (CDC) CLABSI Prevention recommendations. A process to track the infantate infection rate per 1000 line days was implemented in January 2012. The INC policies for central line care were reviewed and updated in March. In April, the nurse educator will implement a nursing educational program which includes a pre-test, review of the INC central line care policies, on line educational modules and videos, hands on demonstration, and a post test. All infantate pediatric nurses are expected to complete the central line competency by June 2012.

Results: The pediatric central venous catheter utilization rate and bloodstream infection rate per 1000 line days at INC is now tracked and reported monthly. A nursing educational initiative for central line care and maintenance is planned to roll out in May. We strive to identify if a correlation exists between infection rate and enforcing best practices for nurses around central line care.

Conclusion: The development of an Infection Reduction program, including challenges and barriers to ensuring best practice in a resource limited setting, will be outlined, with a goal of identifying the impact of a central line educational program on pediatric CLABSI rates.

References

O048

PREVALENCE OF MALNUTRITION IN PEDIATRIC PATIENTS WITH CANCER: A MULTICENTER COHORT STUDY

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Purpose: Malnutrition – in terms of undernutrition – is a common problem in pediatric patients with cancer. Reported prevalence of undernutrition varies widely and usually has been shown only for some types of childhood cancer. There is some evidence that characteristics of the child at the time of diagnosis, such as type and stage of cancer, age, gender and baseline nutritional status help to predict the risk for later malnutrition. This study aimed: 1) to describe the prevalence of malnutrition among pediatric cancer patients at the time of diagnosis; 2) to describe the incidence and course of malnutrition during therapy; and 3) to identify factors associated with malnutrition during therapy.

Methods: In a retrospective cohort study of 327 patients diagnosed from 2003 to 2006 in three Swiss tertiary care hospitals, we assessed patient-, disease- and treatment-related characteristics, and all weight and height measurements during therapy. Malnutrition was defined as body mass index below −2 standard deviation scores (SDS), or an involuntary weight loss greater than 10% during therapy.

Results: At diagnosis, 19 of 327 patients (5.8%) were malnourished. After the start of therapy, cumulative incidence of malnutrition rose to 47% (155 patients). In these 155 patients, malnutrition was associated with a body mass index below −2 SDS, an involuntary weight loss greater than 10% during therapy.

Conclusion: The rapid increase of malnutrition after the start of therapy underlines the urgent need to develop evidence-based and efficient methods to provide nutritional support for children with cancer.

O049

CHANGES IN CHILDREN’S QUALITY OF LIFE SIX MONTHS AFTER BEING DIAGNOSED WITH CANCER: PRELIMINARY RESULTS ON THE EFFECT OF TEEN-CENTRED CARE

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Purpose: The diagnosis and treatment of childhood cancer can have a negative impact on the quality of life (QOL) of children and their family. Early psychosocial identification and intervention may reduce these negative impacts. This multisite, randomized pilot study assessed the benefit of providing psychosocial risk information about the child and family to the treating team on measures of children’s QOL.

Methods: Parents of newly diagnosed children with cancer, aged 2.5 to 18 years, in 4 pediatric centres in Ontario, completed the revised Psychosocial Screening Tool (PAT2) and the Pediatric Quality of Life, Cancer Module (PedQoL) 3–6 weeks post diagnosis (T1) and six months later (T2). The PAT2 is a standardized screening instrument designed to assess psychosocial risk (universal, intermediate, high) in families of children newly diagnosed with cancer. The PedQoL measures the perception of a child’s health-related QOL specific to having cancer, including pain, procedural and treatment anxiety and worries. Participants were randomized to either an experimental (EG) or control group (CG). The EG treating team received the child’s risk information after the initial assessment whereas the CG did not. No specific therapeutic interventions were recommended by the study team for the EG.

Results: Twenty-five of 64 parents (33 EG and 31 CG) who completed measures at T1 have already completed them at T2 (14 EG and 11 CG). While no differences of QOL between the groups were identified at T1, there are emerging trends differentiating the EG and CG, particularly in the subscales of anxiety and worries on the PedQoL at T2.

Conclusion: This is the first randomized study to investigate the benefit of psychosocial screening to help children and families cope with the demand of cancer treatment. Although data collection for T2 is still in progress, we expect to have complete results by August, 2012.

O050

TEEN-CENTRED CARE IS ASSOCIATED WITH TYPE OF CARE AND HEALTH-RELATED QUALITY OF LIFE IN ADOLESCENT ONCOLOGY PATIENTS

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Purpose: Teen-centered care (TCC) is a philosophy and method of health care delivery that emphasizes partnerships between patients, their families and healthcare professionals. A review of TCC shows that better service delivery is associated with better psychosocial wellbeing in adolescents with disabilities. Our study is the first to examine associations between TCC and type of care (treatment vs. survivor) and patient outcomes including health-related quality of life (HR-QOL) in pediatric oncology.

Methods: Patients and survivors aged 12 to 18 years were recruited from 3 Canadian pediatric oncology units between Sept 2010 and Oct 2011. Participants were asked to complete a measure of TCC (Give Youth a Voice (GYV-56)) and HR-QOL (Kidscreen-27). GYV-56 measures the following: supportive and respectful relationships; information sharing and communication; supporting independence; and teen-centered services. Kidscreen-27 measures the following: physical well-being; psychological well-being; parent relations and autonomy; social support and peers; and school environment. Higher scores on both questionnaires reflect better scores. We examined differences between TCC for 2 models of care (active treatment vs. survivorship care) and relationships between TCC and HR-QOL.

Results: Questionnaires were completed by 202 patients (79 on active treatment, 121 survivors). Patients in active treatment reported lower TCC scores than survivors (t-tests) for the GYV-56 total score (p = 0.02) and 2 subscales (p = 0.03) supporting independence; p = 0.03 information sharing and communication). Higher GYV-56 scores (total and all 4 subscales) were significantly associated with better HR-QOL scores (all 5 subscales) (e.g., p < 0.001 with correlations ranged from r = 0.20 to r = 0.34 for the GYV-56 total score).

Conclusion: Delivery of higher quality TCC was associated with better HR-QOL outcomes in keeping with previous research. Patients on treatment were less happy with pediatric oncology care compared with survivors. These findings could be used as a starting point for future research looking at how best to optimize care delivered to adolescents with cancer.

PSYCHOSOCIAL 1

O051

THE WORK-RELATED STRESSORS AND WORK-RELATED REWARDS SCALE FOR PEDIATRIC ONCOLOGY: THE DEVELOPMENT AND VALIDATION OF NEW TOOLS FOR RESEARCH AND CLINICAL PRACTICE

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Purpose: To examine the psychosocial work environment of the health professionals who deliver pediatric oncology care compared with survivors. These findings could be used as a starting point for future research looking at how best to optimize care delivered to adolescents with cancer.
This project has successfully created robust interval level scales measuring the and Safety Executive’s Management Standards Indicator Tool). Interval level scales and a raw ordinal score to interval scale transformation is available when applications and can be administered to both clinical and non-clinical members of the MDT. ‘Organisation’. Given that the data fit the Rasch model, the measures can be treated as Stages 1–5 of the study resulted in the development of the 60 item Work Stressors provides subscale scores for stressors in three domains: ‘Ill Child’, ‘Parent’ and ‘Organisation’. Given that the data fit the Rasch model, the measures can be treated as interval level scales and a raw ordinal score to interval scale transformation is available when required. Evidence of construct validity is provided, with the WSS–PO and WRS–PO moderately correlated with comparator measures (Maslach Burnout Inventory and the Health and Safety Executive’s Management Standards Indicator Tool).

Conclusion: This project has successfully created robust interval level scales measuring the intensity of work-related stresses and rewards experienced by paediatric oncology staff using modern psychometric methods. These new measures have both clinical and research applications and can be administered to both clinical and non-clinical members of the MDT.

**RESULTS**

**TRUTH TELLING: IS IT THE BEST APPROACH FOR CHILDREN WITH CANCER?**

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**Purpose:** It is clear that attitudes and practices of truth telling have shifted greatly throughout the world over time. Being careful with the truth and ‘keeping patients in the dark’ is now seen as outdated paternalistic behaviour to be derided and shunned. So in light of the benefits and professional requirements and patient–parent empowerment, truth telling must be the right approach for children with cancer and their parents? But we are aware that the practice of truth telling remains variable among oncologists and healthcare professionals. We also know that partial and non-disclosure still takes place regularly for adults with cancer. Could this be the same for children with cancer that they receive partial or ‘diluted truths’ and is this wrong?

**Methods:** This issue raises many questions around rights, respect, coping styles, power, control, parenting, protection and relationships. The aim is to explore different perspectives on truth telling and to encourage debate among healthcare professionals. Using data from an ethnographic study on a cancer unit the concept of truth telling will be explored. The sample included children aged 7–16 years (n = 20), their parents (n = 22) and the healthcare professionals (e.g. doctors, nurses, social workers, teachers, play specialists) (n = 40). Data from participants will be used to illustrate experiences and preferences with truth telling. The contrasting perspectives on disclosure and withholding information will be critically considered.

**Results:** Truth-telling about diagnosis and treatment is seen as essential for establishing trust and good relationships between children, parents and healthcare professionals on a cancer unit. However when parents withhold disclosure of diagnosis and withhold information it creates difficulties for all further communication and impacts on relationships.

**Conclusion:** Suggestions will be offered on how the situation may be improved.

**REFERENCES**


**O052**

**COMMUNICATING IN A WAY THAT PARENTS FIND SUPPORTIVE: IS THE GUIDANCE MISTAKEN?**

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**Purpose:** Communication guidance emphasizes the importance of oncologists supporting patients and families by exploring and discussing patients’ emotions. We investigated whether, from the perspective of parents of children with leukaemia, emotional support was accomplished in the way that communication guidelines suggest.

**Methods:** Qualitative study involving 6 childhood cancer principal treatment centres in the UK. Data comprised audio-recorded parent-paediatric oncologist consultations and semi-structured interviews with parents post-diagnosis, and further parent interviews during the year following diagnosis. Data analysis was informed by the principles of the constant comparative method.

**CONSENT COMPETENCY IN AFRIKAANS-SPEAKING CHILDREN IN SOUTH AFRICA**

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**Purpose:** In 2008 South Africa made amendments to the Children’s Act 38 of 2005 that allow children to consent to medical treatment at age of 12 years and surgical treatment at age of 14 years. The aim was to determine the developmental differences in competency of Afrikaans-speaking children for medical informed decision-making within their cultural context with language as the principal determinant.

**Methods:** A 100 children from 10 years to 17 years were randomly selected from 11 schools in the Pretoria municipal district and 25 adults as a control group tested for their ability in medical decision-making. Competency was measured using ‘The Measure of Competency to Render Informed Treatment Decisions’ (MCD; Reference: Weithorn and Campbell, 1983). The tool uses hypothetical narratives of medical diseases (Diabetes, Depression, Emesis and Epilepsy) and a structured interview. Answers were scored according to a standardised scoring formulation and analyzed with multiple ANOVAS and MANOVAS.

**Results:** The findings indicate that children of 12 years of age have the same decision-making capacity as adults. There was a 32–36% correlation in choice with adults for the 10–11year subgroup, 88% for the 12–13 year subgroup, and 100% for the older age groups, which was statistically significant (p < 0.001). There was significant linear trends in the various story boards among the age groups for reasonable outcome (p < 0.05), rational reasons (p < 0.05) and actual understanding (p < 0.01) by using the Schild F test for polynomial contrasts.

**Conclusion:** This is the first study that documents medical decision-making capacity in Africa. Afrikaans speaking children 12 years and older have the ability for medical decision-making and the amendments to the Children’s Act is therefore appropriate. To address cultural influences it will be important to test children with other mother tongue languages in South Africa in future, including their ability to consent to cancer treatment.

**RETINOBLASTOMA**

**O053**

**PRE-ENUCLEATION CHEMOTHERAPY IN ADVANCED INTRAOCULAR RETINOBLASTOMA: CENTRAL AMERICA EXPERIENCE: AIHPCA II**

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**Purpose:** A significant percentage of patients in Central America present with buphthalmons, carrying a high risk of globe rupture and orbital contamination. In 2007, the protocol AIHPCA II introduced a study of chemotherapy before enucleation in children with buphthalmons.

**Methods:** Patients with advanced intraocular disease were considered standard-risk and underwent enucleation. Those with diffuse invasion of choroid, postimamolar optic nerve, or inferior chamber invasion received 4–6 cycles of adjuvant chemotherapy (vincristine 1.5 mg/
MRI FINDINGS AT BASELINE AND AFTER NEOADJUVANT CHEMOTHERAPY

Pediatric Blood Cancer DOI 10.1002/pbc

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Purpose: Retinoblastoma is one of the most common pediatric cancers in Central America, where two common therapy guidelines have been developed by AHOPCA. The first prospective study (1999–2004) showed late diagnosis, high abandonment, and poor outcomes. The next study aimed at improving the outcomes of early disease, address locally advanced disease, and decrease abandonment.

Methods: From 2007–2011, all new patients diagnosed with retinoblastoma in Costa Rica, El Salvador, Honduras, Guatemala and Nicaragua were included in a prospective, standard-of-care study. Two-hundred and forty seven (247) were eligible. Chemotherapy included vincristine 1.5 mg/m² and carboplatin 500 mg/m²/day 1 and etoposide 100 mg/m²/days 1–3. Using the IRSS system, patients with stage 0 received ocular-salvage treatments with chemotherapy and local control, which could include radiation therapy. Stage I had enucleation; those with high-risk histology received adjuvant chemotherapy. High-risk histopathology was defined as diffuse choroidal invasion, post-laminar optic nerve invasion, or anterior chamber involvement. Stage II had enucleation, adjuvant chemotherapy and orbital radiation. Stage III received neo-adjuvant chemotherapy, enucleation and orbital radiation. Stage IV received neo-adjuvant chemotherapy and radiation to involved sites.

Results: Of 247 patients (111 girls), 185 (75%) were unilateral and 62 (25%) were bilateral. Ninety-three had upfront enucleation, 52 had pre-enucleation chemotherapy, 10 were pending enucleation and 1 abandoned before enucleation. In the standard-risk group 38 had risk pathology and 54 had no risk factors; 4 abandoned 3 relapsed and 3 died of toxicity. Of 52 high-risk group, 6 abandoned, 5 relapsed, 3 had toxic deaths and 42 are alive at last follow-up (median time of 2.1 years). The estimated 4.5-year OS (abandonment censored) was 95 ± 0.02 and 85 ± 0.05 for standard-risk and high-risk, respectively (p = 0.14).

Conclusion: AHOPCA was able to address advanced intraocular disease with an innovative approach, while working on early diagnosis. Histopathology at the time of enucleation can define risk. However, for eyes with buphthalmos and patients with risk of abandonment, neo-adjuvant chemotherapy is effective when followed by post-enucleation chemotherapy. This approach may save patients from ocular rupture and intensified therapy; and reduce refusal rate compared to our previous experience.

O056

IMPROVING RETINOBLASTOMA OUTCOMES IN LOW INCOME COUNTRIES: RESULTS FROM THE AHOPCA II STUDY IN CENTRAL AMERICA

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Purpose: The proposed staging at baseline and after neoadjuvant chemotherapy was able to predict EFS (P = 0.0396 and 0.0000 respectively) and OS (P = 0.0128 and 0.0178 respectively). Patients with complete or partial response as per the proposed response evaluation criteria had significantly better EFS (P = 0.0002) and OS (P = 0.0238) than those who had stable or progressive disease.

Conclusion: The proposed MRI based optic nerve staging system and response evaluation criteria were significantly able to predict EFS and OS at baseline and after neoadjuvant chemotherapy.

O057

MRI FINDINGS AT BASELINE AND AFTERNeoADJUVANT CHEMOTHERAPY IN ORBITAL RETINOBLASTOMA (IRSS STAGE III)

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Purpose: The present study evaluates the role of Magnetic Resonance Imaging (MRI) in orbital retinoblastoma [International Retinoblastoma Staging System (IRSS) stage III] being treated with neoadjuvant chemotherapy and correlates it with clinical outcome. We propose a new MRI based optic nerve staging system and response evaluation criteria in locally advanced retinoblastoma.

Methods: Twenty-eight consecutive IRSS stage III retinoblastoma patients were included in the present study. Patients underwent MRI at baseline and after three cycles of neoadjuvant chemotherapy prior to enucleation. The MRI films were reviewed retrospectively by an ophthalmic radiologist who was blinded to the patient outcome. The proposed optic nerve staging system was based on its thickening, contrast enhancement and length of involvement on MRI. The proposed response evaluation criteria were based on the proposed optic nerve staging and change in size of orbital mass on MRI after neoadjuvant chemotherapy. The findings in the study were correlated with event free survival (EFS) and overall survival (OS) using Kaplan Meier survival analysis.

Conclusion: The proposed staging system and after neoadjuvant chemotherapy was able to predict EFS (P = 0.0396 and 0.0000 respectively) and OS (P = 0.0128 and 0.0178 respectively). Patients with complete or partial response as per the proposed response evaluation criteria had significantly better EFS (P = 0.0002) and OS (P = 0.0238) than those who had stable or progressive disease.

Conclusion: The proposed MRI based optic nerve staging system and response evaluation criteria were significantly able to predict EFS and OS at baseline and after neoadjuvant chemotherapy.

O058

CRITERIA DEFINING THE DURATION OF CHEMOREDUCTION WITH FOCAL TREATMENT IN RETINOBLASTOMA: A LONG-TERM UPDATE

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Purpose: With upcoming new treatment modalities for retinoblastoma (Rb), we wish to update our patient cohort having received chemoreduction (CRD) combined with focal treatment (FT) as standard approach and define its role in future.

Methods: Patients received a minimum number of courses of etoposide/carboplatin × 3 days + FT, every 3–4 weeks, according to response: maximal tumor width reduction, retraction from optic nerve/macula, extent of retinal detachment/reaplication, extent of vitreous seeds. Treatment was considered unsuccessful when salvage treatment (ST) such as enucleation (EN) and/or conventional external beam radiation (cEBR) was needed.

Results: One hundred and twenty eyes of 83 patients were treated by CRD + FT. Median age at diagnosis was 8 (IQR 13), median follow-up (FU) 84 months (IQR 61). Forty-three out of 120 eyes (35.8%) needed ST, 13/76 (17.1%) Group A–C and 34/44 (68.2%) Group D–E eyes. Median interval to progression was 3 months, (0–42 months), in 38/43 (88.4%) before 12 months of FU. Response measured by tumor width reduction was significant only after the first cycle (p < 0.001). In univariate logistic regression analysis older age (OR = 1.05 ± 0.02), more than 2 CRD cycles (OR = 4 ± p < 0.0001), disease group D and E (OR = 10.4, p < 0.0001) and presence of vitreous seeding/progression/non-response to CRD (OR = 3.9, p = 0.03) predicted need for ST, whereas in multivariate analysis only the latter two (OR = 9.6, p < 0.0001; OR = 7.8, p = 0.004) remained significant.

Conclusion: The over-time stable results for Group B and C Rb with little chemotherapy allowed to keep CRD + FT as standard treatment. In Group D and E disease however, new treatment strategies have to be developed.

O059

INTRA-ARTERIAL MELPHALAN CHEMOTHERAPY IN RELAPSED RETINOBLASTOMA IS AN EFFECTIVE SALVAGE THERAPY AND A SAFE ALTERNATIVE TO EXTERNAL BEAM RADIOTHERAPY

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Purpose: To determine if intra-arterial Melphalan is an effective salvage therapy in relapsed retinoblastoma.

Methods: Between December 2008–February 2012, 50 patients with retinoblastoma (48 with relapsed disease) were treated with between 1-6 (median 2) courses of intra-arterial Melphalan. 38 children had bilateral disease and 12 had unilateral tumours. The age of the children ranged from 9 months to 12 years. A total of 130 catheterisations were undertaken and there were 9 technical failures. In 8 children a subsequent attempt one week later was successful. Melphalan in doses ranging from 3 mg–7.5 mg (depending on age and response) was infused into the ophthalmic artery over 30 minutes.

Results: Side effects observed included ptosis and 3rd nerve palsies which in the majority of cases were reversible but retinal ischaemic changes were permanent. Afer a median
NOT KNUDSON'S RETINOBLASTOMA: ONE HIT CANCER INITIATED BY THE MYCN Oncogene?

Brenda L. Gall1,2,3, Diane Rushlow3,4,5,6, Kenneth Y. Jennifer6, Berber Mol6, Stephanie Y6, Sanja Pavlovic1, Renee Pang6, Brigitte Theriault7, Nadia Prigoda-Lee5, Clarellen Spencer1, Helen Dimaras4, Tim Corson3, Christine Massey1, Katherine Paton4, Annette Moll4, Claudi Houben8, William Halliday1, Anthony Raizis13, Wan Lam6, Paul Boutros1, Dietmar Loehmann5, Josephine Dorosman5

1Ontario Cancer Institute, University Health Network; 2Department of Ophthalmology and Retinoblastoma is a childhood retinal cancer. Knudson established that two "hits" Purpose: Pediatr Blood Cancer DOI 10.1002/pbc

LIVER TUMOURS

Conclusion: In this series of patients, intra arterial Melphalan was successful in preserving the eye in approximately two out of three eyes with relapsed retinoblastoma after standard intravenous chemotherapy. The salvage rate is equivalent to that seen with external beam radiotherapy in relapsed intraocular retinoblastoma.

References


O060

HMB classification has not been revised, while new variants have been described, and formerly clear-cut distinction between HBL and HCC is currently being evaluated. An international pathology working group was created to resolve the lack of consensus regarding terminology. The aims of the Pathology Expert Committee was to (1) revise histological classification (2) write recommendations for central review, and HBL/HCC pathology CRF (central review form) to optimize the diagnosis of HBL patients.

Methods: 22 pathologists analyzed 53 liver tumors on digitalized slides/microscopies to define morphologic criteria for different entities, review useful markers for HBL/HCC components, and histology of pre- and post-treatment specimens (29 biopsies, 2 resections), highlighting the main disagreements. A new HBL/HCC pathological CRF was discussed.

Results: (1) Cases included 24 HBL, 5 HCC, 1 TLT, 2 rhadoblastoid tumors, and 21 other tumors. A consensus classification was obtained for 6 main HB types: well differentiated (WD), mitotically active and pleomorphic fetal, cholangioblastic, macrotrabecular and SCU (small cell undifferentiated) components. The disagreement concerned 3 HBs with focal SCU, 2 anglastic HBs, 1 WD and 1 WD/HCC. (2) Biopsy specimens (either by Tru-Cut or surgical) are recommended as they should collect enough material to evaluate tumor heterogeneity, and biological studies. FNA/biopsies should be avoided for diagnosis. The panel of recommended antibodies included GS for WD fetal, Glypican3, AFP, β-catenin for embryonal and mitotically active fetal, vimentin, CD56, Opiomican, Bcl2 for SCU, CK19, EpCam for cholangioblastic, AFP, β-catenin, P53 for macrotrabecular HB. (3) Central pathology review will require the pathology report from the local institution, appropriate clinical information, and sufficient diagnostic tissue material for evaluation.

Conclusion: The new consensus classification, best specimen quality and submission forms, will improve HB reporting. Using a panel of antibodies will also allow progressive integration of new parameters, moving towards a classification based on tumour biology.

O062

LIVE DONOR LIVER TRANSPLANTATION FOR HEPATOBLASTOMA IN JAPAN

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Purpose: Hepatoblastoma is the most common malignant liver tumor in children, for which the cornerstone treatment is surgical resection associated with adjuvant chemotherapy regimens. In Japan, live donor liver transplantation (LDLT) has been indicated for hepatoblastoma in 14 Japanese transplant centres to evaluate their outcome.

Methods: Forty cases (28 males and 12 females, the median age at LDLT: 3.7 years), who had undergone LDLT for hepatoblastoma until the end of 2009, were enrolled into this study. Clinical data were collected from their medical records by questionnaire survey at the end of 2011 (the median follow-up period: 4.6 years). Based on pathological findings, the pretreatment extent of disease (PRETEXT) grouping was used for pretreatment staging of the tumor. Pre-transplant treatment was performed according to JPLT protocol. The indication and timing of LDLT on each center's decision. Immunosuppressive treatment basically consisted of tacrolimus and/or low-dose steroids. In Japan, live donor liver transplantation (LDLT) has been indicated for hepatoblastoma as a scheduled operation, based on the Japanese study group for pediatric liver tumor (JPLT) protocol. We retrospectively reviewed the cases undergoing LDLT for hepatoblastoma in 14 Japanese transplant centres to evaluate their outcome.

Results: In terms of PRETEXT, there were grade 1 in 2 cases, II in 1, III in 14, and IV in 23. Thirty-nine cases received chemotherapy, and 16 cases underwent hepatectomy before LDLT. Actuarial 3- and 5-year patient survival rates were 81.2% and 77.9%, respectively. Twenty nine cases were alive without recurrence after LDLT, and 11 patients suffered from recurrence. The most common site of recurrence was lung in 9 cases, followed by graft liver in 6. The median interval from LDLT to recurrence was 4.8 months. Eight patients died due to tumor recurrence. Alpha-fetoprotein level at LDLT, extra-hepatic lesion, and vascular invasion were significant risk factors for recurrence after LDLT.

Conclusion: LDLT provides a valuable alternative with excellent results in children with hepatoblastoma, because it allows optimal timing of the liver transplantation.

References

O065

TARGETED THERAPIES FOR PATIENTS WITH ADVANCED FIBROLAMELLAR HEPATOCELLULAR CARCINOMA: FROM BENCH TO BEDSIDE

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Purpose: Fibrolamellar hepatocellular carcinoma (FL-HCC) is a very rare malignancy predominantly affecting adolescents and young adults. Given the minimal options for advanced disease, we investigated characteristics and outcomes of patients with FL-HCC treated on phase I clinical trials with an emphasis on targeted therapies.

Methods: We reviewed the medical records of all patients referred to the Phase I program at MD Anderson. Molecular testing was performed for mutations in KRAS, NRAS, BRAF, EGFR, PIK3CA, MET, GNAQ, TP53; immunohistochemistry for PTEF, ALK-1 and FISH for her2/neu, CMET amplification and ALK-1 rearrangement.

Results: Ten patients (8 female) were evaluated (median age at diagnosis 23 yrs, youngest 15 yrs). The median number of metastatic sites was 3 (range 2–5). Eight of ten patients underwent prior surgical resection, three radiation therapy, one patient radiofrequency ablation and one patient ytimus–90 radioembolization. Eight patients received treatment with targeted regimens. Sustained responses were seen on combination therapy with sunitinib + valproic acid (41% decrease for 16.5 months), pazopanib + vorinostat (22% decrease for 5.4 months), bevacizumab + sorafenib (9% decrease ongoing for 4 months) and prolonged stable disease for > 9 months with novel proteosome and multikinase inhibitors. In mutational analyses, both patients tested for PTEF showed loss (complete or near-complete) which has been known to correlate with PTEF mutation.

Conclusion: We report the first case series investigating patients with FL-HCC on targeted therapies. Overall patients safely tolerated therapy on our early data showing clinical efficacy and biologic activity of strategies using novel multi-kinase inhibitors targeting VEGF, PDGFR, combined with histone deacetylases. Furthermore, aberrant expression of the tumor suppressor gene PTEF in both tested patients (one with loss, second with very weak staining) suggests that the activation of the PI3K/AKT/mTOR signaling pathway may be a driver of tumor cell proliferation and survival. Clinical trials incorporating targeted agents may represent a viable option for these patients.

References:

O066

A GENOME-WIDE ASSOCIATION STUDY IDENTIFIES NEW CANDIDATE LOCI ASSOCIATED WITH PROGRESSION OF HEPATOBlastOMA IN JPLT2 STUDY EXPERIENCE

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Purpose: Hepatoblastoma (HBL), the most common pediatric liver cancer, may originate from hepatic stem/progenitor cells and demonstrates both low and high grade malignancies such as pure fetal type and undifferentiated small cell types. However, no useful molecular markers except for telomerase activation have been identified. To identify new genetic markers associated with tumor progression, genome-wide association study was conducted in JPLT2 study experience.

Conclusion: Promoter hypermethylation of IGFBP3 and RASSF1 are strong prognostic markers for vascular invasion and/or metastasis. As the detection of tumour-derived methylated DNA in the blood stream of cancer patients is nowadays feasible, our data clearly advocate IGFBP3 and RASSF1 methylation assays to be used for future risk assessment in HB patients.
Methods: Out of 299 HBL cases registered in IPLT-2, 112 tumor samples were analyzed by Affymetrix SNP 6.0 arrays. These microarray data were analyzed by several softwares (CGAP, GTExBrowser, PRETEXT). In PRETEXT classification, 12 were I, 35 were II, 41 were III and 24 were IV tumors. Distant metastasis was detected in 35 cases.

Results: The data of SNP array revealed that chromosomal aberrations were observed in 104 cases (95%). Gain in chromosomes 1q, 2, 6, 7q, 8, 11, 12, 13, 17q, 19p, 20, and 22 and losses in chromosomes 1p, 4q, 14q, 17, and 19q were frequently identified. Insulin-like growth factor II (IGF2), TSSC5 and ORCTL2 genes were included in 11p, while IGF2BP1 were involved in 17q gain region. In advanced tumors with metastasis, several types of deletions including 6p, 8q, 17q and 20 were identified. Interestingly, chromosomes 1p loss, 1q gain, and 2p gain were more frequently detected in tumors diagnosed at more than 2 years old. These regions contained tumor growth related genes involving TSSC1, ERMN, HSFPI, BCL211, and NROX and non-coding RNA genes including NCNRNA01888, mir1288, mir2250 and mir3130. These genes and their target genes such as IGF2 and HGFAC genes might be correlated with the clinical features of BHL.

Conclusion: SNP microarray analysis revealed the main activated pathway due to chromosomal aberrations in hepatoblastoma. The aberrations of gene dosage might regulate the expression of genes and correlate to tumorigenesis and progression of HBL.


PEDIATRIC ONCOLOGY GROUP (COG) TRIAL AALL0622


Purpose: Historically, Ph+ ALL had poor outcomes, with modest survival improvements from hematopoietic stem cell transplantation (HSCT). Development of tyrosine kinase inhibitors (TKIs) targeting BCR-ABL1 has revolutionized treatment of Ph+ leukemias. COG AALL0301 demonstrated the safety of adding imatinib to intensive chemotherapy, resulting in 3-year event-free survival of 80% that was more than double historical control rates, and called into question the need for routine use of HSCT in first complete remission in children with Ph+ ALL. AALL0622 tested the effect of incorporating dasatinib, a more potent BCR-ABL TKI with the same chemotherapy backbone as AALL0301.

Methods: Dasatinib was given at 60 mg/m² daily either discontinuously (2 weeks per cycle, N = 41) or continuously (N = 16) starting on day 15 of induction, compared to AALL0301 where imatinib was given continuously beginning at the start of consolidation. We compared bone marrow response and minimal residual disease (MRD) levels (by multiparameter flow cytometry) on day 29 (end of induction) and 78 (end of consolidation) 2) between AALL0301 and AALL0622.

Results: Introducing dasatinib on day 15 of induction increased the rate of achieving an M1 marrow at induction day 29 from 89% on AALL0301 (n = 91) to 98% on AALL0622 (n = 57, P = 0.048). Furthermore, 25% vs 59% of patients had MRD < 0.01% at end induction (P < 0.001). 71% of patients on AALL0301 treated continuously with imatinib had MRD < 0.01% at the end of consolidation compared with 89% (n = 55) of patients on AALL0622, despite two-thirds of patients being treated discontinuously with dasatinib (P = 0.37).

Conclusion: Introducing TKI therapy during induction and substituting dasatinib for imatinib significantly improved early response in Ph+ ALL. Longer follow-up is necessary to determine the impact on EFS. Dasatinib in combination with a less intensive chemotherapy backbone is currently being tested in a joint COG/EpSALL Ph+ ALL trial.

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Purpose: Over the last 20 years cooperative projects developed through MSHPO and IOP have allowed to institute pediatric-oncology initiatives in Central America. Major problems were: deaths in induction, in CR, abandonment of treatment. Since 2008 Costa Rica, El Salvador, Honduras, Nicaragua and Panama started a common protocol, BFM oriented, for the treatment of acute lymphoblastic leukemia (ALL) in childhood.

Methods: Patients are stratified into three risk groups (Standard, SR, Intermediate; IR; High; HR) on the basis of age, white blood cell count, immunophenotype, CNS involvement, peripheral blood prednisone response, marrow response to induction therapy. SR received a three drugs induction therapy, a reinduction phase, maintenance with protracted intrathecal therapy, IR and HR received in addition a fourth drug in induction and an induction consolidation phase. Two or three reinduction phases where given to SR or HR respectively.

Results: From 01/08/2008 to 31/07/2011, 959 patients were entered: 264 in SR, 403 in IR, 292 in HR. CNS radiotherapy was given to 7.5%. Deaths occurred in induction in 3.1%, in CR in 3.4%. Abandonment occurred in 2.7% in induction, in 6.5% in subsequent phases. 1.0% was resistant to induction, 93.1% obtained CR. Relapse rate at a median observation time of 1.7 years was 12.6%. 3-year EFS when abandonment is censored or event is respectively 64.9% and 58.2% overall, 82.2% and 74.6% for SR, 64.8% and 57.2% for IR, 46.4% and 41.8% for HR.

Conclusion: This experience shows that common international studies are feasible in Low-Income countries (LIC). Deaths in induction, in CR and abandonment remain major obstacles in treatment of ALL. Intensity of treatment to improve results must be carefully balanced to avoid excess of toxicity. Our experience suggests that inter-group experience in LIC may be very beneficial to this purpose.

MAJOR RESULTS FROM THE IR-NBL/SIOPEN TRIAL FOR HIGH RISK NEUROBLASTOMA

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Purpose: This trial of the European SIOP Neuroblastoma Group aims to optimise treatment strategies for HRNBL patients (pts) by randomisation based on event free survival (EFS). Methods: From 2002–2012, a total of 1720 pts (168 MYCN amplified (MYCN) stages 2B+3,155 stages) were recruited in 20 countries. A total of 293pts were randomised between
0072

**EPIGENETIC THERAPY TARGETING SYK IN PRECLINICAL MODELS OF RETINOBLASTOMA**

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**Purpose:** Retinoblastoma (RB) affects 5,000–8,000 children each year worldwide. Survival for patients with intraocular disease is excellent; however, mortality approaches 50% for patients with metastatic disease. Recently, whole genome sequencing of RB revealed that alterations in epigenetic factors associated with Rb1 mutation are essential for tumor development. The proto-oncogene SYK (spleen tyrosine kinase), which has no expression in normal eye development, is upregulated in RB and required for tumor cell survival. Immunohistochemical studies showed that SYK is ubiquitously overexpressed in treated and untreated intraocular RB as well as metastatic RB specimens. This study tested the efficacy of a SYK inhibitor, R406, administered in combination with topotecan in preclinical models of RB and characterized the pharmacokinetics and toxicity profile.

**Methods:** We developed an ocular formulation using FDA approved adjuvants for ocular delivery. We performed pharmacokinetics of subconjunctival R406 (scR406) and compared the vitreal penetration to systemic R406 and R788 (prodrug). Two genetic RB mouse models with strong syngeneic tumors were monitored with intraocular pressure (IOP), blood counts and retinopathy (vision) during chemotherapy. Eyes with progressive disease underwent enucleation. Response to therapy was documented by IOP, vision testing, imaging and SYK enzyme activity.

**Results:** Comprehensive preclinical testing with scR406 (18 weeks) was compared to the current standard of care while monitoring toxicity. Subconjunctival delivery of R406 resulted in improved intraocular penetration of drug compared to oral or intravenous dosing. Administration of scR406 every 3 weeks resulted in little ocular or systemic toxicity in RB mouse models as well as wild-type (C57Bl/6) controls. Efficacy in an orthotopic xenograft, established from a human RB tumor sample known to over-express SYK, was documented in combination with standard chemotherapeutic agents. Conclusion: scR406 is a promising epigenetic therapy for retinoblastoma. Our studies support a standardized approach to evaluate novel agents for incorporation into future clinical trials for intraocular and extracocular RB.

**References**

0073

**THE PAEDIATRIC ONCOLOGY SPECIALTY TRANSITION PROGRAM: AN EDUCATIONAL INITIATIVE TO SUPPORT THE TRANSITION OF NURSES NEW TO THE PAEDIATRIC ONCOLOGY SETTING**

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**Purpose:** The Pediatric Oncology Specialty Transition Program aims to support nurses in their transition into a pediatric oncology role. This program includes an orientation, mentorship, and ongoing support. The effectiveness of the program is evaluated through feedback from participants. The current initiative focuses on preparing nurses for the unique challenges of pediatric oncology, including emotional support, symptom management, and transitions of care.

**Recommendations:** The program should be expanded to include more mentorship opportunities, online resources, and peer-to-peer support groups. Additionally, the program should be evaluated more frequently to assess its impact and make necessary adjustments.

**Conclusion:** The Pediatric Oncology Specialty Transition Program is an effective support system for nurses transitioning into the field. Further refinement and evaluation will ensure continued success in supporting nurses in their new roles.
**990 SIOP ABSTRACTS**

**Purpose:** Oncology Services at The Children’s Hospital at Westmead focus on the care and welfare of infants, children, adolescents and young adults with oncological conditions. The service provides inpatient and outpatient care to metropolitan, rural and international patients and their families. When caring for children with oncological conditions, nurses are confronted with both personal and professional challenges and stressors on a day-to-day basis. Due to its chronic nature, cancer is currently identified as one of three national health priorities by the Australian Institute of Health and Welfare. Cognisant of these facts, development of a Specialty Transition Program in the paediatric oncology setting was identified as a priority for the organisation to address a recognised need for a suitably qualified and experienced clinical nursing workforce. This paper will provide an overview of the program and highlights the impact of the pilot program.

**Methods:** The program provides a supportive environment to gain clinical experience over a 12 month period. It is designed to enable the development and integration of specialist knowledge and clinical skills through formal and work-based learning opportunities whilst providing day to day care for children and their families. Learning opportunities include preceptorship, clinical supported time, study days, clinical competencies, case scenario assessments, learning packages and compilation of a professional portfolio.

**Results:** Through active participation in structured learning activities participants developed specialist knowledge, advanced critical thinking and problem solving skills. The pilot program concluded March 2012 with all participants continuing fulltime employment.

**Conclusion:** The program is currently underway and includes surveys and retrospective clinical observations.

**O074 EMBRACING THE CHALLENGE: EVALUATING CULTURAL COMPETENCE OF REGISTERED NURSES AT A TEACHING HOSPITAL**

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**Purpose:** The current breadth of ethnic and cultural backgrounds in the United States requires that the nursing profession be culturally competent. Cultural competence calls for a conscious process whereby providers respect values, beliefs, and worldviews of diverse populations, whereby the diversity of patients, families and co-workers is appreciated. Although the prevalence of diverse individuals is steadily rising in the United States, the nursing workforce has yet to reflect such rapid growth. The purpose of this descriptive study is to evaluate registered nurses’ self-ratings of cultural competency. The Purnell Model of Cultural Competence serves as the study’s guiding conceptual framework, as it stresses health care professions’ need to provide sensitive and culturally competent care.

**Methods:** Cross-sectional, descriptive. The study is being conducted on the hematology/oncology unit at a large urban pediatric teaching hospital in the northeastern United States using a convenience sample of registered nurses. The Inventory for Assessing the Process of Cultural Competence among Healthcare Professionals (IAPCC-R), a self-administered and well-established tool, was used to measure five constructs of cultural competence: cultural desire, cultural knowledge, cultural skill, cultural encounters, and cultural awareness.

**Results:** The study is currently underway and the data analysis will be complete by August 2012.

**Conclusion:** It has been suggested that patient compliance increases when nursing practice is culturally competent. Nurses must increase their knowledge of diverse cultures in order to provide culturally competent care. The results of the survey will be used to develop targeted programs to support the cultural evolution of the nursing unit.

**O075 SOCIAL NETWORKING AND THE IMPACT ON THE ONCOLOGY COMMUNITY**

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**Purpose:** The Pediatric Oncology setting is often referred to as a community with unique challenges. Long term relationships, acuity, and the general anxiety invoked by a cancer diagnosis contribute to a close relationship where the interdisciplinary team and the patient/family unit can become enmeshed. The concept of family centered care takes on a life of its own. The advent of social media presents further complications to this relationship. Boundaries are blurred and confidentiality and privacy compromised. Despite having an institutional policy regarding the use of social media, it continues to be a practice among staff to allow patients and their families to become friends on Facebook and other public blogs. This quantitative study is seeking to explore the behaviour of staff and the ethics of social networking within the oncology community.

**Methods:** An anonymous questionnaire using survey monkey was sent to all the staff in the pediatric oncology department. The data were collected over a 30 day period, allowing for shift changes and vacation/sick leave. Data analysis was done using descriptive statistics.

**Results:** The survey revealed that despite having a policy in place, privacy, confidentiality, boundaries and professional conduct remain a challenge. Of the staff surveyed, 63% have a social media account of which 20% have patient/family members on their “friend” list. Perhaps the most revealing results are that 24% were unsure about the legal implications associated with the usage of social media and that 19% did not think or were not sure there were any ethical concerns.

**Conclusion:** The study will endeavour to raise awareness of the ethical and legal implications associated with social media when used in the oncology community. Results from the study will be used to develop guidelines and teaching models to educate and support both the staff and the patient/family unit.

**O076 CHILDREN AND ADOLESCENTS SURVIVING CANCER: PSYCHOSOCIAL HEALTH AND QUALITY OF LIFE**

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**Purpose:** Childhood cancer involves a crisis for the child and their family. The purpose was to explore and describe psychosocial health and QoL of children and adolescents surviving cancer at least 3 years after their cancer diagnosis, compared with a healthy control group.

**Methods:** Case-control study included 50 children and adolescents diagnosed with cancer between 1993–2003, treated at the Department of Pediatrics, St. Olavs University Hospital, Trondheim, Norway. Data were collected by using The Inventory of Life Quality in Children and Adolescents Questionnaire (ILC) and the KINDL, QoL questionnaire (parent and self reports), as well as data about somatic late effects and psychological symptoms from the medical records of children surviving cancer.

**Results:** Adolescents surviving cancer as a group assessed their QoL as similar to that of their peers. Yet, adolescents surviving brain tumours or those with late effects reported more emotional problems and a poorer QoL, even many years after diagnosis and treatment. Parents generally reported more emotional problems and a poorer QoL for their children surviving cancer, compared with parent controls.

**Conclusion:** To improve the child’s psychosocial health and QoL our results indicate the need to develop pertinent and adequate supportive interventions and programs when planning and implementing long-term follow-up care and rehabilitation of children and adolescents surviving cancer, especially for survivors with brain tumours, and those with late effects. Our results also indicate the need to take into account subjectively perceived and proxy reported psychosocial health and QoL for children surviving cancer.

**O077 DEVELOPING A TRANSITION TO LETTER FOLLOW UP PROGRAM AT BC CHILDREN’S HOSPITAL FOR YOUNG ADULT SURVIVORS OF PEDIATRIC CANCER**

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**Purpose:** To develop a program that will maintain contact with adult survivors of pediatric cancer who are transitioning from follow up care. In the province of British Columbia, about 70 patients “graduate” from the pediatric follow up program per year and the majority of these adult survivors continue their follow up care with their family physicians.

**Methods:** A letter follow up program was established as part of the comprehensive long term follow up program. Transitioning to letter follow up includes teaching patients about their disease, treatment and potential late effects and providing them with a written summary. On the patient’s last visit, patients are consented for annual letter follow up as well as for contact with their family physician. A questionnaire to the adult survivor and a physician based questionnaire to the family physician are sent annually to ascertain general health status and compliance with recommended surveillance. All returned questionnaires are reviewed by the nurse clinician and any questions or concerns from the survivor are followed upon. Pertinent data on surveillance are entered in a database to enable tracking of late effects information.

**Results:** To date, 250 patients have been enrolled in the letter follow up program. The questionnaire return rate has been 57% from patients and 89% from physicians.

**Conclusion:** The letter follow up program has been successful in providing a communication between the original treatment team and the survivor. Although a life-long surveillance program would be ideal, with budget constraints, this was one way of keeping in touch with the survivors. Maintaining contact allows the treatment centre to capture ongoing information on late effects and medical surveillance as well as informing survivors of pertinent new health information. Ongoing monitoring of response rate will inform whether patient contact can be sustained by letter follow up.

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BONE TUMOURS

O078

EWING SARCOMA FAMILY OF TUMORS(SET): DOES MODALITY OF LOCAL THERAPY IMPACT OUTCOME? SURGERY VERSUS RADIOTHERAPY VERSUS COMBINED MODALITY APPROACH

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Purpose: There have been no randomised controlled trials(RCTs) to compare outcomes using different modalities of local therapy (Surgery (Sx) vs Radiotherapy (RT) vs Surgery + Radiotherapy (Sx + RT) in ESFT. Feasibility of surgery (axial – Appendicular) and indication of radiotherapy (positive surgical margins and % necrosis post surgery) may induce a bias where such randomization may be ethically unacceptable. We have analyzed the results from our prospective clinical trial database.

Methods: An Institutional Review Board approved prospective study of 409 patients of histologically proven non-metastatic ESFT registered from January 2001 – December 2010 was analyzed for disease characteristics, local therapy modality and outcomes.

Results: Of the 409 patients registered, 274 had appendicular primary and 135 had axial primary tumors. Of the Appendicular PNET patients 263/274 patients received local therapy (RT – 37, Sx – 144, Sx + RT – 82). The local recurrence rates were RT – 5/37 (13%), Sx – 12/1214 (8.3%), Sx + RT – 7/82 (8.5%). The EFS, at median follow up of 37 months, of the three groups respectively were RT – 62.3%, Sx – 75.4%, Sx + RT – 73.1%. Although Sx showed a trend towards better outcome it was not found to be statistically significant(Sx vs RT – p = 0.07, Sx vs Sx + RT – p = 0.271, RT vs Sx + RT – p = 0.309). Of the patients with Axial primary 132/135 received local therapy (RT – 40, Sx-41, Sx + RT – 51). The local recurrence rates were RT – 10/40 (25%), Sx – 6/41 (14.6%), Sx + RT – 5/51 (10%). There was no statistically significant difference in the EFS between any of the three modalities (RT – 45.3%, Sx – 72.1%, Sx + RT – 64%, Sx vs RT – p = 0.173, Sx vs Sx + RT – p = 0.730, RT vs Sx + RT – p = 0.242). The EFS of RT alone group vs others (Sx + Sx + RT) was significantly inferior (57% vs 73%, p = 0.009).

Conclusion: Our prospective analysis of a large cohort of non-metastatic ESFT indicates that Surgery, if feasible, should be included in the local therapy planning. RT alone is usually used in apparently favorable (inoperable) cases and hence the outcome is inherently biased. In the absence of possibility of an RCT, our study reaffirms the importance of multimodality approach for local control and outcomes.

O079

SALVAGE RATES AND PROGNOSTIC FACTORS AFTER RELAPSE IN CHILDREN AND ADOLESCENTS WITH SYNOVIAL SARCOMA

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Purpose: Our study confirmed that prognosis after recurrence was largely unsatisfactory

Methods: Results on oncological outcomes after salvage therapy in patients with relapsed ES were acquired using different modalities of local therapy (Surgery (Sx) vs Radiotherapy (RT) vs Surgery + Radiotherapy (Sx + RT) in ESFT. Feasibility of surgery (axial – Appendicular) and indication of radiotherapy (positive surgical margins and % necrosis post surgery) may induce a bias where such randomization may be ethically unacceptable. We have analyzed the results from our prospective clinical trial database.

Methods: An Institutional Review Board approved prospective study of 409 patients of histologically proven non-metastatic ESFT registered from January 2001 – December 2010 was analyzed for disease characteristics, local therapy modality and outcomes.

Results: Of the 409 patients registered, 274 had appendicular primary and 135 had axial primary tumors. Of the Appendicular PNET patients 263/274 patients received local therapy (RT – 37, Sx – 144, Sx + RT – 82). The local recurrence rates were RT – 5/37 (13%), Sx – 12/1214 (8.3%), Sx + RT – 7/82 (8.5%). The EFS, at median follow up of 37 months, of the three groups respectively were RT – 62.3%, Sx – 75.4%, Sx + RT – 73.1%. Although Sx showed a trend towards better outcome it was not found to be statistically significant(Sx vs RT – p = 0.07, Sx vs Sx + RT – p = 0.271, RT vs Sx + RT – p = 0.309). Of the patients with Axial primary 132/135 received local therapy (RT – 40, Sx-41, Sx + RT – 51). The local recurrence rates were RT – 10/40 (25%), Sx – 6/41 (14.6%), Sx + RT – 5/51 (10%). There was no statistically significant difference in the EFS between any of the three modalities (RT – 45.3%, Sx – 72.1%, Sx + RT – 64%, Sx vs RT – p = 0.173, Sx vs Sx + RT – p = 0.730, RT vs Sx + RT – p = 0.242). The EFS of RT alone group vs others (Sx + Sx + RT) was significantly inferior (57% vs 73%, p = 0.009).

Conclusion: Our prospective analysis of a large cohort of non-metastatic ESFT indicates that Surgery, if feasible, should be included in the local therapy planning. RT alone is usually used in apparently favorable (inoperable) cases and hence the outcome is inherently biased. In the absence of possibility of an RCT, our study reaffirms the importance of multimodality approach for local control and outcomes.

O080

RESULTS OF THE IRSG D9602 LOW-RISK PROTOCOL FOR 35 PATIENTS WITH ALVEOLAR RHABDOMYSARCOMA (ARMS), 1997–1999

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Purpose: Describe 35 patients with low-risk ARMS treated on IRSG D9602 Protocol, treatment, and outcomes.

Methods: Retrospective chart review.

Results: In D9602, the definition of ARMS included any alveolar histologic feature. Thirty-five patients with ARMS were enrolled; 7 had focal anaplasia, 4 had diffuse anaplasia, and 24 (69%) had none. They received VAC for localized Stage 1 ± 2, N0 (regional lymph-node-negative) nonparameningeal tumors of the head/neck (n = 12), orbit (11), paratestis (8), extremity (3), and abdominal wall (1). Eighteen patients received radiotherapy for gross tumor after biopsy (10) or residual microscopic disease after subtotal excision (8). The median age at diagnosis was 5 years (range, 0–17); 25 were males and 10, females (2:5:1).

Conclusion: Although the 5-year FRS was lower in the D9602 patients than in IRS-III IV, 5-year survival rates were identical. However, because the definition of alveolar histology differed between the 2 groups of patients, direct statistical comparison of outcomes is inappropriate.

O081

ANALYSIS OF THE VALUE OF HIGH DOSE CHEMOTHERAPY IN RELAPSED EWING SARCOMA PATIENTS AND COMPARISON OF HIGH DOSE CHEMOTHERAPY REGIMENS BUSULFAN-MELPHALAN VERSUS TRESUFLAN-MELPHALAN FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANTATION

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Purpose: The event free survival (EFS) in patients with relapsed Ewing sarcoma (ES) remains poor with a 5-year EFS of 13%. We analysed the value of high dose chemotherapy (HDTX) in relapsed ES and compared the most frequently used high dose regimens versus HDTXs in terms of outcome.

Methods: Data from 239 patients with first relapse of ES registered from 2003–2006 into the ES registry database of the German Society of Pediatric Hematology and Oncology were analyzed. Outcome was assessed descriptively by event-free survival (EFS) and overall-survival (OS) controlled for risk factors by multivariate regression analysis.

Results: Amongst 73 pts who received HDTs: 15 received busulfan-melphalan (bus-mel), 38 treosulfan-melphalan (treo-mel) and 20 other regimens. Status prior to HDTx was remission in 25 pts, stable disease in 3 pts, progressive disease in 1pt and not known in 15 pts. The 3-year overall survival (3y-OAS) (14% (SE = 0.27) or 63% (SE = 0.14) or 63% (SE = 0.14) after bus-mel and treo-mel HDTXs, respectively. The 3-yOAS in pts with late relapse was 33% (SE=0.08) without HDTx and 67% (SE = 0.27) or 67% (SE = 0.14) after bus-mel and treo-mel respectively.

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**BRAIN TUMOURS 2**

**O082 PROGNOSTIC AND THERAPEUTIC ROLE OF TP53 MUTATIONS IN MEDULLOBLASTOMA SUBGROUPS: THERAPEUTIC ROLE OF LITHIUM IN ABRROGATION OF TP53 MUTATION ASSOCIATED RADIATION RESISTANCE**

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**Purpose:** Recent discoveries enabled us to divide medulloblastoma (MB) into molecular sub-groups and uncover novel mutations in these tumors. However, except for superior survival of the WNT sub-group, the prognostic and therapeutic implications of these observations remain unclear. TP53 mutations which confer radioresistance revealed conflicting clinical relevance in different studies. We hypothesized that the effect of TP53 mutations on survival is modulated through molecular sub- grouping. This is especially important since therapeutic targeting of WNT can be achieved with administration of Lithium.

**Methods:** We compiled survival and TP53 mutation data from all international groups involved in the MAGIC consortium. Human MB cell lines harbouring either wild-type or mutant TP53 were used to investigate radiation resistance and radiosensitizing capacity of Lithium by clonogenic assays. Normal neuronal stem cells (NNSC) were used to assess radiation (p < 0.01) accompanied by activation of DNA damage by immunofluorescence. In contrast, normal neural stem cells were protected from Lithium induced radiation damage.

**Conclusion:** Our collaborative effort uncovered the prognostic role of TP53 mutations in MB molecular sub-groups. Lithium represents an attractive novel therapy for MB patients. Genetic alterations and genomic sub-typing can serve as tool for individualized medicine for children with medulloblastoma.

**O084 OUTCOME OF CHILDREN TREATED FOR INTRACRANIAL EPENDYMOMA: THE FIRST SIOP TRIAL**

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**Purpose:** The clinical management of ependymoma in children and young adults is complex and the clinic-pathological correlates of outcome remain poorly understood. The first International Society of Paediatric Oncology (SIOP) study of combined modality treatment of older children with intracranial ependymoma is now reported.

**Methods:** A total of 89 children with ependymoma aged between 3 and 21 years were enrolled from 6 European countries between May 1999 and November 2007. Patients were stratified according to the extent of surgical resection. Those with complete resection (CR) underwent involved field radiotherapy to 54 Gy; those with an incomplete resection (IR) received up to 4 courses of VEC (Vincristine, Etoposide, Cyclophosphamide) chemotherapy and the clinic-pathological correlates of outcome remain poorly understood. The first International Society of Paediatric Oncology (SIOP) study of combined modality treatment of older children with intracranial ependymoma is now reported.

**Results:** Of 89 patients enrolled, 7 were excluded following central pathological review, 4 received up to 4 courses of VEC (Vincristine, Etoposide, Cyclophosphamide) chemotherapy followed by radiotherapy. Second-look surgery was advocated where possible.

**Conclusion:** Of 82 patients enrolled, 7 were excluded following central pathological review, 4 had metastatic disease at diagnosis. 33 eligible patients had a complete surgical resection (CR) and 45 patients (55%) had an incomplete resection (IR). With a median follow-up of 4.17 years (range 0.8 – 10.7), the 5-year EFS and OS for IR was 39.4% (95% CI: 25.2 – 53.3) and 53.7% (37.5 – 67.1), and CR 55.4% (35.1 – 71.7) and 76.2% (56.1 – 88.0). Despite clear trial strategy, 15 with IR went on to receive Radiotherapy alone thus violating the protocol; leaving 30 evaluable chemotherapy patients. 60% (95% CI 43.2 to 75.4) of evaluable IR patients responded to chemotherapy, exceeding the 45% rate set as evidence of efficacy. WHO grade did not affect outcome.

**Conclusion:** VEC is effective therapy for residual ependymoma, although the overall outcome following incomplete resection remains poor. 30% of those enrolled were ineligible for analysis. The outcome for ependymoma is likely to be enhanced by simply improving the accuracy of diagnosis and harmonising the standard of care following initial surgery, as well as investigating enhanced adjuvant strategies as planned in the next SIOP study.

**O085 MOLECULAR SUBGROUPS OF PAEDIATRIC EPENDYMOMA**

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**Purpose:** The current standard therapy for paediatric ependymoma is still based on combination chemotherapy and radiation therapy, with surgery for the primary tumor. This approach ensures an overall survival rate of 80% in favorable histology ependymoma. However, clinical and biological heterogeneity is high even within these histological subtypes. The current standard therapy for paediatric ependymoma is still based on combination chemotherapy and radiation therapy, with surgery for the primary tumor. This approach ensures an overall survival rate of 80% in favorable histology ependymoma. However, clinical and biological heterogeneity is high even within these histological subtypes. The current standard therapy for paediatric ependymoma is still based on combination chemotherapy and radiation therapy, with surgery for the primary tumor. This approach ensures an overall survival rate of 80% in favorable histology ependymoma. However, clinical and biological heterogeneity is high even within these histological subtypes. The current standard therapy for paediatric ependymoma is still based on combination chemotherapy and radiation therapy, with surgery for the primary tumor. This approach ensures an overall survival rate of 80% in favorable histology ependymoma. However, clinical and biological heterogeneity is high even within these histological subtypes. The current standard therapy for paediatric ependymoma is still based on combination chemotherapy and radiation therapy, with surgery for the primary tumor. This approach ensures an overall survival rate of 80% in favorable histology ependymoma. However, clinical and biological heterogeneity is high even within these histological subtypes.

**Methods:** To test the hypothesis that the effect of TP53 mutations on survival is modulated through molecular sub- grouping, this is especially important since therapeutic targeting of WNT can be achieved with administration of Lithium. Our collaborative effort uncovered the prognostic role of TP53 mutations in MB molecular sub-groups. Lithium represents an attractive novel therapy for MB patients. Genetic alterations and genomic sub-typing can serve as tool for individualized medicine for children with medulloblastoma.

**Results:** Of 82 patients enrolled, 7 were excluded following central pathological review, 4 had metastatic disease at diagnosis. 33 eligible patients had a complete surgical resection (CR) and 45 patients (55%) had an incomplete resection (IR). With a median follow-up of 4.17 years (range 0.8 – 10.7), the 5-year EFS and OS for IR was 39.4% (95% CI: 25.2 – 53.3) and 53.7% (37.5 – 67.1), and CR 55.4% (35.1 – 71.7) and 76.2% (56.1 – 88.0). Despite clear trial strategy, 15 with IR went on to receive Radiotherapy alone thus violating the protocol; leaving 30 evaluable chemotherapy patients. 60% (95% CI 43.2 to 75.4) of evaluable IR patients responded to chemotherapy, exceeding the 45% rate set as evidence of efficacy. WHO grade did not affect outcome.

**Conclusion:** VEC is effective therapy for residual ependymoma, although the overall outcome following incomplete resection remains poor. 30% of those enrolled were ineligible for analysis. The outcome for ependymoma is likely to be enhanced by simply improving the accuracy of diagnosis and harmonising the standard of care following initial surgery, as well as investigating enhanced adjuvant strategies as planned in the next SIOP study.
Brain tumours are the most common cause of cancer-related death in childhood. Ependymoma is the third most common paediatric brain tumour. Knowledge of the pathological, clinical and molecular differences of Group-A and Group-B tumours will allow better stratification in future clinical trials of pediatric PF ependymomas.

Methods: Two independent cohorts of 102 and 75 ependymomas were analysed using two different gene expression profiling platforms (Agilent, Affymetrix). Multiple clustering methods (unsupervised consensus-HCL and consensus-NMF) were performed and consistently showed three principle clusters, namely two distinct subgroups of posterior fossa (PF) ependymomas. Biological signalling pathways distinguishing these PF subgroups were identified by gene set enrichment analysis. The most significant classifying markers were validated by immunohistochemistry on a tissue microarray containing an independent set of 265 PF ependymomas. Additionally, we investigated whole-exome sequencing (Illumina HiSeq-technology) of 38 PF ependymomas representing both posterior fossa subgroups, to identify somatic mutations.

Results: We identified two posterior fossa ependymoma subgroups (Group-A and Group-B), showing significant prognostic differences, and distinct biological features. Patients in Group-A were mainly young children, had a balanced genome, more frequently developed secondary metastases, and were much more likely to have a fatal outcome as compared to Group-B patients. To stratify both groups, we identified LAM2A as a single molecular marker that showed the strongest prognostic value independently of clinical and molecular variables (Hazard-ratios: PFS: 8.45, OS: 10.55). Based on whole exome-sequencing we discovered ~13 mutations per tumour, and highlighted several genes not previously implicated in ependymoma tumorigenesis.

Conclusion: The identification of prognostic molecular markers to discriminate Group-A and Group-B tumours will allow better stratification in future clinical trials of pediatric PF ependymoma.

EPIDEMIOLOGY

AGE-INCIDENCE PATTERNS OF LYMPHOMAS IN CHILDREN AND YOUNG ADULTS IN ENGLAND 1995–2008

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Purpose: Lymphomas comprise 10% of tumours in children (ages 0 to 14) and 18% in young adults (ages 15 to 29) but only 4% in older adults. With the developments in diagnostic techniques and classification more extensive information is becoming available. This enables more closely targeted therapies and more detailed analyses of the incidence patterns of these tumours.

Methods: National cancer incidence data for England for individuals aged 0 to 29 were extracted from the National Cancer Registration (NCR). Lymphomas were classified as non-Hodgkin (HL) and non-Hodgkin (NHL). Those with detailed morphological information were further subdivided into six classes for NHL and four for HL. Incidence rates were calculated per million person years at risk (PMY) and analysed using Poisson regression.

Results: There were 381,774 lymphomas in 0 to 29 year olds from England from 1995 to 2008. The rates were 17 PMY in 0 to 14 year olds and 57 PMY in 15 to 29 year olds. There is a peak in NHL incidence at about age 5, mainly due to Burkitt lymphoma in males and lymphoblastic lymphoma in females. By age 20 diffuse large B-cell lymphoma is the most common type in both males and females. Both diffuse large B-cell lymphoma and follicular and nodular NHL have higher proportions of males in the 10–24 year old group than other age groups. HL has a peak in incidence at around 20, mainly due to nodular sclerosing HL, which has similar rates in males and females. For other types of HL the rate in males is greater than that in females.

Conclusion: The difference in the age distributions for different subtypes of NHL and HL is explained by the age-specific incidence rates in the general population and age-variability in the sex ratio imply that the aetiologies vary by age and subtype.

DELAYED DIAGNOSIS OF CHILDREN WITH CANCER IN RECIFE, BRAZIL MANIFESTS AS ADVANCED DISEASE AND SIGNIFICANTLY DECREASES EVENT-FREE SURVIVAL

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Purpose: Event-free survival (EFS) of children with cancer in low- and middle-income countries (LMIC) is much lower than the 80% expected in high-income countries (HIC). Those working in pediatric cancer units in LMIC have employed strategies to decrease treatment failure, but in some cases EFS remains unacceptably low. We explored the effect of delayed diagnosis and an excess of advanced disease at presentation on outcome in children with cancer.

Methods: The stage at presentation and EFS of children with cancer treated from 1994 to 2011 at the Instituto Materno-Infantil of Pernambuco, Recife, Brazil were compared to published norms from the USA (SEER plus study group publications) to determine the difference in stage distribution and EFS by disease and stage. The survival gap between Recife and HIC was divided into two components: (1) advanced stage at presentation, and (2) center effect.

Results: From 1994 to 2011, 938 children with selected solid tumors (Wilms tumor n = 223, neuroblastoma n = 169, germ cell tumor n = 126, thalidomysarcoma n = 56, Ewing sarcoma n = 30) or lymphomas (Hodgkin n = 122, non-Hodgkin n = 213) were treated. Stage at diagnosis was higher in Recife than in HIC, with excess stage 3 and 4 disease. For example, Wilms tumors were stage 1 (43% in HIC vs. 9% in Recife), stage 2 (22% vs. 11%), stage 3 (23% vs. 63%), stage 4 (10% vs. 13%), and stage 5 (5% vs. 4%). 33% stage 3/4 Wilms in HIC vs. 76% in Recife. In Recife neuroblastomas were stage 3 (37%) or 4 (57%). Five-year EFS in HIC was 78% vs. Recife 57%. Of this 21% gap, 12% could be accounted for by advanced stage at presentation.

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994 SIOP ABSTRACTS

Conclusion: Achieving optimal cure rates in LMC requires not only an excellent pediatric cancer unit, but also community outreach and expedited referral of children when their cancer is less advanced.

**O089**

THE RISK OF CHILDHOOD CANCER WITH SYMPTOM/SIGNS PRESENTING IN PRIMARY CARE IN THE UK: A POPULATION-BASED CASE–CONTROL STUDY

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Purpose: Guidelines describing symptoms in children that should alert general practitioners (GPs) to consider cancer have been developed in the UK, but without any supporting primary care research. We aimed to identify symptoms and signs presenting in primary care which might strongly alter the likelihood of a cancer diagnosis, to assist GPs in their selection of children for investigation.

Methods: A population-based, case-control study using electronic primary care records in the UK General Practice Research Database. 1,267 children aged 0–14 years diagnosed with childhood cancer were matched to 15,318 controls. We identified clinical features associated with subsequent diagnosis of cancer, using conditional logistic regression, and estimated likelihood ratios and positive predictive values (PPVs) for them.

Results: Twelve symptoms were individually associated with a PPV ≥0.04%, representing a greater than tenfold increase in prior probability. The six highest PPVs were pallor (OR = 17; PPV = 0.30; 95% CI: 0.10, 0.84), masses elsewhere (OR = 22; PPV = 0.11; 95% CI: 0.06, 0.20), lymphadenopathy (at any site) (OR = 10; PPV = 0.09; 95% CI: 0.06, 0.13), symptoms/signs of abnormal movement (OR = 16; PPV = 0.08; 95% CI: 0.04, 0.14) and bruising (OR = 12; PPV = 0.08; 95% CI: 0.05, 0.13). When any of these symptoms are combined with at least 3 consultations (for any reason) in a three month period, the probability of cancer is at least 13 in 10,000.

Conclusion: We identified 12 symptoms, each of which increased the risk of cancer at least tenfold. When combined with multiple consultations in primary care, these warrant careful evaluation and consideration of referral. Individual PPVs nevertheless remain small in view of the overall rarity of a diagnosis of cancer.

NURSES 4

O090

IMPLEMENTING A NEW ELECTRONIC TOOL TO SUPPORT EFFECTIVE CARE COORDINATION FOR FAMILIES OF CHILDREN WITH CANCER: AN UPDATE ON THE FAMILY ROADMAP PROJECT

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Purpose: In early 2011, the Paediatric Integrated Cancer Service (PICS) in Victoria, Australia, identified the need to provide an accurate, clear and concise summary of planned treatment and care pathways, to better inform and support families of children with cancer. PICS, in collaboration with the Health Service partners and the Consumer Reference Group, sponsored and facilitated the Family Roadmap Project. The aim of the project was to deliver individual customised roadmaps, in an easy to read calendar format that included all planned health appointments, admissions (including duration), tests and investigations.

Methods: Following a comprehensive review and assessment of tools, it was decided to utilise commercially available task and scheduling software. A priority list of protocols was identified for each disease category – each protocol represented by individual templates in a calendar format defining each block of treatment. This project has now been implemented within the Cancer Service at the Royal Children’s Hospital in Melbourne. The templates, along with procedures for governance of the process, have been incorporated in the Cancer Service’s accredited quality management system. The Project Officer implemented the process and provided education to the clinical nurse group responsible for supporting and coordinating patient care and generating the Family Roadmap. Each individual Family Roadmap is available in the patient medical record in order to communicate the care pathway.

Results: Since November 2011, 42 treatment protocols have been defined by 169 validated templates. Currently there are 80 families with customised Family Roadmaps. Evaluation of the Family Roadmap process will be available after May 2012, assessing qualitative feedback from patients, family and staff. Quantitative data will measure compliance with the process.

Conclusion: It is anticipated the project will implement Family Roadmaps across all protocols in Paediatric Cancer Services state-wide, providing access to information on planned healthcare for all patients and families in Victoria, Australia.

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**O091**

USING THE SEE-HEAR-DO-METHOD (SHDM) BY CARTOON PICTURES IN PEDIATRIC CANCER CARE IN NORWAY

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Purpose: Evaluation of the efficient of a pedagogical model with SHDM used by nurses to teach children, their families, network and other nurses about the cancer disease.

Methods: A new tool based on SHDM with cartoon pictures and instruction DVD, aimed to help nurses with information and explanations, to children with cancer, their siblings, parents, schools, kindergarten and colleagues, was introduced in Norway from 2010. The method aimed to increase the understanding of cancer in children, explaining aspects as blood and cancer cells, diagnoses, infections, transfusion and family relations. The SHDM was performed by key nurses at all the 5 Norwegian child cancer centres. They participated in a 2 days education program before using the method. An evaluation investigated the success of the SHDM by using a questionnaire of 55 questions one year from start in Norway.

Questions scored were on a scale of 1–5, where 5 were the best score.

Results: 26 nurses, who have worked for 5–25 years in the field, performed the SHDM and were used for the majority of 150 new patients in Norway yr year. The evaluations given by the key nurses were overwhelming positive. Regarding of information on cancer treatment, mostly used was the pictures that deal with healthy cells, blood cells, bone marrow healthy or sick, cancer diagnosis, chemotherapy and immune-compromised. According to the nurses’ view, the artwork has increased the patients and their families understanding of cancer and its treatment.

Conclusion: By learning and using the SHDM, nurses were able in a better way to explain about cancer disease. The result showed that nurses experienced they have new tools using SHDM together with their knowledge and in a difficult situation the pictures assisted the nurses in helping patients, families and colleagues to understand.

**O092**

SIBLINGS OF CHILDREN WITH CANCER – THEIR EXPERIENCES BEFORE AND AFTER PARTICIPATING IN A SUPPORT INTERVENTION COMBINING EDUCATION, LEARNING AND REFLECTION

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Purpose: The objective was to evaluate an intervention that combines education, learning and reflection about cancer delivered via internet and email, regarding the provision of support and prevention of illness in siblings with a brother or sister newly diagnosed with cancer.

Methods: A descriptive qualitative approach was used. The intervention consisted of lectures and e-mail conversations with siblings supplemented by a personal diary, designed to encourage reflection, using open questions concerning thoughts and experiences of being the sibling of a child with cancer. Fourteen siblings with a brother or sister newly diagnosed with cancer participated and were interviewed before and after the intervention. A qualitative content analysis was used for the analyses.

Results: The analysis revealed the theme ‘to live as normal a life as possible’ comprising five subthemes; ‘sleeping problems’, ‘physical pain’, ‘emotional affections’ and ‘changes in the future for the whole family’. Life was affected by the child with cancer. Before the intervention the siblings mostly described how new situation led, in everyday life, to suffering, fear, feelings of insecurity and doubts about the future. After the intervention the siblings were more informed about and prepared for the cancer treatments and their side-effects and the threat of death so close to them.

Conclusion: The siblings reflected on and dealt with difficult existential questions. The intervention helped the siblings to better understand cancer, their own reactions and their family situation. This should encourage health-care professionals to acknowledge siblings and to support them when their sister or brother has been diagnosed with cancer.

**O093**

USING ANIMATION ON CHILDREN’S AND TEENAGE CANCER UNITS: DEVELOPING SELF EsteEM IN HARd TO REACH PATIENTS WITH A STEP BY STEP APPROACH TO EXPLORATION AND DISCOVERY

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Purpose: The aim of the project is to support the development of self esteem and peer relationships in children and young people with cancer through patient led animation.

Reference Group, sponsored and facilitated the Family Roadmap Project. The aim of the project was to deliver individual customised roadmaps, in an easy to read calendar format that included all planned health appointments, admissions (including duration), tests and investigations.

Methods: Following a comprehensive review and assessment of tools, it was decided to utilise commercially available task and scheduling software. A priority list of protocols was identified for each disease category – each protocol represented by individual templates in a calendar format defining each block of treatment. This project has now been implemented within the Cancer Service at the Royal Children’s Hospital in Melbourne. The templates, along with procedures for governance of the process, have been incorporated in the Cancer Service’s accredited quality management system. The Project Officer implemented the process and provided education to the clinical nurse group responsible for supporting and coordinating patient care and generating the Family Roadmap. Each individual Family Roadmap is available in the patient medical record in order to communicate the care pathway.

Results: Since November 2011, 42 treatment protocols have been defined by 169 validated templates. Currently there are 80 families with customised Family Roadmaps. Evaluation of the Family Roadmap process will be available after May 2012, assessing qualitative feedback from patients, family and staff. Quantitative data will measure compliance with the process.

Conclusion: It is anticipated the project will implement Family Roadmaps across all protocols in Paediatric Cancer Services state-wide, providing access to information on planned healthcare for all patients and families in Victoria, Australia.

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sessions, designed to encourage creative risk taking and exploration of personal talents and ideas.

Methods: This project works with patients to create short animated films. One to one and small group sessions offer supported access to a dynamic and accessible creative tool-set. The step by step nature of the process and open-ended, patient led approach affords the opportunity to manipulate and re-imagine the film as they are making it, stimulating development, growth and discussion. Engaging patients in value, take control of and develop these processes invites them to generate their own energy and take creative risks. Successfully engaging patients in this activity during treatment requires the facilitator to be working as part of the ward team. Tuning into individual needs and interests is crucial in designing and employing the tool set to offer an appropriate, supportive and stimulating platform.

Results: Over the 5 years that the project has been running, 475 films have been created by patients ranging from 3 to 18 years. A selection of films by young patients will be shown. The project has led to the development of a toolkit for animation projects in the clinical setting.

Conclusion: The animation project supports development of self esteem in young cancer patients in by empowering them to explore and express personal talents and ideas. It utilises a toolset developed over 5 years in the clinical setting to support and challenge them in stepping beyond their expectations of themselves during their treatment.

References

NEUROBLASTOMA 1

O094

FACTORS THAT CONTRIBUTE TO INFERIOR SURVIVAL OF LOW-RISK STAGE 2B NEUROBLASTOMA PATIENTS: A CHILDREN'S ONCOLOGY GROUP STUDY

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Purpose: We have previously reported that patients with low-risk (LR) INSS stage 2B neuroblastoma (NBL) who are >18 months of age at diagnosis and who have unfavorable histology or diploid tumors have significantly inferior event-free (EFS) and overall survival (OS) rates compared to other LR NBL patients. We studied these patients to determine if the degree of surgical resection affected outcome and to identify the biologic factor(s) that most significantly contributed to lower EFS.

Methods: Of 915 eligible LR NBL patients on P9641, 237 patients had MYCN non-amplified INSS stage 2B disease. We examined their age at diagnosis, degree of initial tumor resection, tumor histopathology, ploidy, and 1p and 1q status. Survival tree regression analysis was performed using a Cox proportional hazards model, identifying the statistically significant factor(s) that had the highest hazard ratio (HR).

Results: Within the 237 stage 2B patients (3-year EFS: 85% ± 3%), only ploidy and histology were significant in univariate analysis. Degree of resection was not associated with outcome. Ploidy was the most highly prognostic factor (n = 222; p = 0.003; HR = 2.7); within the hyperdiploid patients, no factors were significant. Within diploid patients (3-year EFS: 72% ± 7%), histology was prognostic (n = 52; p = 0.006; HR = 5.9). Within unfavorable histology (3-year EFS: 54% ± 11%), 1q was prognostic (n = 11; p = 0.03; HR = 12.0). All three patients with 1q LOH had an event.

Conclusion: Ploidy, histology and the status of 1q are powerful prognostic factors for patients with INSS stage 2B NBL. Although image defined risk factors have not been assessed in these patients, tumor biology and patient outcome indicate that they likely have International Neuroblastoma Risk Group L2 tumors. The lack of impact of surgical resection on outcome suggests that more intensive chemotherapy treatment regimens will be required to improve EFS in stage 2B patients with unfavorable histology and genetics.

O095

TANDEM HIGH-DOSE CHEMOTHERAPY (HDC) WITH THIOTEAPE AND BU-MEL AND AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT): THE WAY TO IMPROVE VERY HIGH RISK NEUROBLASTOMA PATIENTS PROGNOSIS?

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Purpose: To evaluate the predictive power of paired-like homeobox 2b (PHOX2B), tyrosine hydroxylase (TH) and doublecortin (DCX) mRNA detected by reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR) in bone marrow (BM) taken from children with high risk neuroblastoma entered into the European trial HR-NBL-1/SIOPEN (www.SIOPEN-R-NET.org) at the time of entry into the study (DX) and post-induction therapy (PIT). Method: RT-qPCR was performed for PHOX2B, TH and DCX mRNA in BM of children at diagnosis (DX) and at post-induction therapy (PIT). Results: The level of TH, PHOX2B or DCX mRNA in BM at DX strongly predicts for event-free survival (EFS), showing independent predictive power in this high risk group of children. Levels of TH, PHOX2B and DCX mRNA in BM at DX above statistically defined cut-points predicted EFS of 31%, 33% and 30% respectively at 3 years, compared to those with mRNA levels below the defined cut-points that had a 3-year EFS prediction of 55%, 59% and 61% respectively. Expression of each mRNA was highly correlated with expression of the other mRNAs. After PIT, predictive significance was maintained with EFS of 26%, 21% and 25% at 3 years for children with TH, PHOX2B and DCX above the cut-points, as compared to that of 52%, 40% and 42% for those with mRNA levels below the cut-points. Analysis of all three or the clearance of mRNA from DX to PIT did not increase the predictive power of any single mRNA.

Conclusion: High levels of PHOX2B, TH or DCX mRNA detected by RT-qPCR in bone marrow from children with high risk neuroblastoma at DX and PIT predict EFS. These observations require validation in a second independent data set.

References

O097

QUANTIFICATION OF BONE MARROW DISEASE IN HIGH RISK NEUROBLASTOMA PATIENTS WITH ANTI-GD2 IMMUNOCYTOCHEMISTRY AT DIAGNOSIS AND AT END OF INDUCTION THERAPY – IMPACT ON EVENT-FREE AND OVERALL SURVIVAL. A SIOPEN HIGH RISK STUDY

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Purpose: The administration of Bu-Mel and ASCT has been recently demonstrated to allow the best prognosis for patients with high-risk neuroblastoma (HR-NBL-1 SIOPEN Study). However, patients with less than a partial remission after 2 lines of conventional chemotherapy and adolescents are considered as very high risk (VHR) patients.

Methods: We developed an intensified HDC strategy with 2 courses of HDC to improve VHR patients prognosis. The first course consisted in thiotepa (300 mg/m²/id × 3) followed by ASCT. In absence of major toxicity or disease progression, a 2nd course of melphalan (140 mg/m²) Busulfan (600 mg/m²) and ASCT was administered 2 months later. From April 1986 to April 2009, 22 patients (12 males, 10 females), median age 3.5y (0.9–15.9) entered this programme.

Results: 20/22 had less than a partial remission after conventional chemotherapy. 2 were adolescents with a metastatic CR, 1 had a MYCN amplified tumour. Thiotepa-related toxicity was mainly digestive with a grade >2 mucositis and diarrhoea in 14 and 16 patients, respectively. Hospitalisation duration was 25 days (19–49). Mel-Bu was administered in 18 patients. Patients had a progressive disease after thiotepa. Toxicity was digestive with a grade >2 mucositis and diarrhoea in 15 and 7/18 patients, respectively and hepatic with 6/18 hepatic veno occlusive disease. Toxic related death occurred in 1 patient due to alveolar haemorrhage. The 3-year EFS survival is 42.6% (24–64).

Conclusion: This intensified HDC strategy in VHR patients seems to be feasible and to improve survival. It will be compared to a combined mIBG-Mel-Bu strategy in the future VHR neuroblastoma European Protocol.

References

SIOP ABSTRACTS 995
A SYSTEMATIC REVIEW OF 131I-META IODOBENZYL GUANIDINE THERAPY IN NEUROBLASTOMA

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Purpose: The optimal use of 131I-meta iodobenzylguanidine (mIBG) molecular radiotherapy for neuroblastoma is not defined, and its effectiveness remains uncertain. A Systematic Review of the published evidence should improve understanding of the data and define uncertainties to be addressed in future clinical trials.

Methods: Medline, Embase, and Cochrane Central databases were searched up to 2011 using search terms for neuroblastoma and mIBG. Phase I, II, and III trials, and prospective, non-comparative case series (10 or more patients) that had investigated the treatment of patients with neuroblastoma treated with 131I-mIBG therapy were included. Two reviewers independently assessed papers for inclusion using the title and abstract with consensus achieved by discussion. Data were extracted by one reviewer and checked by a second. Studies with multiple publications were reported as a single study.

Results: The electronic searches yielded 1,062 citations, of which 41 publications reporting 28 studies met our inclusion criteria. Two studies where 131I-mIBG had been used as induction therapy and two studies where it had been used for consolidation were identified. Twenty five studies for relapsed and refractory disease were identified (33 publications).

Results: The electronic searches yielded 1,062 citations, of which 41 publications reporting 28 studies met our inclusion criteria. Two studies where 131I-mIBG had been used as induction therapy and two studies where it had been used for consolidation were identified. Twenty five studies for relapsed and refractory disease were identified (33 publications).

Conclusion: 131I-mIBG is an active treatment for neuroblastoma. Its place in the management of neuroblastoma remains unclear. Prospective randomised trials are essential to strengthen the evidence.

O099

MOLECULAR IMAGING PATTERN AT DIAGNOSIS DISTINGUISHES THE GENOMIC TYPE AND OUTCOME OF NEUROBLASTOMA

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Purpose: (1) To evaluate the prognostic impact of the number of infiltrating tumor cells in bone marrow (BM) at diagnosis and after induction chemotherapy and (2) to compare the results of anti-GD2 ICC performed on BM aspirates with those of conventional cytomorphology and trephines.

Methods: Mononuclear cells were prepared from 400 BM aspirates, stained with anti-GD2 and evaluated according to international consensus guidelines. Time to death (overall survival OS) and time to progression (EFS) were analyzed using the Kaplan-Meier method. ROC analysis was applied to evaluate possible cut-offs for continuous predictors.

Results: We analyzed the prognostic impact of tumor cell infiltrates at similar levels of sensitivity, i.e. in samples containing comparable numbers of investigated BM cells. ROC analyses of the sensitivity and specificity of various numbers of tumor cells to predict EFS and OS at diagnosis showed that only samples containing more than 2 x 10^6 BM cells provided prognostic information. Before treatment, the number of infiltrating GD2-positive tumor cells was prognostic of EFS (p = 0.005) and OS (p = 0.03) as it was for BM positivity by conventional cytomorphology (EFS p = 0.035, OS p = 0.031) and trephines (EFS < 0.001, OS p = 0.011). However, after induction, only ICC but not cytomorphological and trephine results could statistically significantly predict outcome, especially in children older than 18 months (EFS p = 0.004, OS p = 0.014). Similar survival data were observed when the BM cleared of tumour cells after induction chemotherapy in this age group (EFS p = 0.008, OS p = 0.015).

Conclusion: While ICC, cytomorphology and trephines are prognostic of outcome at diagnosis, only anti-GD2 ICC predicts survival after induction chemotherapy. The ICC assay may be helpful to identify patients at ultra-high risk when clinical criteria for this subgroup are defined.

References
Beiske K et al. Consensus criteria for sensitive detection of minimal neuroblastoma cells in bone marrow, blood and stem cell preparations by immunocytology and QRT-PCR: Molecular imaging is fundamental for the diagnosis and surveillance of neuroblastoma (NB), but the clinical role of novel application of positron emission tomography (PET) scans in NB is less understood. In this study, we examined the correlation between diagnostic 18F-FDG and 18F-FDOPA PET imaging signals and overall genomic pattern and treatment outcome of NB.

Methods: As MBIG scans are not available for routine practice in Taiwan, NB patients were enrolled for 18F-FDG and 18F-FDOPA PET scans since 2008. Each primary NB tumor’s maximal standard uptake value (SUVmax) was normalized to liver uptake, generating a tumor-to-liver SUV ratio (T/L) for each scan. The ratio between diagnostic 18F-FDG and 18F-FDOPA (T/L/18F-FDOPA) was used as a novel biomarker to compare with major clinical parameters.

Results: Twenty-one patients (median age at-diagnosis, 2.0 [range, 0.2–6.9] years; male:female, 16:5) were eligible for analysis, with a median follow-up of 21.6 months. Ten (83%) of the 12 NBs with array comparative genomic hybridization (array-CGH) and/or chromogenic in situ hybridization for MYCN status belong to one of the major genomic types, i.e. numerical changes of whole chromosomes only (Num: n = 5), segmental alterations involving 1q and/or 1p (Seg: n = 6), or MYCN amplification (MNA: n = 2). In contrast to Num NBs, Seg and MNA NBs were associated with older age (p = 0.024), stage 4 disease (p = 0.008), higher 18F-FDG uptake (p = 0.0163), lower 18F-FDOPA uptake (p = 0.0281), and higher FDG/FDOPA (p = 0.009). Among all 21 eligible patients, FDG/FDOPA ≥ 1 significantly correlated with stage 4 disease (p = 0.007) and worse progression-free survival (2.7-YES, 68% vs. 0%, p = 0.0348), but not with age (p = 0.64) or overall survival (2-YES, 88% vs. 96%, p = 0.23).

Conclusion: Major genomic types of NB can be distinguished with diagnostic 18F-FDG and 18F-FDOPA PET scans. NB patients with initial FDG/FDOPA ratio ≥ 1 might have an inferior outcome.
Salvage Therapy for Refractory or Recurrent Pediatric Germ Cell Tumors: The French SFOP Experience

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Purpose: Less than 10% of children with extracranial germ cell tumors (GCT) relapse or fail to respond after first-line treatment including chemotherapy and surgery, but a minority of these patients achieves long-term survival despite multidisciplinary salvage treatment. Prognostic factors in this situation remain to be elucidated.

Methods: Nineteen children (8%) of the patients prospectively enrolled onto the French Protocol for non-seminomatous GCT (TGM95), had refractory or recurrent extracranial GCT (one after AML) and were analyzed in order to identify prognostic factors and determine which salvage treatment can provide best results.

Results: At the end of first line treatment, 10 children were in complete and 9 in incomplete remission. Events occurred within 2 years (5–23 months) after initial diagnosis. Fourteen patients progressed with treatment in at least an initially involved site. Two patients showed purely biologic relapse (isolated raising markers), and 4 patients suffered from purely metastatic relapse (brain location in 3 cases). After salvage treatment combining surgery and various types of chemotherapy (platinum-salt based chemotherapy in 13 cases and high-dose chemotherapy in 10 cases), the OS rates of the cohort was 32% (IC95%: 15%–54%). Survival was higher for patients undergoing total surgical resection (or without any detectable tumor) compared to those with no or incomplete surgical resection (p < 0.05) at first relapse. Only one case of resistance to cisplatin was observed. Although not statistically significant, there was a trend for a better OS in patients who had received intensified chemotherapy (p = 0.37).

Conclusion: Local control of the tumor appears to be the cornerstone of treatment. Cisplatin based chemotherapy seems to be the most appropriate regimen at relapse, provided that the initial cumulative dose allows retreatment. The role of high-dose chemotherapy remains a matter of debate.

Non Seminomatous GCT (NSGCT) in Children: Final Long Term Results of the French SFOP/SPCE TGM 95 Protocol

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Purpose: To improves survival of NSGCT, excluding pure immature teratoma, with cisplatin-based chemotherapy adapted to initial resection, aFoproteine (AFP) level and presence of metastases (M).

Methods: Based on previous TGM85/90 studies, including worse prognosis of patients with metastases (M).

Results: From January 1995 to December 2005, 239 pts were registered: 60 LR, 65 IR and 114HR (51 M) pts. Median age: 3 years (0–18). Sites: 66 testes/77 ovaries, 57 sacrococcygeal and 39 others. Median number of courses: 4 in IR and 5 in HR. Twenty-six failures occurred: 19 IR/relapses/bilatéralisation (all within 24 months after diagnosis), 1 toxic death of concomitant AML with iso12p, 1 accidental death in CR, 2 AML (11 and 35 months) and 3 other 2nd malignancies (after 8 years). Seventeen pts died. With a median follow-up of 5 years, overall survival is 93%: 5 yrs EFS is 90% for all pts and 94%, 87% and 89% respectively for LR, MR and HR. Presence of metastases (5 yrs EFS: 82% M+ vs 92% M0) and age (EFS 86% if > 10 yrs vs 93% if < 10 yrs) were prognostic, while AFP level (EFS 91% if > 15,000 vs 89% if < 15,000) was not any more.

Conclusion: Outcome of NSGCT greatly increased compared to previous studies. Next protocol will redefine risk group categories including age and will focus on the decrease of the total dose of drugs by fixing the number of courses.

DO GermiNoma Elements in intracraniAL NoN-germimaNomaT GerM Cell TuMors (NGGCT) Increase the Risk of VentricuLar relAPses?

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Purpose: About 30% of pts with secreting NGGCT will present germinoma elements in their tumor tissue. The biological behaviour of germinoma in respect of tumor spread and ways of dissemination are different from secreting GCTS. Therefore we investigated in the cohort of CNS NGGCT treated under SIOP CNS GCT 96 those patients (pts) with additional histological diagnosis of germinoma/teratoma.

Methods: 157 pts with NGGCT were registered up 24/09/2010. Progression-free survival (PFS) of pts with localised disease 0.69 ± 0.04 (median follow-up 74 months; overall survival (OS) 0.78 ± 0.04), in pts with metastases 0.67 ± 0.07 (median follow-up 56 months; OS 0.70 ± 0.09). 101 pts had a histological verification at diagnosis, 30/101 were biopsied, 71/101 were resected. 80/101 pts showed additional histological components: 17/ 80 teratoma, 30/80 germinoma and 28/80 both germinoma/teratoma (in total 63 with germinom + teratoma). The age range was 0–28 years (median 13 years), 61/80 were boys. 59/63 were localised, 13/63 had a metastatic disease.

Results: PFS of 46 pts with localised disease and germinomatous component (± teratoma) was 0.66 ± 0.08 (median follow-up 48 months; OS 0.79 ± 0.06) whereas PFS in 33 patients with localised disease without germinomatous component was 0.62 ± 0.09 (median follow-up 47 months; OS 0.72 ± 0.09). PFS of 13 pts with metastatic disease and germinomatous component (± teratoma) was 0.69 ± 0.13 (median follow-up 50 months; OS 0.76 ± 0.12) whereas PFS in 4 patients with metastatic disease without germinomatous component was 0.50 ± 0.25 (median follow-up 12 months; OS 0.75 ± 0.22). 18 relapses occurred in the group of patients with additional germinomatous components, 10 local, 1 ventricular, 2 combined, 4 distant, 1 progression). The ventricular relapse was diagnosed in a pt with localised disease.

Conclusion: Germinoma as additional histology appears not to increase the risk for ventricular relapses in localised disease with local RT. Germinoma/teratoma as additional component does not influence the outcome.

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EPCM – a Novel Molecular Target for the Treatment of Pediatric Gern Cell Tumors

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Purpose: Germ cell tumors (GCTs) are thought to develop from totipotent primordial germ cells. Although the epithelial cell adhesion molecule (EpCAM) is expressed on embryonic stem cells as different tumor cells at adulthood, it has not yet been extensively studied in GCTs. Thus, we analyzed various GCTs for EpCAM expression and evaluated EpCAM as a target for GCT immunotherapy.

Methods: EpCAM expression was analyzed in 48 fresh-frozen primary GCT and the four GCT cell lines NCCIT, TE671, T.JAR and 2102EP by quantitative real-time reverse transcription PCR and correlated with AFP and b-HCG levels, histology and follow-up data. Superficial EpCAM expression was visualized by immunohistochemistry of corresponding paraffin embedded tumor tissues or flow cytometry of used cell lines. Finally, cytotoxicity of an EpCAM specific antibody was measured by a functional in vitro assay of JAR and 2102EP cell lines.

Results: EpCAM is expressed in malignant in contrast to benign GCTS irrespective of age, sex, site and clinical tumor stage (p = 0.001). In particular, EpCAM expression of primary tumors increases in teratomas with their grade of immaturity (mean 2.2 ± 0.6 values: mature

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teratomas 0.230, immature teratomas 1.605, p = 0.007) and significantly correlates with serum AFP (p = 0.033) and b-HCG (p = 0.033) levels in malignant GCTs. Extraordinary high EpCAM expression levels were determined in primary non-seminomatous GCTs such as yolk sac tumors (8.494) and a choriocarcinoma (13.535). Similarly in vitro, the highest EpCAM expression was measured in GCT cell lines expressing yolk sac (2102Ep: 5.548; 99.6% EpCAM+) or choriocarcinoma (JAR: 10.647; 99.7% EpCAM+). Components. Addition of EpCAM specific antibody to both cell lines incubated with PRM (ratio 50:1) resulted in dose-dependent cell lysis by 23% (JAR) and 91% (2102Ep).

Conclusion: For the first time our study identifies EpCAM as a new molecular target for antibody-based immunotherapy in GCTs, in particular for malignant non-seminomatous GCTs such as yolk sac tumors.

References

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O105

**LIN28 IS OVER-EXPRESSED IN MALIGNANT GERM-CELL-TUMOURS, RESULTING IN let-7 DOWN-REGULATION AND INCREASED LEVELS OF PRO-ONCOGENIC GENE TARGETS**

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Purpose: Despite their histopathological and clinical heterogeneity, malignant germ-cell-tumours (mGCTs) share fundamental biological and molecular abnormalities. We previously shown that all nine members of the tumour-suppressor let-7 microRNA family were significantly down-regulated in paired mGCTs [1]. As restoring levels of down-regulated microRNAs is an attractive strategy for cancer therapy, we investigated the basis and significance of this observation.

Methods: We analysed global mRNA and microRNA array data in order to identify upstream causes of let-7 down-regulation in mGCTs and investigate downstream effects on let-7 target genes. We utilised these findings from clinical samples to inform investigations of the effects of restoring endogenous let-7 levels in mGCT cells in vitro.

Results: We found that the negative let-7 regulator LIN28 was significantly over-expressed in mGCTs from paediatric (n = 20) and adult (n = 25) patients, regardless of tumour site or histological type, with a highly significant negative-correlation between LIN28 and let-7 levels in matched datasets (p = 0.00003). Using Syramer analysis, the top-ranking microRNA seed complementary region in the 3'UTR of LIN28 mRNA was 'TACCT', corresponding to the 2–7 common seed 'GAGGUA' of the let-7 family (p = 0.0019). We identified twenty-eight let-7 mRNA targets that were up-regulated in both the paediatric and adult mGCTs and had significant negative association with mean let-7 levels. For six genes with known/putative pro-oncogenic function (MYCN, AURKB, CCNF, RRM2, MKI67, C12orf5) we confirmed a negative-association with LIN28 and the UK, of whom 3,222 had received external radiotherapy. The dose received by thyroid gland during each course of radiotherapy was estimated after reconstruction of the actual conditions.

Results: After a mean follow-up of 22 years (range: 2–56), 46 patients developed a thyroid in a cohort of 4,506 2/3-year survivors of a solid childhood cancer treated between 1942 and 1985 in 8 centers in France and the UK, of whom 3,222 had received external radiotherapy. The dose received by thyroid gland during each course of radiotherapy was estimated after reconstruction of the actual conditions.

Results: After a mean follow-up of 22 years (range: 2–56), 46 patients developed a thyroid in a cohort of 4,506 2/3-year survivors of a solid childhood cancer treated between 1942 and 1985 in 8 centers in France and the UK, of whom 3,222 had received external radiotherapy. The dose received by thyroid gland during each course of radiotherapy was estimated after reconstruction of the actual conditions.

Purpose: To study the role of treatment in the risk of differentiated thyroid carcinoma following childhood cancer.

Methods: We studied the long-term risk of a thyroid tumor in a cohort of 4,506 2/3-year survivors of a solid childhood cancer treated between 1942 and 1985 in 8 centers in France and the UK, of whom 3,222 had received external radiotherapy. The dose received by thyroid gland during each course of radiotherapy was estimated after reconstruction of the actual conditions.

Results: After a mean follow-up of 22 years (range: 2–56), 46 patients developed a thyroid in a cohort of 4,506 2/3-year survivors of a solid childhood cancer treated between 1942 and 1985 in 8 centers in France and the UK, of whom 3,222 had received external radiotherapy. The dose received by thyroid gland during each course of radiotherapy was estimated after reconstruction of the actual conditions.

Conclusion: Our results confirm that for dose higher than a tenth of grays to thyroid, the risk of thyroid cancer results in a plateau and decreases afterward. The role of chemotherapy in the risk of thyroid cancer needs further investigations.

O108

**PREDICTION OF EXCESS RISKS OF RADIATION-INDUCED CARDIAC MORBIDITY AND SECONDARY CANCERS AFTER RADIOThERAPY FOR Hodgkin LYMPHOMA**

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Purpose: Secondary cancers are one of the most serious complications after successful treatment of childhood acute lymphoblastic leukemia (ALL). With improvement in survival, it is important to evaluate the impact of treatment on secondary cancers in ALL survivors.

Methods: A retrospective cohort of 2,600 children diagnosed with ALL and enrolled on Tokyo Children’s Cancer Study Group (TCCSG) protocols between 1984 and 2003 were observed to determine the incidence of secondary cancers overall and by protocol. Results: Thirty-five patients developed secondary cancers, including brain tumors (n = 14), acute myeloid leukemia (AML) (n = 9), myelodysplastic syndrome (MDS) (n = 5), non-Hodgkin lymphoma (NHL) (n = 1) and other solid tumors (n = 6). The median follow-up duration was 113 months. The cumulative incidence of any secondary cancers was 1.9% at 10 years (95% confidence interval (CI): 0.6–4.6%) and 3.9% at 20 years (95% CI: 2.3–6.3%). The median incubation times to secondary cancers were 33 months for AML/MDS/NHL, 160 months for brain tumors and 182 months for other solid tumors. Females were predominant (11/4 in secondary AML/MDS/NHL. Cumulative incidence rates of brain tumors increased in proportion to the rates of prophyllactic cranial irradiation. Actuarial survival at 10 years from diagnosis of secondary cancers was 43% (AML/MDS/NHL: 14%, brain tumors: 56%, other solid tumors: 83%). There was no statistical difference in secondary cancer incidence between protocols based on the intention to treat analysis (log-rank: p = 0.969).

Conclusion: Follow-up of this large cohort treated with risk-based therapy showed that the incidence of secondary cancers are similar across treatment protocols after diagnosis of childhood ALL.

References

Purpose: To evaluate the potential reduction of risk of late radiation-induced effects for young patients with Hodgkin lymphoma treated with intensity modulated proton therapy (IMPT) as compared to 3D conformal involved-field photon radiotherapy (3D-CRT). The late effects considered were cardiac mortality and secondary cancer in the lungs and breasts (for female patients).

Methods: Patient data were acquired for twenty-two patients (13 male, 9 female; ages 12–29) who were treated with radiotherapy for Hodgkin lymphoma in 2010. The original CT simulation images were used to re-plan the patients with IMPT using commercially-available treatment planning software. The contours of the organs at risk were reviewed for each patient by a single physician and modified for consistency when necessary. The dose for the IMPT plans was calculated using the proton convolution superposition algorithm (version 8.9.0.8, Varian Medical Systems, Palo Alto, CA). The dose-volume data of the 3D-CRT plans and the new IMPT plans were then analyzed to model the risk of late effects. The relative seriality model was used to predict excess risk of cardiac mortality at fifteen years post-irradiation. The organ equivalent dose concept was utilized in conjunction with a modified linear quadratic model to predict the Excess Absolute Risk (EAR) for induction of lung cancer and breast cancer at thirty years post-irradiation.

Results: The mean excess risk of cardiac mortality was 1.0% for 3D-CRT plans and 0.6% for IMPT plans. Mean EAR for lung cancer was 18.7 per 10,000 persons per year (PY) for 3D-CRT plans and 10.7 per 10,000 PY for IMPT plans. Mean EAR for breast cancer was 9.1 per 10,000 PY for 3D-CRT plans and 3.6 per 10,000 PY for IMPT plans.

Conclusion: IMPT may significantly reduce the risks of radiotherapy-induced cardiac mortality and secondary cancer in the lungs and breasts of young patients receiving radiotherapy for Hodgkin lymphoma.

References

O109
ISCHEMIC AND HEMORRHAGIC CEREBROVASCULAR DISEASES FOLLOWING CHILDHOOD CANCER TREATMENT: DOSE RESPONSE WITH BRAIN RADIATION DOSE

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Purpose: To establish the risk factors for ischemic and hemorrhagic cerebrovascular diseases following childhood cancer treatment.

Methods: We followed a cohort of 3,297 2-year childhood cancer survivors treated before 1986 in France and followed 25 years in average, by medical records review and questionnaires. Radiation dose received to various sites in the brain during radiotherapy has been estimated for all patients who received radiotherapy, whatever the site of the cancer, using a specific software.

Results: A total of 48 strokes were validated, 2/3 of them being ischemic. Radiation dose received to the brain, and particularly to the pons of the brain stem was found to be the alone risk factor for the ischemic stroke, the cerebrovascular ones being also related to previous brain surgery for childhood cancer. The dose response for radiation was clearly linear without any quadratic component (p < 0.6), nor negative exponential term for cell killing (p = 0.9). At the age of 40 years, the cumulative incidence of stroke was 13% (95% CI, 8%–20%) among the patients who had received more than 30 Gy to the pons of the brain stem, i.e. more than 25 times the risk in patients who did not received radiotherapy.

Conclusion: Cerebrovascular pathology is not uncommon following radiotherapy for a childhood cancer. This has to be considered in Treatment Planning Systems (TPS). Because of the linear dose-response pattern, our results could also have some implications in public health.

O110
CARDIAC DISEASES FOLLOWING CHILDHOOD CANCER TREATMENT: COHORT STUDY

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Purpose: Cardiac disease is probably one of the major side effects of childhood cancer therapies. Nevertheless, up to now, very little is known about the relationship between the radiation dose received to the heart during radiotherapy for childhood cancer and the risk of cardiac diseases. The objective is to assess the incidence and risk factors for cardiac disease among survivors of childhood cancers.

Methods: A cohort of 3,312 2-year survivors of a solid childhood cancer treated before 1986 was established. The average length of follow-up was 24 years. All cardiac diseases were validated by contacting GP or cardiologist. Information on chemotherapy was collected and radiation dose delivered to the heart (“heart dose”) is defined as the median (D50,median) dose, which is the dose absorbed by 50% of the cardiac volume.

Results: A total of 500 cardiac diseases were reported by patients. Among them, 302 were confirmed in 207 patients. The cumulative incidence of all cardiac diseases at 40 years of age, was 10.8% (95% CI: 9.2–12.6), and 18.0% (95% CI: 14.9–21.6) at 50 years of age. This rate was 5.9% (95% CI: 7.3–4.8) and 9.6% (95% CI: 7.4–12.5) at 40 and 50 years of age, respectively, when only cardiac diseases graded 3 or more were considered as cases. Anthracyclines treatment significantly modified the dose-response effect of the radiotherapy on cardiac diseases (p for interaction < 0.001): among patients treated without anthracyclines the excess relative risk per Gy (ER/Gy) of developing cardiac diseases was 30% (95% CI: 16%–58%), as compared to 4% (95% CI: 1%–10%), among patients treated by anthracyclines.

Conclusion: Survivors of childhood cancer treated with radiotherapy and/or chemotherapy are at substantial risk for cardiac diseases than those who did not receive these therapies. Healthcare professionals must be aware of these risks in the management of patients with history of childhood cancer.

NURSES 5
O112
MENTORING PEDIATRIC ONCOLOGY NURSES IN COUNTRIES WITH LIMITED RESOURCES: A TWO-WAY STREET

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Purpose: Mentoring can be considered as a professional relationship during which an experienced person works with another in “developing specific skills and knowledge to enhance the less-experienced person’s professional and personal growth”. However, for nurses working with children with cancer in countries with limited resources, mentoring by visiting nurses is a unique relationship.

Methods: While nurses from a resource-rich country participating in a twinning project or a one-time nursing training program may have more knowledge of cancer diagnoses, protocol-
driven care and patient/family education models there is much that they can learn from the local nurses. There is no doubt that local nurses mentor visiting nurses in what can be done with the limited resources and severe shortages of staff. The ingenuity of local nurses in countries with limited resources is apparent when visiting nurses witness their nursing care as well as when their nursing experience is shared at international conferences.

Results: For example, strategies to address teenagers’ experiences of cancer treatment in South Africa, parental support with a local coffee ceremony in Ethiopia, and community education about Burkitt lymphoma strategies in Cameroon, help to inform nurses working with children and adolescents with cancer across the globe.

Conclusion: Thus, mentoring of local nurses during a “training” visit is a mutual experience. The local nurses teach the visiting nurses many strategies that can be utilized in their own home countries. This presentation will provide examples of mentoring from both sides of a nursing collaboration and demonstrate the power of international nursing exchange. Supporting nurses from resource-poor countries to attend international conferences, like SIOP Africa, is essential to ensure that nurses from well-resourced medical centers can learn about improving their nursing care while sharing their academic and clinical knowledge.

References

ETHIOPIAN NURSES CARING FOR CHILDREN WITH CANCER AND THEIR FAMILIES: CHALLENGES AND REWARDS
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Purpose: To describe the experience of nurses caring for children with cancer at Black Lion Hospital in Addis Ababa, Ethiopia (the only cancer center in the country).

Methods: Addressing the challenges of caring for children with cancer, the majority of whom arrive with advanced tumors and no financial or social resources. We will describe our strategies of supporting these children and their families who often arrive from rural areas. We will discuss how we cope with the death of the children in our care. We also will present how new nurses are oriented to work on our unit.

Results: When a cure is not possible, we Inform parents about the disease status making them understand that such is so. We offer counseling and comfort to the parents and inform them that a decision to send them home, with supportive care such as analgesia, has been made (there are no hospices for children). Nurses on the unit are emotionally attached with the kids being managed there. Some have been receiving their treatment for years and when they pass away the pain and agony is too much. The passing of a child on the unit is very traumatic to the nurses. Nurses feel as if they have lost one of their own and often try to console parents/caregivers. Ethiopian nurses work in very challenging and demanding environment (limited/no medicines, and very expensive oncology meds, limited analgesia). We have a double burden of communicable and non-communicable disease on our ward. We have no/limited structured mentorship program as well as a knowledge gap: treatment protocols, meds.

Conclusion: We still lack many skills, however, after we began participating in the Twinning program with nurses from the Georgetown University/INCTR project, the nurses on the floor in the pediatric ward have become more knowledgeable and skilled in their care of children with cancer.

IMPROVING THE QUALITY OF PEDIATRIC ONCOLOGY NURSING CARE IN GUATEMALA
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Purpose: When the International Outreach Program (IOP) at St Jude Children’s Research Hospital first began to establish partner sites in low-income countries, a lack of nurses with pediatric oncology skills was a major impediment to the implementation of quality care. A comprehensive nursing program was developed to promote the quality nursing care, and in this study we evaluate the program’s impact on 20 selected Joint Commission International (JCI) quality standards at the National Pediatric Oncology Unit in Guatemala. JCI standards were developed to assess public hospitals in low-income countries and are recognized as the gold standard of international quality evaluation.

Methods: We compared the number of JCI standards met before and after the nursing program was implemented using the following evaluations: direct observation of nursing care; review of medical records, policies, procedures, and job descriptions; interviews with nursing, medical and administrative staff; and a nursing survey.

Results: In 2006, only 1 of the 20 standards was met fully, 2 partially, and 17 not met. In 2009, 16 were met fully, 1 partially, and 3 not met. Standards not met were related to documentation of patient education and implementation of nursing care plans.

Conclusion: Several factors contributed to the improvement in the number of quality standards met. The program quality evaluation provided objective and credible findings and an organizational framework for implementing change. The evaluation promoted a focused approach to specific areas that needed improvement: nursing education and clinical skills, patient education, assessment, and continuity of care, as well as medication administration; and pain management. The medical, administrative, and nursing staff worked together as a team to improve nursing standards and met 16 of 20. Programs have been developed to document patient education and implement nursing care plans to fully meet the remaining 4 standards.

PROVISION OF TWO FULL TIME DEDICATED PEDIATRIC ONCOLOGY (PO) NURSES MAKES A BIG DIFFERENCE: EXPERIENCE FROM A PEDIATRIC CANCER CARE UNIT (PCU) IN A DEVELOPING COUNTRY, B. J. WADA CHILDREN HOSPITAL, INDIA
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Purpose: PCU’s require dedicated nurses to deliver optimum care. In developing countries the lack of availability of trained nurses in PO results in deficient services, recognizing this lacuna we appointed two full time PO nurses at our PCU at B J Wadia Hospital For Children in 2010. This study assesses the impact of this measure after 2 years.

Methods: Prior to 2010 only one PO nurse was working at our PCU. 2 additional PO nurses were appointed since June 2010. Their responsibilities include; managing day care services; preparation & administration of chemotherapy; indoor patient management; hygiene & nutritional counseling of patients & children, motivation of children & parents to follow up. The impact of their presence was assessed at the end of 2 years from departmental statistics & parent feedback.

Results: In our settings, parents often express inability of treatment decision making, continuing the treatment and follow up due to lack of awareness and education. Hence, there is need for parents to be provided with constant clear information and guidance. PO nurse act as aids, advocates, easy to approach. Anxiety and depression in parents and children dramatically comes down by additional intervention of pediatric oncology nurses with their Inter Personal Relation skills & advocates. These facts were confirmed by parents feedback. The department statistics revealed a decrease in infection rates during chemotherapy from 20%, & the dropped rate dramatically dropped from 60% to less than 20% in 2012.

Conclusion: Dedication in rendering a comprehensive patient care comes with support and harmony with additional helping hands and team work assuring great satisfaction to the parents & families, also to the care providers. The infection & dropout rate improved dramatically with this simple intervention. We recommend provision of dedicated PO nurses in all PCUs in developing countries to provide optimum services.

References
Statistical record from PCU at B J Wadia Hospital for Children.

THE NURSE PRACTITIONER IN A MISSION HOSPITAL IN CAMEROON: KEY ROLE OF PROVIDING CANCER TREATMENT TO CHILDREN
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Purpose: A lack of trained doctors in our hospital has created the opportunity for trained nurses to successfully apply standardized treatment protocols for children with Burkitt lymphoma (BL). Banzo Baptist Hospital has 48 paediatric medical and surgical beds, including a separate 11 bed Burkitt ward.

Methods: I joined was developing an as RN it when it started in 2003, with the responsibility to counsel parents, provide nursing care, maintain patient records and arrange follow-up of BL patients. I trained as a screener in 2006, and worked in a large health clinic for 3 years. In 2010, I completed a nurse practitioner course. In 2011, I was appointed in charge of the pediatric ward (including the BL ward). I have assessing all children identified as possible BL, arrange (and often do) initial investigations including a fine needle aspirate, lumbar puncture and bone marrow aspirate, commence and administer chemotherapy, assess the response, and the need for intensified consolidation treatment as per protocol.
Results: I teach and train nurses and new young doctors, and report to the hospital's chief medical officer. I promote parents, advocacy and the development of parent support groups. I am assisted by a dedicated registered nurse (M.G.), obtain guidance from a resident internist (G.S.) and training and internet support (P.H. and P.W.). Our BL program has assisted by a dedicated registered research nurse (M.G.), obtain guidance from a resident medical officer. I promote parents, advocacy and the development of parent support groups. I

SETTING UP A BONE MARROW TRANSPLANT UNIT FOR CHILDREN WITH THALASSEMAIA MAY FACILITATE PEDIATRIC CANCER CARE

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Purpose: We will describe two transplant units for thalassemia major (TM) and the nursing experience. At least 100,000 children a year are diagnosed with TM worldwide. Although transplant appear complex for limited resource countries, it is easier to prepare nurses for specific TM transplant care than for general pediatric oncology. Bone marrow transplant (BMT) for low-risk young TM patients with a compatible sibling is medically, ethically and financially reasonable in hemoglobinopathy common countries. In many countries with limited resources, TM is more frequent than pediatric cancer. Children with thalassemia are generally in good health at BMT and nursing care is relatively straightforward; for example mucositis isn’t severe and nutritional issues are minimal. Transplant-related complications are low, neutropenia is short (7–10 days), only a three-drug chemotherapy course is required and follow-up is few months. This BMT approach requires fewer nurses than oncology units and the nursing education is quite focused. Parent motivation is key to BMT represents the only care for TM, and the end to the continuous financial burden of TM treatments, which can consume the majority of the family’s income (up to $3000/year). Thus, parents have a strong partnership with the healthcare team for the entire treatment process, which is considerably shorter than for a child with leukemia.

Methods: Our nursing role focuses on affording both technical and educative support, in addition to monitoring follow up in the patient’s home country.

Results: We succeeded to establish a BMT unit in Islamabad, Pakistan opened in 2009, and another one in Jaipur, India in 2012. This has demonstrated that transplantation is possible in a country with limited resources and nurses can be successfully trained in a relatively short period of time.

Conclusion: Our hope that this model will open the door for the potential to add pediatric oncology as a transplant option in these countries.

PSYCHOSOCIAL

O118

ANXIETY AND DEPRESSION IN FATHERS AND MOTHERS OF CHILDREN WITH A LIFE-THREATENING OR A CHRONIC DISEASE

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Purpose: We aimed to determine the levels of anxiety and depression in parents of children with a life-threatening or chronic disease compared to a reference group and to study which parental and child characteristics are associated with parental anxiety and depression.

Methods: Parents with a child with cancer or a chronically ill child (0–18 years) were eligible and informed with announcements or actively approached at the outpatient clinics of the Emma Children’s Hospital and VU medical centre. After providing their email-address, parents received a login to complete online questionnaires. Anxiety and depression was assessed with the HADS (Hospital Anxiety and Depression Scale). Scores were compared to parental and child variables were associated with parental anxiety and depression.

Results: n = 689 parents participated, with n = 72 from oncology. Fathers’ anxiety scores were comparable to the norm. However, fathers of the ill children showed significantly more feelings of depression than fathers in the reference group (p < 0.05). Mothers had significantly higher scores (p < .0001) on both anxiety and depression. The amount of mothers in the clinical range of anxiety (31.8% vs 20.7%) and depression (23.0% vs 12.0%) was also significantly higher. Highest scores were reported by parents of children with cancer and end-stage renal disease. Problems in the practical domain and parenting stress showed the strongest association with anxiety and depression.

Conclusion: Mothers reported seriously high levels of anxiety and depression. Disease related characteristics of the child did not predict parental anxiety and depression. Parenting stress and problems in the practical domain showed the strongest association with anxiety and depression. Structural attention and supportive care by health care specialists is necessary.

UTILITY OF PARENTAL INTAKE FORMS TO IDENTIFY CHILDHOOD CANCER SURVIVORS WITH BEHAVIORAL ADJUSTMENT PROBLEMS

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Purpose: Screening is widely advocated as a means of identifying pediatric cancer survivors with behavioral problems, but little research has been done to identify practical and valid screening measures. In this study, parental report on a five-item intake form (IF) was compared with parental report on the Brief Pediatric Symptom Checklist-17 (BPSC), to assess utility and accuracy of the IF.

Methods: Parents of 118 pediatric cancer survivors (ages 6–17) completed the IF and the BPSC-17 at a survivorship clinic and their visit records were reviewed. The IF inquires about emotional, behavioral, attention, school and ‘other’ problems, asking parents to report no/mild/moderate or severe problems for each item. The BPSC inquires about internalizing, attention and externalizing symptoms, with significant elevations defined using published norms.

Results: Parents reported 53 (44.9%) survivors had no problems on the IF. Of these 53, none reported serious symptoms on the BPSC, and only 3 (5.8%) endorsed moderate elevations. For the 65 parents reporting symptoms on the IF, 14 (23.7%) reported moderate BPSC elevations, and 10 (16.9%) reported significant elevations. Even children whose parents reported “minor” problems on the IF were at risk for having moderate (28.1%) or significant problems (3.1%) on the BPSC, indicating that any report of problems on the IF requires additional assessment.

Conclusion: Parental report on the IF accurately identified non-symptomatic child and adolescent cancer survivors. As a brief measure that can identify survivors without significant adjustment problems, the IF is of particular value as it can be readily integrated into routine medical intake forms, and permit limited psychosocial resources to be focused on survivors at elevated risk. Results support a two-step screening process using the IF for all survivors and additional rating scales for those screening positive on the IF.

RELATIONSHIP BETWEEN PARENT-REPORTED COGNITION AND QUALITY OF LIFE REPORTED BY PEDIATRIC ONCOLOGY PATIENTS

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Purpose: Parent-reported cognition (PCF) is used as a reference for clinicians to refer children for further cognitive testing. In a previous study on children with neurological conditions, three clusters were identified; children with (1) severe fatigue, depression & PCF, (2) mild fatigue, depression & PCF, and (3) severe PCF but mild fatigue & depression. The current study examined whether similar clusters exist in children with cancer and their relationship to quality of life (QOL).

Methods: 565 oncology patients (53% brain tumor, BT; 47% non-BT) aged 7–21 (mean = 14 yrs; 56% males) and their parents were recruited. 34% received radiation therapy, 72% chemotherapy, 71% surgery. Mean years since diagnosis = 5.7. PCF was measured using a validated 43-item pediatric PCF item bank (pedPCF). Patients completed neuropsychological tests (NPT;CogState), NeuroQOL Depression, PedsQL Fatigue and Generic Core which produces physical (PF), emotion (EM), social (SOC) and school function (SCH) scores. K-Means clustering was used to group patients based on depression, fatigue and pedPCF. Correlations were used to examine associations within clusters.

Results: PedsPCF significantly (p < .001) correlated with pedQL, r = 0.19, 0.26, 0.34 SCH, respectively. Three clusters were identified: 1) average depression but slightly elevated fatigue; 2) slightly elevated PCF complaints and even further elevated fatigue and depression scores. Cluster membership was significantly related to Karnofsky, treatment, parent education, classroom type, age, and gender. Within clusters, PedsPCF was significantly correlated with: cluster-1: depression & fatigue; cluster-2: NPT scores in non-BT patients; cluster-3: NPT in BT patients. Within clusters, BT and non-BT QOL scores did not significantly differ, with the exception of SOC (cluster 1).

Conclusion: Multiple factors were associated with PCF, including QOL. Results suggest it also measured cognition to some extent. Further studies to explore clinical implications are warranted.

PEDIATRIC RESEARCH PARTICIPATION QUESTIONNAIRE FOR AYA WITH CANCER

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Pediaitr Blood Cancer DOI 10.1002/plbc
1002 SIOP ABSTRACTS

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Purpose: The mortality reduction rate for adolescents and young adults (AYA) with cancer has remained unchanged compared to impressive gains for children and adults. This disparity is partly due to insufficient clinical trial enrollment. A measure of perceived barriers and benefits to enrollment is needed to better understand this problem. This study describes the development of an AYA oncology version of the Pediatric Research Participation Questionnaire (PRPQ), a validated measure assessing perceived barriers and benefits to clinical trial enrollment for children with chronic health conditions and their caregivers.

Methods: Participants were AYA (15–29 years) diagnosed with cancer and offered a Phase III clinical trial within the last 2 years. Medical providers were also interviewed. Interview scripts assessed the participants’ a) interpretation of the PRPQ questions, b) perceived relevance of questions to their decision-making context, c) opinion on whether questions should be retained or removed, and d) suggestions for modifying wording.

Results: Eleven providers, 16 caregivers, and 12 AYA were interviewed. Feedback resulted in adding 3 questions (e.g. “Researchers communicated clearly during the family diagnostic meeting”), removing 7 questions referencing other psychosocial studies or religion (e.g. “The trial does not meet my child’s medical or psychosocial needs”), and tailoring the wording of 10 items (e.g. “The healthcare team will view my child only as a “guinea pig” if we enroll”). The original and revised measures will be presented along with qualitative data supporting modifications made.

Conclusion: Findings suggest the PRPQ is relevant for systematically evaluating decision-making of AYA with cancer and their caregivers. The measure will be further refined and validated via think-aloud interviews and the evaluation of psychometrics. Once established, we enroll.”

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O122 INFORMATION NEEDS IN CHILDHOOD CANCER SURVIVORS: WHAT THEY GOT AND WHAT THEY WANT

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Purpose: Knowledge about cancer, treatment, follow-up and risk for late effects is important, as it allows childhood cancer survivors making thoughtful and precautionary health decisions. We aimed to assess: (1) the information survivors reported to have ever received from a doctor on: illness, treatment, follow-up and late effects; (2) their rating of the importance of information on these 4 topics; and (3) what information survivors desired to have today, and in what form.

Methods: As part of the Swiss Childhood Cancer Follow-up Study (CCFSU) we sent a questionnaire to all survivors (>18 years) who previously participated in the Swiss Childhood Cancer Survivor Study (SCCSS) and who were diagnosed after 1998 at an age of <16 years. [1] We included questions on the information the survivors had ever received from a doctor/nurse, and how they received it, asked them to rate the importance of information (1 = very important to 3 = not important), and assessed what information survivors would like to have today, and in what form.

Results: We included 286 survivors (response rate: 40%, study on-going; 44% males, 56% females; mean age at study = 23.8 years, range: 18–36; mean time since diagnosis = 15.2 years, range: 6.7–22.8). Most survivors had received only oral information (on illness: oral: 84%; written: 39%, none: 8%; on treatment: oral: 81%, written: 36%, none: 12%; on follow-up: oral: 78%, written: 24%, none: 12%; on late effects: oral: 70%, written: 14%, none: 26%). Younger patients received written information more often. There was no major difference by gender, diagnosis, treatment and education. More than 90% of survivors rated information in above topics as rather or very important. Only 14% of survivors did not wish to receive any information. On the contrary, 39% of survivors would like to have personalised written information on these topics (general written: 27%; oral: 28%; online: 13%).

Conclusion: There is a need to provide written information to survivors early after treatment and to continue with information long into adulthood.

References

O123 FOLLOW-UP CARE OF ADOLESCENT CANCER SURVIVORS: THE ROLE OF HEALTH-BELIEFS

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Purpose: Regular follow-up is necessary for many childhood cancer survivors to detect and prevent late effects. Previous studies have shown that only a small proportion of adult survivors attend follow-up regularly and that health beliefs might play a major role.[1] In this study we aimed to describe 1) the proportion of adolescent survivors of childhood cancer attending follow-up, and 2) identify factors associated with attendance in adolescent survivors, especially health beliefs, socio-demographic and illness factors.

Methods: For the Swiss Childhood Cancer Follow-up Study (SCCSS) we sent questionnaires to adolescents (age: 16–21 years at study) who had been diagnosed with cancer between 1976 and 2005 and survived for more than five years. We assessed follow-up attendance, and health-beliefs (perceived susceptibility, severity, benefits and barriers). Medical and demographic information was extracted from the Swiss Childhood Cancer Register.[3]

Results: With a response rate of 59%, we received replies from 410 survivors (males 55%, females 44%). Overall, 229 (56%) reported to attend follow-up (48% at a cancer centre, 8% at a general practitioner). In a multivariable logistic regression adjusting for clinical and demographic information health-beliefs were significantly associated with follow-up attendance. Odds ratios (OR) were 1.63 (95% CI: 1.11–2.38, p = 0.015) for perceived barriers (“follow-up helps detecting and preventing late effects”) and 0.70 (95% CI: 0.49–1.00, p = 0.005) for perceived barriers (“follow-up is not necessary”). Among medical characteristics, patients diagnosed recently (< p = 0.001) and those treated with bone marrow transplantation (OR: 18.61; 95% CI: 2.17–159.64, p < 0.001) were more likely to attend follow-up.

Conclusion: Only around half of adolescent survivors in Switzerland still attend follow-up at a cancer centre. Our findings suggest that health beliefs might have a major influence on follow-up attendance. Information on the importance, effectiveness, and necessity of long-term follow-up should be given to all patients at the conclusion of their therapy.

References

BRAIN TUMOURS 3

O124 NESTIN PROTEIN EXPRESSION DISCRIMINATES WHO I EPENDYMOMA WITH POOR OUTCOME

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Purpose: Ependymomas are common brain tumors in children and adults and can arise throughout the CNS. Ependymomas are classified into grade I-III according to the current WHO classification. However, it is recognized that the difference between grade II and III is virtually arbitrary in daily practice, and thus may contribute to imprecise risk stratification. Therefore, prognostic markers enabling more precise stratification that can be routinely used are urgently needed.

Methods: We have examined nestin expression in a large cohort of 379 ependymoma primary tumors.

Results: High protein expression of nestin, as assessed by immunohistochemistry, is associated with poor prognosis. Most importantly, nestin separates grade II ependymomas with the same poor prognosis as grade III anaplastic ependymomas. Additional information is gained when combining nestin IHC with classifications according to cytogenetic groups 1–3, and/or adding 3 questions (e.g. ”Researchers communicated clearly during the family diagnostic meeting”), removing 7 questions referencing other psychosocial studies or religion (e.g. ”The trial does not meet my child’s medical or psychosocial needs”), and tailoring the wording of 10 items (e.g. ”The healthcare team will view my child only as a “guinea pig” if we enroll”). The original and revised measures will be presented along with qualitative data supporting modifications made.

Conclusion: Findings suggest the PRPQ is relevant for systematically evaluating decision-making of AYA with cancer and their caregivers. The measure will be further refined and validated via think-aloud interviews and the evaluation of psychometrics. Once established, we enroll.”

References

O125 THE NOVEL HUMAN HIGH-RISK EPENDYMOMA STEM CELL MODEL DKFZ-EPINS REVEALS THE DIFFERENTIATION-INDUCING POTENTIAL OF TREATMENT WITH THE HISTONE DEACETYLASE INHIBITOR VORINOSTAT

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Purpose: To identify the potential of histone deacetylase (HDAC) inhibitors for the treatment of ependymoma.

Methods: Human epidermal stem cells were treated with different HDAC inhibitors, and subjected to functional and molecular analyses.

Results: Treatment of ependymoma stem cells with the HDAC inhibitor Vorinostat led to a significant induction of differentiation markers and a decrease in proliferation. Furthermore, the expression of nestin, a differentiation marker for ependymoma stem cells, was significantly reduced.

Conclusion: Our findings suggest that HDAC inhibitors, such as Vorinostat, have potential for the treatment of ependymoma.
**SIOP ABSTRACTS**

**Till Milde**, 2 Susanne Kleber, 2 Andrey Korschunov, 6 Hendrik Witt, 2, Thomas Hiebelsch, 2 Philipp Koch, 2 Hans-Georg Kopp, 2 Manfred Jagdolf, 2, Hedwig E. De Bruere, 2 Ina Ordem, 2 Marco Lodris, 2 Hermann-Josef Grönn, 2, Axel Benner, 3 Oliver Brustle, 4 Andreas von Driman, 2 Andreas E Kulosek, 2, Stefan M Pfister, 1, Ana Martin-Villalba, 1 Olaf Witt, 1

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**Purpose:** Curative therapy of ependymomas remains a challenge, especially when incompletely resected, despite intensive radio- and chemotherapy. The development of novel treatments has been hampered by the lack of appropriate preclinical models.

**Methods:** We here report on the generation of a novel high risk cytogenetic group 3 and molecular group C ependymoma model (DKEZ-EPI-NS), which is based on primary ependymoma cells obtained from a patient with metastatic supratentorial ependymoma.

**Results:** The model displays stem cell features like self renewal capacity, differentiation capacity and specific marker expression. A high tumorigenic potential was seen in vivo, and xenograftsotypically recapitulated the original tumor in a niche dependent manner. Serial transplantation of DKEZ-EPI-NS cells from orthotopic xenografts is shown, and a shift from a neural stem cell-like program towards a profile of primary ependymoma tumor upon in vivo transplantation was seen in gene expression profiling. The EPI-NS cells were resistant to temozolomide, vincristine and cisplatin, but responded well to histone deacetylase inhibitor (HDACi)-treatment in therapeutically achievable concentrations. Loss of stem cell marker expression and incompletely resected, despite intensive radio- and chemotherapy. The development of novel treatments has been hampered by the lack of appropriate preclinical models. 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Purpose: After a previous trial with nimotuzumab/radiation and continuing for a total of 37 patients from 2006 to 2009 according to this new combination, we obtained a median DFS of 4.8 years, being shortest for hematological malignancies (2.9 years) and longest for solid tumors (7.9 years). The median time interval to SMN diagnosis was 4.0 years with a male:female ratio of 1.2. Eighty-four patients (1.3%) developed a total of 87 SMNs after five years. Median time to development of SMN was 13 months and a median OS of 11 months, i.e. consistent with best literature data and those of the new combination. Patients from 2006 to 2009 according to this new combination, we obtained a median PFS of 70 months and a median OS of 12 years, i.e. consistent with best literature data and those of the new combination.

Methods: Vinorelbine was adopted at a dose of 20 mg/sqm/weekly together with nimotuzumab at the standard dose of 150 mg/sqm during the 6 weeks when radiotherapy was delivered and 25% daily in any other week, with the same dose of nimotuzumab during the consolidation courses, planned until tumor progression or for a total of 2 years.

Results: From August 2009, we have treated 20 children, 12 males and 8 females, age range of 2–17 years (median 7), enrolled according to the standard MRI inclusion criteria. After a follow-up of 14 months, 12/20 were alive, their PFS/OS at 12 months were 32%/81%, respectively; OS at two years was 28%. According to MRI, 12 had PR, 5 SD with 100% symptom amelioration, 1 early PD and 2 local PR but spinal dissemination. The nimotuzumab/vinorelbine combination was very well tolerated, with no acute side-effects.

Conclusion: This combination has promise, with significant differences with previous institutional and literature reported experiences.

References

ACUTE LYMPHOBLASTIC LEUKAEMIA 2

O130

RISK OF SECONDARY MALIGNANT NEOPLASMS IN SURVIVORS OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKAEMIA

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Purpose: With current therapy, survival of childhood acute lymphoblastic leukemia (ALL) has improved dramatically with cure rates of 80–85% for standard risk patients. Survivors of childhood cancer are now known to have an increased risk of secondary malignancy neoplasms (SMNs). The purpose of this study was to evaluate risk and characteristics of secondary neoplasms in survivors of childhood ALL.

Methods: We investigated the occurrence of SMNs in survivors of childhood ALL using the surveillance, epidemiology, and end results (SEER) database. A total of 6,656 patients diagnosed between the ages of 0–18 years that survived at least 5 years were included for analysis.

Results: Median follow-up was 11 years (range 5–36 years). Median age at leukemia diagnosis was 4.0 years with a male:female ratio of 1:2. Eighty-four patients (1.3%) developed a total of 87 SMNs after five years. Median time to development of SMN was 13 years (range 5–35 years). Median age at diagnosis of a secondary tumor was 21 years. Male:female ratio of patients diagnosed with a SMN was 0.85. Secondary neoplasms consisted of 19 malignant brain tumors, 16 thyroid cancers, 10 cases of myelogenous leukemia or myelodysplastic syndrome, 10 sarcomas, 7 salivary gland tumors and 25 others. Median survival after development of secondary malignancy was 33 months. Risk of a SMN for all patients was 1.3%. The cumulative incidence of a secondary malignant neoplasm at 30 years was 3.2%. The risk of secondary malignancy did not increase with the use of radiotherapy (1.7% vs. 1.2%, p = 0.23, cumulative incidence at 30 years 2.9% versus 3.7%, p = 0.72).

Conclusion: Although the risk of secondary malignancies is low in long term survivors of ALL, our study underscores the importance of long term follow of those patients and continued monitoring for development of secondary malignancies. Our data show an increased risk with time that does not seem to plateau.

O131

SECOND NEOPLASMS AFTER TREATMENT OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKAEMIA

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Methods: During the first part of consolidation 353 newly diagnosed ImRG patients were randomly allocated to the LDMTX/30 mg/m²/weekly or to the HD-MTX (2000 mg/m²/weekly). The HD-MTX patients received only 2.5x7.6 MP during this first part of consolidation and the LDMTX patients received additional ITT as the HDMTX patients. After recruitment from May 2002 to December 2007 (37 Russian and Belarusian centres), the 5.9 years median follow-up data were analyzed.

Results: EFS was slightly, but not significantly higher for patients, randomised to the LDMTX (79% ± 3% vs. 75% ± 3%; p = 0.21). Benefits of HDMTX in any patients subgroup, including T-ALL patients and patients with initial leukocyte counts more than 10^9/µL, was not shown. The rate of the remission deaths was higher in the HDMTX arm (11.6% vs. 8.4%), p = 0.54 and OS was significantly higher in HDMTX patients (87% ± 3% vs. 79% ± 3%; p = 0.05). Rate of isolated CNS relapses was lower in the HDMTX arm (1.75% ± 0.88% vs. 4.98% ± 1.2%; p = 0.09). If only HDMTX patients without increasing intervals between administrations included in the analysis, also no differences in survival rate and any advantage of HD-MTX were revealed.

Conclusion: In MB 2002 study high dose methotrexate did not result in significant reduction of relapse or survival improvement as compared to low dose MTX. However, mercaptopurine for maintenance therapy during the first consolidation with 2000 mg/m²MTX was only without increasing intervals between administrations included in the analysis, also no differences in survival rate and any advantage of HD-MTX were revealed.

O133

OUTCOME OF CHILDREN TREATED FOR RELAPSED ACUTE LYMPHOBLASTIC LEUKEMIA IN CENTRAL AMERICA

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Purpose: Outcomes for relapsed childhood acute lymphoblastic leukemia (ALL) are uncertain in resource-limited settings. We examined survival for relapsed ALL in Central America.

Methods: We performed a retrospective cohort study and included children with ALL diagnosed with relapsed ALL in Guatemala, Honduras and El Salvador between 1990 and 2011, generally treated according to common protocols. Event-free survival (EFS) and overall survival (OS) were described using the Kaplan-Meier method. Predictors of EFS and OS were analyzed with the Cox proportional hazard model. Events censored for EFS included death, relapse, refractory disease, and abandonment. Data were collected from the POND online database.

Results: There were 755 children identified with relapsed disease. Median time to relapse from original diagnosis was 1.66 (0.8–3.1) years, most occurring during (53.9%) or following (24.9%) maintenance chemotherapy. Most relapses were in the bone marrow (63.1%). Following the initial relapse, subsequent EFS was 21.9 ± 1.7%, and OS was 28.2 ± 1.9% at three years. In multivariable analysis, better post-relapse survival was associated with age <10 years, white blood cell count < 50 × 10^9/L, initial central nervous system status 1 or 2, extramedullary relapse and relapse after 18 months of therapy, or following abandonment. These predictors were used to identify risk groups, with a 3-year EFS and OS of 41 ± 7.6% and 54.2 ± 7.7% favoring the favorable, and 7.1 ± 2.7% and 11.7 ± 2.7% among the unfavorable groups respectively.

Conclusion: Prognosis after relapsed ALL in Central America is poor although some children do survive. Predictors of subsequent outcome can be used to help guide therapeutic decision-making following relapsed ALL. Future studies should evaluate treatments received and quality of life, to gain more insight into optimal treatments of relapsed ALL in this setting.

O134

FREQUENCIES AND PROGNOSTIC IMPACT OF RAS MUTATIONS IN MLL-REARRANGED ACUTE LYMPHOBLASTIC LEUKEMIA IN INFANTS

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Purpose: Acute lymphoblastic leukemia (ALL) in infants represents an aggressive malignancy associated with a high incidence (~80%) of MLL translocations like t(4;11) generating MLL–AF4 fusion proteins. Recent attempts to mimic MLL fusion-driven leukemogenesis in mice raised the question whether or not these MLL fusions require secondary hits to induce leukemia. Based on previous reports, RAS mutations may represent likely candidates, but results are inconclusive and contradicting on the incidence of these mutations in MLL-rearranged ALL. Therefore, we studied RAS mutations in infant ALL patiences.

Methods: Using PCR and sequence analysis we screened a large cohort (> 100) samples of infant ALL cases for the presence of RAS mutations, and linked our results to known clinical parameters, prognostic factors, and clinical outcome.

Results: RAS mutations were detected in ~14% of all cases tested, with a significantly higher frequency of ~24% in t(4;11)-positive patients (p = 0.04). Furthermore, we identified the presence of a RAS mutation as an independent predictor (p = 0.019) for poor outcome in MLL-rearranged infant ALL, with a hazard ratio of 3.194 (95% confidence interval: 1.211–8.429). Also, RAS-mutated patients appeared to have significant higher white blood cell counts at diagnosis (p = 0.013), and are significantly more resistant to glucocorticoids in vitro (p < 0.05). Finally, we demonstrate that RAS mutations, but not the lack of HOXA9 expression nor the expression of AF4–MLL are associated with poor outcome in t(4;11)- rearranged infant ALL.

Conclusion: We conclude that RAS mutations represent genuine secondary hits in MLL- rearranged infant ALL and are an independent predictor for clinical poor outcome in this unfavorable type of childhood leukemia. Moreover, we propose future risk-stratification based on abnormal RAS-pathway activation and that RAS-mutated infants could benefit from additional treatment with RAS-pathway inhibitors.

O135

OUTCOME OF ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) PATIENTS WITH MLL GENE REARRANGEMENTS (MLLR) TREATED ON CONTEMPORARY CHILDREN’S ONCOLOGY GROUP (COG) PROTOCOLS

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Purpose: While outcomes for infants with MLLs ALL remain poor, the outcome for older children with MLLs ALL is not well established. We assessed outcome of patients > 1 year old with newly diagnosed MLLs ALL who enrolled on COG Standard Risk (SR) and High Risk (HR) trials AALL0331/AALL0232 between 2004 and 2011.

Methods: After excluding patients with BCR/ABL or hypodiploidy from this analysis, 155/695 (22.2%) had MLLs ALL detected by FISH, including 103/2407 (4.3%) with HR and 52/4511 (1.1%) with SR ALL. 108/153 (70.6%) of MLLs patients were rapid early responders (RER), M1 bone marrow (BM) morphology by day 15 and BM minimal residual disease (MRD) burden <0.1% measured by flow cytometry on day 29 and received augmented BFM therapy with HR patients eligible for a steroid randomization during induction and a methotrexate (MTX) randomization during the first interim maintenance phase. The remaining SR patients (45/153, 29.4%) were removed from protocol therapy at early induction but contributed to this analysis.

Results: Overall, SR and HR MLLs patients had inferior outcomes compared to those without MLLs with 5-year event-free survival (EFS) 77.7% (SE 0.07) versus 86.0% (SE 0.01) (p < 0.0001). MLLs patients were more likely to be MRD positive (>0.1%) at day 29 (25.5% versus 11.1%, p < 0.0001). Overall differences in EFS for RER vs. SR MLLs patients trended towards statistical significance (p = 0.052) and were significant amongst HR patients (SER: 56.3% (SE 0.21) vs RER: 79.1% (SE 0.10); p = 0.026). However, multivariable analysis revealed that MLLs was not an independent predictor of outcome when modeled with MRD age, white blood cell count, or sex.

Conclusion: ALL patients > 1 year old with MLLs have inferior outcomes compared to those without, but these outcomes are better than anticipated, particularly for the 70% with RER to induction therapy.

NEW DRUGS/EXPERIMENTAL THERAPEUTICS

O136

TYROSINE KINASE INHIBITOR SCREEN OF B – CELL PRECURSOR ALL IDENTIFIES THE MULTIKINASE INHIBITOR, DOVITINIB, AS A CANDIDATE FOR THE SENSITISATION OF TREATMENT-RESISTANT TUMOURS TO CORE CHEMOTHERAPIES

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Pediatr Blood Cancer DOI 10.1002/pbc
Purpose: Deregulation of tyrosine kinases (TKs) has been implicated in high risk non-Philadelphia chromosome positive ALL. This project investigated the role of TK inhibitors (TKIs) in childhood ALL.

Methods: We screened 5 pre-B ALL cell lines and a panel of 20 primary samples, representative of common biological features for sensitivity to a library of 33 TKIs. Active compounds were defined as reducing cell viability > 50% at 1 μM with a concomitant dose-dependent reduction at 10 μM.

Results: Significant heterogeneity in sensitivity was observed in the panel of leukemia cells. No correlation was evident between response to TKIs and current clinical or biological stratification parameters in the primary cell panel. In both cell lines and primary cells, 3 categories of TKIs were most effective: (i) the FLT3/PDGFR/VEGFR multikinase inhibitors (vargatel, lestaurtinib, dovitinib, foretinib), (ii) the irreversible pan - EGFR quinazoline inhibitors (carnertinib, afatinib) and (iii) dual Met/ALK inhibitors (NVPPA568, crizotinib). As observed in previous studies, the expression of a putative target at mRNA level did not predict or directly correlate with the response to a TKI. Based on our preliminary screen, the multitkine inhibitor dovitinib was selected as one of several promising candidates for further pre-clinical testing. Dovitinib inhibited leukemica proliferation with IC50 in the nanomolar range (0.19–0.84 μM) in cell lines. Cell cycle analysis revealed dovitinib induced cytostasis and cell death in the cell lines. PARP protein cleavage confirmed that the mechanism of cell death was by apoptosis. Co-incubation with dovitinib sensitised ALL cell lines to dexamethasone and doxorubicin, with predominantly synergistic drug interactions.

Conclusion: Overall these data support further exploration of TKIs as potential therapeutic agents in childhood ALL. We are currently investigating the direct anti-leukemia activity of dovitinib in childhood ALL in vivo using our NOG mouse primograft model for ALL.

O137

INHIBITION OF MCL1 AND GLYCOLYSIS SYNERGISTICALLY SENSITIZES TO PREDNISOLONE IN PEDIATRIC ACUTE LYMPHOBластIC LEUKEMIA

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Purpose: Prednisolone resistance is a poor prognostic factor of pediatric precursor B acute lymphoblastic leukemia (ALL). Recently, we demonstrated that knockdown of the anti-apoptotic gene MCL1 sensitised leukemic cell lines to prednisolone. We also observed that the glycolytic inhibitor 2-deoxyglucose (2-DG) had the same effect. Because glycolytic and apoptotic pathways are related survival pathways, we investigated a possible synergistic mechanism of MCL1 and glycolysis in prednisolone resistance. We also tested a newly developed locked nucleic acid against MCL1 (MCL1-LNA).

Methods: Pediatric ALL patients’ cells were treated in vitro with prednisolone and MCL1 levels were determined by RPPA. MCL1 knockdown by lentiviral shMCL1 and MCL1-LNAs was assessed with qRT-PCR and Western blot. Cell viability and cell count were analyzed by MACSQuant. Glucose consumption was measured using a glucose assay kit. Prednisolone-induced toxicity was determined by an MTT assay. Mann-Whitney U-tests were performed in SPSS.

Results: Prednisolone decreased MCL1 protein expression in prednisolone-sensitive ALL patients’ cells but not in prednisolone-resistant cells (p < 0.05). 2-DG treatment increased apoptosis by 1.4–4.7-fold (p < 0.05) and decreased MCL1 protein expression by 1.8 to 8.08-fold (p < 0.05). Interestingly, MCL1 knockdown stimulated glucose consumption by 1.1–2.5-fold (p < 0.05), indicating that MCL1-silenced cells upregulate glycolysis to enable survival. Indeed, inhibition of glycolysis by 2-DG reduced proliferation of MCL1-silenced cells by 1.3 to 3.9-fold (p < 0.05). Moreover, silencing of MCL1 and inhibition of glycolysis synergistically sensitized leukemic cells to prednisolone by at most 34.8 +/− 24.5%.

Conclusion: MCL1 is a potent target to therapeutically convert prednisolone resistance in pediatric ALL. However, MCL1 silenced cells upregulate glycolysis to prevent prednisolone induced apoptosis. Inhibiting MCL1 and glycolysis synergistically induces prednisolone sensitivity in pediatric ALL.

O138

THERAPEUTIC MONOCLONAL ANTIBODIES TARGETING NEUROBLASTOMA OR B CELL MALIGNANCIES LICENSE HUMAN GAMMA DELTA T LYMPHOCYTES FOR PROFESSIONAL ANTIGEN PRESENTATION

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Purpose: Human gamma delta T lymphocytes have many properties of innate lymphocytes including antibody dependent cell mediated cytotoxicity. Recent reports have suggested that, like dendritic cells, γδT cells are capable of professional antigen presentation to induce primary immune responses. We hypothesized that therapeutic antibodies against paediatric tumour antigens (CH14.18 and Rituximab) could promote both innate killing of, and generation of secondary immune responses against, tumour antigen-expressing target cells, by human gamma delta T cells.

Methods: γδT cells were purified from blood of healthy volunteers by two rounds of positive selection and co-cultured with neuroblastoma or lymphoma cells coated or not with CH14.18 or Rituximab antibodies respectively. Killing was determined by chromium release assay and cross presentation of tumour antigens from lysed cells was determined by measuring CFSE dilution of naïve or antigen experienced γδ T lymphocytes from the same donors, stably transduced with γδ T cell receptors against defined target antigens. The requirement of physical interaction with opsonized target for APC function was demonstrated by modifying these co-cultures with transwells to separate defined cell populations.

Results: Rituximab and CH14.18 promote killing of CD20 positive lymphoma cells and GD2-positive neuroblastoma cells by purified γδT cells, resulting in professional antigen presentation of tumour antigens from the lysed cells, and generation of secondary immune responses against the cancer cells. However the professional antigen presentation function is dependent on a physical interaction with the opsonized cell via CD16 ligation, a process we have described as “licensing for antigen presentation”.

Conclusion: Licensing of γδT cells by therapeutic monoclonal antibodies used in the treatment of childhood cancers suggests a new paradigm for cancer combination therapy whereby, in the context of γδT cell expansion and activation (for example by bisphosphonates), antibody treatment might function primarily by the development of secondary adaptive memory response against tumour antigens.

O139

T-CELLS GRAFTED WITH GD2-SPECIFIC ANTITUMOUR ACTIVITY: DEVELOPMENT OF IMMUNOTHERAPY FOR NEUROBLASTOMA

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Purpose: Chimeric antigen receptors (CARs) are generated by connecting the variable fragment of a monoclonal antibody (mAb) to the intracellular portions of T-cell signalling proteins. Transduction of autologous T-cells with vectors coding for a CAR allows us to generate large numbers of T-cells with arbitrary specificity. CAR therapy may be more effective than mAb therapy, since engineered T-cells can home to sites of disease, extravasate, proliferate in the tumour bed and can engender a long-lasting rejection of tumour. Most neuroblastoma tumours express high levels of disialoganglioside (GD2), the expression of which is largely absent in normal tissues making it an excellent target for CAR therapy. A recent phase I study of anti-GD2 CAR therapy showed clinical responses in patients with refractory neuroblastoma.

Methods: We have sought to improve the receptor and the retroviral cassette to work towards more robust clinical responses.

Results: (1) To reduce the chances of immunological rejection of the CAR-T-cells, we generated an anti-GD2 CAR derived from humanized mAb sequences. (2) Next, we compared different spacer domains identifying the hinge and Fe portion of human IgG1 as ideal spacer. (3) We incorporated tri-partite co-stimulatory domains supplying CD28 and OX40 co-stimulatory signals supplying proliferative and survival signals in cis. (4) We incorporated an epitope-based sort-suicide gene using the foot-and-mouth 2A sequence, allowing deletion of infused cells with rituximab in the face of unacceptable toxicity. (5) We codon-optimized the entire open-reading frame allowing increased surface expression. (6) We incorporated a scaffold attachment sequence (SAR) into the retroviral cassette resulting in tighter homogenous expression after transduction. (7) We tested this receptor in an immunocompetent mouse model of neuroblastoma.

Conclusion: By improving our retroviral cassette and receptor design we hope to implement a clinical study which delivers increased and sustained clinical responses.

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SUPPORTIVE CARE/PALLIATIVE CARE

O140

GLOBAL MAP OF PEDIATRIC PALLIATIVE CARE IN LOW- AND MIDDLE-INCOME COUNTRIES: SYSTEMATIC REVIEW OF THE AVAILABILITY OF CORE ELEMENTS

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Purpose: Palliative care is critical to quality of life for patients with life-limiting conditions, particularly in low- and middle-income countries (LMIC) when curative treatment is unavailable. A systematic review was conducted to assess core elements of pediatric palliative services in LMIC, examine relationships of reported services to health/economic indicators, and identify programmatic outcomes.

Methods: PubMed was searched by two reviewers for publications (1980–present, not restricted for publication type or language) discussing palliative care, hospice, end-of-life or pain management for children and adolescents with life-limiting conditions in LMIC. Publications were scored using a fifteen-item, five-domain checklist (access, pain/symptom management, end-of-life support, capacity-building, and health system support). Scores were compared with health/economic indicators, including population opiod use.

Results: Of 835 records generated, 319 met criteria for full-text review of eligibility; 53 from 23 countries qualified for data extraction. After excluding five sites with fewer than five evaluable items, median score was 8 (range 1–14) out of 10 (range 5–14). Prominent gaps in reported elements included pain assessment, and end-of-life and bereavement support. Scores correlated with per capita morphone consumption (rs = 0.61, p = 0.0089) and government and total health expenditures (rs = 0.53 and 0.59 respectively, p < 0.025) but not with the Multidimensional Poverty Index (UN Human Development Report 2011). While outcomes were infrequently reported, these included practice improvements such as support for patient preferences (e.g. place of death or life-support use).

Conclusion: Unmet needs reported in pediatric palliative services in LMIC include gaps in health policy and limited support for community-based care. More consistent reporting, particularly regarding practices at end-of-life and programmatic outcomes, could help target resources. Provision of high-quality services is nonetheless possible in resource-limited settings.

O141

ECOLOGIC IMPACT OF ADVANCED PEDIATRIC CANCER ON FAMILIES ENROLLED IN THE PEDIQUEST STUDY

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Purpose: Limited data exist to delineate the financial impact of life-threatening pediatric illness on families. We describe the perceived financial hardship, work disruptions, income losses and associated outcomes in families of children with advanced cancer.

Methods: Prospective cross-sectional survey of 86 parents of children with progressive, recurrent or non-responsive cancer enrolled in the Pediatric Quality of Life and Evaluation of Symptoms Technology (PediQUEST) study at three children’s hospitals. Response rate: 82%.

Results: Parental work disruptions secondary to cancer treatment were ubiquitous with 79 (92%) families reporting some disruption. At least one parent quit a job because of their child’s illness in 30 (35%) families. Resultant financial impact—both objective and perceived—was significant. Twenty-five (30%) families described their child’s illness as a great economic hardship. Ten (14%) families lost more than 40% of their annual income as a result of the child’s illness in 30 (35%) families. Resultant financial impact—both objective and perceived—was significant. Twenty-five (30%) families described their child’s illness as a great economic hardship. Ten (14%) families lost more than 40% of their annual income as a result of the child’s illness in 30 (35%) families.

Conclusion: The economic impact of pediatric advanced cancer on families is significant and perceived financial hardship is associated with high parental distress. Further investigation is needed to identify intervention strategies as well as downstream societal costs of childhood cancer.

O142

RISK-ADAPTED APPROACH FOR FEVER AND NEUTROPENIA IN PEDIATRIC CANCER PATIENTS

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Purpose: To describe changes in nutritional status and body composition during the first year after diagnosis in patients with hematological, solid, and brain malignancies.

Methods: Measurements of weight, height, skinfolds, and bioelectrical impedance analysis (BIA) were performed regularly till one year after diagnosis.

Results: 133 children (median age 8.1 years) with hematological (39.8%), solid (33.1%), and brain malignancies (27.1%) participated in this study. During the first 3 months after diagnosis significant weight loss (> 5%) was found in 13.8% of the patients, particularly in patients with hematological and solid malignancies. Almost 36% of the patients gained weight (> 5%) and 14.6% both lost and gained > 5% weight within those 3 months. After the 3 months period, significant weight gain was found in about 50% of the patients within both 3–6 and 6–12 months period. One year after diagnosis, mean z-scores of weight-for-age, body mass index, and sum of skinfolds were increased in all diagnosis groups. The three patient groups did not differ with regard to z-scores or increases in z-scores between 0–12 months. Prevalence rates of obesity (zBMI > 2SDS) doubled from 4.5% at diagnosis till 11.0% after one year while the prevalence of malnutrition (zBMI < −2SDS) decreased from 7.6% till 1.8%. The mean percentages body fat (%BF) increased in patients with hematological and brain malignancies from 23.9% (SD 9.7) to 28.1% (SD 12.6) and from 29.1% (SD 11.0) to 33.9% (SD 8.2) respectively and remained stable in patients with solid malignancies.

Conclusion: During the first year after diagnosis, not only patients with hematological malignancies, but also patients with solid and brain malignancies increased in weight resulting in doubling of percentages of obese patients. The weight gain is alarming, especially since the %BF increased in patients with hematological and brain malignancies. Probably, concern about weight loss in the first three months, resulted in the opposite: neglect of weight gain.

ACUTE LYMPHOBLASTIC LEUKAEMIA 3

O144

RELAPSED ACUTE LYMPHOBLASTIC LEUKAEMIA IN THE NORDIC COUNTRIES – PROGNOSTIC FACTORS, TREATMENT AND OUTCOME

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Purpose: In this national multicenter intervention study, we examined the feasibility of shortening the duration and withholding antibiotics in selected pediatric cancer patients with febrile neutropenia.

Methods: Outpatients with febrile neutropenia were allocated to one of three groups by a risk assessment model which combined objective clinical parameters and the plasma IL-8 level. High-risk patients comprised patients with signs of local bacterial infection and/or abnormal vital signs indicating sepsis, and received regular antibiotic treatment. Patients with two IL-8 levels below the cut-off level within a 24 hour period were considered low-risk for bacterial infection, and did not receive any antibiotics. Patients with at least one IL-8 above the cut-off level were considered medium-risk, they started antibiotic treatment and were reevaluated after 72 hours.

Results: 134 pediatric cancer patients with 234 febrile neutropenic episodes were included, 64 (28%) high risk, 123 (53%) medium risk (73 (31%) with full treatment; 50 (21%) with only three days of antibiotic treatment), and 47 (20%) low risk. Duration of antibiotic treatment and admission were significantly lower in the experimentally treated patients, only three days of antibiotic treatment, and 47 (20%) low risk. Duration of antibiotic treatment and admission were significantly lower in the experimentally treated patients, only three days of antibiotic treatment, and 47 (20%) low risk. Shortening the duration and withholding antibiotics in selected pediatric cancer patients with febrile neutropenia.
Abandonment of therapy is a major cause of treatment failure in low- and middle-income countries (LICs). Rates of abandonment (ARs) have been shown to range from 0-63% in acute lymphoblastic leukemia (ALL) and 0-44% in acute myeloid leukemia (AML) studies met inclusion criteria. ARs were determined in 61/127 (48%) ALL studies and 50/127 (40%) AML studies. When the reasons for abandonment were analyzed, the following conclusions were made:

- 30% of patients were lost to follow-up.
- 30% of patients were considered treatment failures.
- 20% of patients were considered lost to treatment.
- 20% of patients refused treatment.

Conclusion: Abandonment of treatment is a major cause of treatment failure in low- and middle-income countries. The flow cytometric analysis based on a single EuroFlow ALOT tube is fast and efficient of the patients suspected of AL. Results obtained with ALOT allow fast and efficient orientation of AL diagnostics towards a full BCP-ALL, T-ALL and/or AML characterization panel.

References

0146
RAPID DIAGNOSIS OF CHILDHOOD ACUTE LEUKEMIAS USING SINGLE EUROFLOW ACUTE LEUKEMIA ORIENTATION TUBE

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Purpose: The acute leukemia orientation tube (ALOT) composed of 8 monoclonal antibodies was designed by the EuroFlow consortium for initial assessment of immature lymphopoietic cells in acute leukemia samples in order to allow appropriate orientation towards the complementary B-cell precursor acute lymphoblastic leukemia (BCP-ALL), T-lineage acute lymphoblastic leukemia (T-ALL), and acute myeloid leukemia (AML) antibody panels. The study aimed to assess, whether the use of ALOT in a diagnostic procedure allows the proper classification of acute leukemias (AL) and distinction from non-leukemic malignant infiltrations or normal samples.

Methods: The study group consisted of 706 consecutive children with suspicion of AL treated in the factors of the Polish Pediatric Leukemia/Lymphoma Study Group. In all patients, bone marrow (n = 681) or peripheral blood samples (n = 25) obtained at diagnosis were analyzed with 8-color flow cytometry using ALOT in the first step of diagnostic procedure in order to assign each case to the appropriate disease category.

Results: The combination of antibodies included in ALOT enabled correct initial diagnosis in 686 out of 706 patients (97.5%). This group of patients included 503 cases of BCP-ALL, 48 cases of T-ALL, 84 cases of AML, and 53 cases with no leukemic infiltration. The aberrant population was detected also in 20 remaining cases, however their proper classification became possible only after further stainings. This group consisted of acute biallelic leukemia (n = 5), acute undifferentiated leukemia (n = 5), Burkitt lymphoma/leukemia (n = 5), non-Hodgkin lymphomas (n = 3), thymidylate synthase (n = 3), and neuroblastoma (n = 1).

Conclusion: The flow cytometric analysis based on a single EuroFlow ALOT tube is fast and simple method enabling appropriate classification of acute leukemia in vast majority of the patients suspected of AL. Results obtained with ALOT allow fast and efficient orientation of AL diagnostics towards a full BCP-ALL, T-ALL and/or AML characterization panel.

0116
THE MAGNITUDE AND PREDICTORS OF ABANDONMENT OF THERAPY IN PEDIATRIC ACUTE LEUKEMIA IN LOW-INCOME AND MIDDLE-INCOME COUNTRIES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Purpose: Abandonment of therapy is a major cause of treatment failure in low- and middle-income countries (LMICs). Our primary purpose was to determine the magnitude of abandonment in LMICs through a systematic review of pediatric oncology abandonment rates (ARs). Secondly, we aimed to identify patient, center and country-specific predictors of abandonment.

Methods: We searched 11 international and regional databases. All pediatric oncology cohorts of > 20 patients followed from diagnosis, treated in LMICs and published after 2000 were included, without language restrictions. Two reviewers independently assessed titles for inclusion, and extracted data. Authors were contacted for additional information when necessary. Subgroup analyses were planned a priori. Meta-analyses used a random effects model.

Results: From 22,384 titles, 318 manuscripts in 8 languages were further reviewed; 127 leukemia studies met inclusion criteria. ARs were determined in 61/127(48%), representing 14,401 children from 21 countries. ARs ranged from 0–63% in ALL and 0.44% in AML. ALL ARs were higher in low-middle income countries (LCIs) vs. upper-middle income countries (25% [95% CI 19–32%] vs. 2% [95% CI 1–3%]; p < 0.0001). Significant heterogeneity existed among ALL ARs (I² = 97%; p < 0.0001). On subgroup analysis, neither center-specific (e.g. free treatment provision) nor country-specific (e.g. government health expenditure) variables explained the heterogeneity. Seven studies identified patient-level predictors of abandonment; younger age, rural and lower social-economic status were significant in some but not all studies. Two studies showed decreased ARs when treatment intensity was reduced. Analysis of outliers suggested that social environment may be a factor in unexpectedly low ARs.

Conclusion: ARs are highest among LCIs. However, significant heterogeneity suggests that low ARs are possible even in very resource-constrained settings. Methodologically appropriate reporting of ARs’ should be adopted by the pediatric oncology community. Future research should monitor ARs when treatments are intensified and evaluate interventions targeting abandonment.

Pediatri Blood Cancer DOI 10.1002/pbc
Methods: UKALL 2003 was open to all children aged 1–18 years with ALL. Parents were asked to report their child’s Quality of Life (QOL) using the PedsQL 4.0 generic core and cancer specific modules. Parents also commented on measures of their own Caregiving Burden. Questionnaires were completed on five occasions during routine hospital visits (T1: first week of treatment to describe QOL before diagnosis; T2: Week 4 end of induction chemotherapy; T3: Start of maintenance therapy (to distinguish effects of 1 versus 2 intensifications and Regimen C versus standard therapy); T4: 18 months (maintenance chemotherapy); T5: end of treatment).

Results: 2397 patients were recruited to the trial and 1440 (60%) parents/guardians responded to at least one time point of the QOL study; 307 (13%) responded at all five time points. There was a significant decline in overall mean QOL from T1 to T2 (total QOL: T1 78.10 (Normal = 100); T2: 42.23, that then improved (T3 = 60.08; T4 = 62.43; T5 = 66.77), but never attained T1 levels. Cancer specific QOL, (pain, nausea, anxiety, worry, concern for appearance, communication) declined sharply from T2 to T3. Nausea and anxiety continued to decline slowly from T3 to T5 although scores on other subscales remained stable Care-giving burden also declined initially but then improved over time.

Randomised outcomes are being analysed and will be reported separately.

Conclusion: This is the largest study of QOL in ALL. Results confirm previous findings that child QOL is significantly compromised, in all QoL domains, in the period immediately following diagnosis and remains lower than before the diagnosis. This applied to both boys and girls, despite the fact that girls completed treatment after 2 years and boys after 3 years.
throughout therapy. These samples were compared to respectively 96 and 64 age- and gender-matched samples from healthy subjects using a mixed effects model. Classification models were used to validate the quality of samples obtained from the COG and to classify subjects.

Results: 84 proteins out of 116 identified proteins were differentially abundant in osteosarcoma and 100 out of 130 identified proteins were differentially abundant in Wilms tumor. Validation with local samples showed an average specificity of 94.09% (osteosarcoma) and 97.74% (Wilms tumor) and an average sensitivity of 83.33% (osteosarcoma) and 93.28% (Wilms tumor). Furthermore, when the classification models were applied to post-treatment and relapse samples, they were classified correctly. Comparing samples collected at Indiana University with samples collected through the COG demonstrate that samples collected at multiple institutions are capable of producing results similar to those obtained at a single institution using a stringent protocol.

Conclusion: This study demonstrates that multiple proteins form an accurate signature that can distinguish healthy and diseased subjects, with the potential to be used to distinguish cancer types and for early relapse detection.

O152

FREQUENCY OF WT1 AND 11P15 CONSTITUTIONAL ABERRATIONS AND PHENOTYPIC CORRELATION IN CHILDHOOD WILMS TUMOR PATIENTS

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Purpose: A genetic predisposition is described in 9–17% of the Wilms tumor patients. The most common Wilms tumor predisposing syndromes are WT1-associated syndromes and overgrowth syndromes. Constitutional WT1 mutations or epigenetic changes on chromosome 11p15 have also been described in Wilms tumor patients without phenotypic abnormalities. So, the absence of phenotypic abnormalities does not exclude the presence of a genetic predisposition, suggesting that more Wilms tumor patients may have a constitutional abnormality. Therefore, we investigated the frequency of constitutional aberrations in combination with phenotype.

Methods: We offered clinical genetic assessment in combination with molecular analysis of WT1 and locus 11p15 to a single-center cohort of 109 childhood Wilms tumor patients. Results: 20% (21/109) of the Wilms tumor patients analysed had a constitutional aberration: 12% had a WT1 defect, 8% a locus 11p15 aberration. 9% had a Wilms tumor predisposing syndrome: 5% had a WT1-associated syndrome and 4% had Beckwith-Wiedemann syndrome. 11% non-syndromic Wilms tumor patients carried a constitutional WT1 or locus 11p15 aberration: 6% had congenital anomalies or features that may indicate a constitutional WT1 mutation namely genitourinary anomalies, early age of onset, bilateral disease and stromal-predominant histology. 2% had minor features that may indicate a constitutional 11p15 aberration namely hemihypertrophy and high birth weight (>97%), and 3% had no features.

Conclusion: Constitutional WT1 or 11p15 aberrations are frequent in Wilms tumors patients and careful clinical assessment identifies the majority of these patients. So, we advise to offer routinely clinical genetic counseling to all Wilms tumor patients and molecular analysis to Wilms tumor patients with clinical signs of an underlying syndrome or with morphological or clinico-pathological features that may indicate a constitutional WT1 or locus 11p15 aberration. However, a small percentage of Wilms tumor patients carrying a constitutional WT1 or 11p15 defect without specific phenotypic features will remain undiagnosed.

O153

CHARACTERISATION OF INTRA-TUMOURAL GENETIC HETEROGENEITY IN WILMS TUMOURS

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Purpose: Biomarkers are used to support risk stratification and clinical decisions in Paediatric Oncology. Implicit in the clonal evolutionary theory of carcinogenesis is the evolution of cells derived from an initiating clone through natural selection acting upon intra-tumoural genetic heterogeneity. Studies show the presence of intra-tumoural genetic heterogeneity in a range of tumours. Wilms tumours frequently present as large macroscopically heterogeneous masses. This study sought to characterise intra-tumoural genetic heterogeneity within Wilms tumours.

Methods: Multiple snap frozen samples were taken from post chemotherapy Wilms tumour nephrectomy specimens at Great Ormond Street Hospital, May-October 2011. DNA was analysed using the Illumina CytoSNP array for copy number variation.

Results: 23 samples were analysed from 10 separate tumours from 10 individuals. 2 tumours showed clear heterogeneity between samples. In one, gains of chromosomes 8 and 13 were observed across two tumour samples however gains of chromosome 2 and 12 was present in one sample and of chromosome 7 in the other. In another tumour partial gain of 22q was present in both samples and 1q and partial 1p gain in only one sample. A third tumour showed localised heterogeneity with loss of 7p and gain of 7q present in two samples whilst gain of chromosome 8 was more apparent in only one sample. In three other tumours, changes were observed between two or more samples. Four tumours had no apparent copy number changes.

Conclusion: 6 of 10 tumours showed copy number aberrations. In these cases certain copy number variations were conserved by samples of an individual tumour, consistent with a single clonal origin. In three cases there was intra-tumoural genetic heterogeneity. Understanding such heterogeneity may aid in deciphering the genetic changes in the development of Wilms tumours and, as the use of biomarkers enter clinical practice, will be important for establishing appropriate sampling strategies.

O154

LOOKING FOR THE OPTIMAL THERAPY FOR STAGE I WILMS TUMOUR (WT). DATA FROM THE ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA (AIEOP) - TW3-2003 PROTOCOL

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Purpose: Treatment options for stage I favourable histology WT range over protocols from nephrectomy-only to adjuvant 19 weeks of vincristine-actinomycin D (VA). We reviewed the results concerning the children with stage I WT treated according to the AIEOP-TW3-2003 protocol.

Methods: The AIEOP-TW3-2003 approaches for stage I tumours included: adjuvant 6-week VA (13 children received further 4 weeks of VA preoperatively); nephrectomy alone for children younger than 2 years with small (≤ 550 g), epithelial-type tumours.

Results: Ninety-six stage I WT (7 had diffuse anaplasia) of 357 eligible monolateral WT were the object of this analysis. Median aged was 21 months (range 1–89; 53 children aged ≤2 years). Five children entered the nephrectomy-only trial. At 55 months (median) of follow-up the 4-year EFS and OS rates were 88.1% (± 3.4%) and 97.7% (± 1.6%). Respectively, for the series as a whole, and 89.7% (± 3.3%) and 97.6% (± 1.7%) for the 91 patients who received adjuvant chemotherapy. There were 10 relapses (contralateral kidney, 4–with lung in one case; distant; 5, local; 1), one child eventually died. Two of the 10 tumours that relapsed were centrally reclassified as stage II, one had diffuse anaplasia, and two were initially treated by surgery alone. One A-related toxic death occurred. Lymph nodes were not sampled in 26 children. The age ≥ 2 years (p = 0) and failure to sample lymph nodes (p = 3) did not seem to influence outcome.

Conclusion: The outcome for stage I WT is excellent. The short 6-week VA regimen did not seem to prevent the evolution of nephrogenic rests into tumours (40% of relapses were metachronous WTs) nor to significantly improve the EFS comparing to a surgery-only strategy like the COG one for young children. A finer tuning of the therapy for stage I WT should be driven by clinical, histological and genetic parameters.

References


O155

SINUSOIDAL OBSTRUCTION SYNDROME DURING TREATMENT FOR RENAL TUMORS IN NWTS 3, 4 AND 5: INCIDENCE, SEVERITY AND EFFECT ON PLANNED TREATMENT AND OUTCOME

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Purpose: Sinusoidal obstruction syndrome (SOS) is a complication of treatment of renal tumors, associated with chemotherapy (dactinomycin, doxorubicin, vincristine, cyclophosphamide) and radiotherapy. SOS is defined in Children’s Oncology Group (COG) renal protocols by: (a) pathologic confirmation; or (b) reversal of portal flow; or (c) ≥2 of the following: (1) bilirubin > 1.4 mg/dL; (2) weight gain > 10% or acute; (3) hepatomegaly or RUQ pain. Thrombocytopenia and respiratory distress, often observed, are not part of any classification system. Re-institution of inciting agents after severe hepatopathy is left to the discretion of the treating physician. To better inform clinical practice, we reviewed the experience of hepatopathy of all NWTS 3–5 patients.

Methods: 188 patients of 8862 registered on NWTS 3–5 had been scored with hepatopathy; these charts were reviewed. As laboratory data were variably collected on the NWTS studies, we used three published grading scales for SOS: Seattle, WHO, and Modified Seattle, to classify patients as Definite, Probable or Possible SOS. Inciting agents, radiotherapy, dose modifications, and outcome were recorded.

Results: 45 (0.5%) patients met criteria for SOS on ≥1 of the grading scales; 12 Definite, 19 probable, 14 possible. Median elapsed days from therapy start was 57. 35 patients received abdominal or flank radiation. 28 tumors were right-sided. 35 patients were re-challenged with chemotherapy, including inciting agents, 23 eventually received full dosage, 16 continued chemotherapy during SOS. 3 patients died of SOS (none had received further chemotherapy), 1 had liver transplant. Severe thrombocytopenia occurred in 28 (median reported platelet count 15 × 10^9/L, range 3–92).

Conclusion: The incidence of severe SOS on NWTS protocols 3–5 was low. Chemotherapy was successfully re-challenged in all patients with clinical recovery from SOS, supporting the safety of reintroducing chemotherapy in an escalating fashion. Thrombocytopenia may be appropriate to include in the definition of non-transplant associated SOS.

O156
THE EFFICACY AND TOXICITY OF SIOP PREOPERATIVE CHEMOTHERAPY IN MALAWIAN CHILDREN WITH A WILMS TUMOUR

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Purpose: Wilms tumour has a survival rate of 85–90% in well-resourced countries. In Malawi, sub-Saharan Africa, preoperative chemotherapy for patients with a Wilms tumour is a logical strategy, but detailed information on toxicity and efficacy in such a resource limited setting has been unavailable.

Methods: We evaluated the outcome of a treatment guideline including preoperative chemotherapy, supportive care and strategies to enable parents to complete treatment.

Results: Between 2006 and 2011, 95 patients were initially diagnosed with a Wilms tumour; 11 were later excluded due to misdiagnosis. At diagnosis, 28% of patients with a unilateral tumour had an estimated maximum tumour diameter of more than 25 cm; 29% of patients had metastases. Eight children (11%) died during preoperative chemotherapy. More than half (59%) of the patients developed moderate neutropenia (N < 1.0 × 10^9/L) and 27% severe neutropenia (N < 0.5 × 10^9/L). Severe neutropenia occurred significantly more frequently in children receiving the three drug regimen compared to the two drug regimen. Fifty seven percent of all patients had CTC grade 4 anemia (Hb < 6.5 g/dL) during treatment. Most tumours (92%) showed a response to chemotherapy but 14% remained unresectable. Overall survival of patients was 78%.

Conclusion: Challenges remain to improve survival for children with Wilms tumour in Malawi. Earlier diagnosis would reduce disease-related deaths as numbers of unresectable disease and relapse are high. Effective strategies, including social support, to enable parents to complete treatment need to be continued. Preoperative chemotherapy causes considerable haematological toxicity and treatment-related mortality. Improved supportive care and nutritional support and possibly less intense preoperative chemotherapy in acutely malnourished children are needed to reduce treatment-related deaths.

O157
REPORT OF 384 PEDIATRIC CASES OF CUTANEOUS MELANOMA REGISTERED WITH THE GERMAN CENTRAL MALIGNANT MELANOMA REGISTRY BETWEEN 1984 AND 2011

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Purpose: Melanoma in children is less rare than expected. Better survival and different independent significant prognostic factors in adults, in children, only ulceration (p < 0.0001) was found as strong prognostic factor in Cox regression and AICc stage (< 0.0001), tumor thickness (p = 0.0002) and Clark-Level (p = 0.0002) in univariate analysis. Conclusion: Melanoma in children is less rare than expected. Better survival and different prognostic factors are seen. We encourage clinicians to report pediatric cases to the existing registries and support biological studies in order to enable further research leading to evidence based guidelines for children.

O158
OUTCOME OF EXTRACRANIAL MALIGNANT RHABDOID TUMOURS (MRT) REGISTERED ON THE EPPSG NRSTS 2005 STUDY

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Purpose: Extracranial malignant rhabdoid tumours are rare, highly aggressive and frequently lethal tumours of mainly very young children. The Epsg NRSTS study set out to register cases and recommend a standard treatment protocol of intensive chemotherapy.

Methods: Treatment recommended consisted of upfront or early surgical resection of the primary tumour, chemotherapy with 5 cycles of vincristine, doxorubicin and cyclophosphamide, and 5 cycles of cyclophosphamide, carboplatin and etoposide, with radiotherapy to the primary tumour and metastatic sites following surgery.

Results: 53 patients from 7 European countries were registered from 2005 to 2012. 20 pts were ≤1 year of age, with a median age of 18.4 (range 0.4–131.2) months. Post surgical staging at diagnosis was IRS I in 9 patients, IRS II in 7 and IRS III in 17, the commonest site was liver (no = 9) with 50% of tumours extending beyond the tissue of origin. Complete treatment data were available in 45 pts with 21 receiving chemotherapy as described and radiotherapy, and 24 receiving chemotherapy alone. Radiotherapy dose was ≤45.0 Gy for 13 patients, and > 45.0 Gy for remaining patients. The median follow-up is 34.5 (range 0.6–60.7) months, with a 3 year EFS of 31.6% (95% CI 17.5–46.9%). Twenty patients stopped treatment prematurely, 3 due to death, 15 due to progression and 2 due to physician’s choice.

Conclusion: The recommended chemotherapy can be delivered to children with MRT but it is noteworthy that a proportion will progress before treatment is finished. Considering that this MRT series contains patients with MRT at less favourable sites outside the kidney, the outcome appears to be better than historical cohorts, however more effective approaches are needed for this tumour. It is noteworthy that upfront surgery cannot be delivered to the majority of patients.

O159
RHABDOID 2007 AND EU-RHIAB – RESULTS OF TWO EUROPEAN REGISTRIES WITH CONSENSUS TREATMENT RECOMMENDATIONS FOR 139 CHILDREN WITH RHABDOID TUMORS

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Purpose: Cutaneous melanoma is a rare pediatric malignant neoplasm. This study was performed in order to understand, if there are differences in characteristics and prognosis of malignant melanoma in children compared with adult cases.

Methods: 384 patients age < 18 years and 90.975 adult cases with cutaneous melanoma were registered with the German Central Malignant Melanoma Registry between 1984 and 2011. Cases were collected from 62 participating centers. Only 296 pediatric and 43.419 adult cases were evaluated. Survival probabilities and prognostic factors were evaluated by Kaplan–Meier and multivariate Cox proportional hazard models.

Results: Median follow-up time of pediatric cases was 52 months (IQR 22.96–95), of adult cases 46 months (21.83; p = 0.025). 10-year overall survival (OS) for children and adults were 92.4% and 84.0% (p = 0.005), respectively. 10-year OS in children was 96.3%, 92.4%, 33.3%, 44.4% for AICC stages I, II, III and IV, respectively. Patient and tumor characteristics were similar in children and adolescents. While Cox regression revealed tumor thickness, ulceration, body site, Clark’s level, histopathologic subtype and stage at diagnosis as independent significant prognostic factors in adults, in children, only ulceration (p < 0.0001) was found as strong prognostic factor in Cox regression and AICc stage (< 0.0001), tumor thickness (p = 0.0002) and Clark-Level (p = 0.0002) in univariate analysis.

Conclusion: Melanoma in children is less rare than expected. Better survival and different prognostic factors are seen. We encourage clinicians to report pediatric cases to the existing registries and support biological studies in order to enable further research leading to evidence based guidelines for children.
O160

CHILDREN AND ADOLESCENTS WITH ADRENOCORTICAL CARCINOMAS IN GERMANY – RESULTS OF THE GPOH-MET 97 TRIAL

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Purpose: Evaluation of diagnosis, treatment and outcome of children with adrenocortical carcinomas (ACC) in Germany.

Methods: 60 children with ACC aged 0.2 to 17.8 years were admitted to the GPOH-MET 97 trial, a national prospective interdisciplinary multicenter study including malignant endocrine tumors in children and adolescents. The protocol suggested in complete resected tumors without lymph node involvement no additional chemotherapy. In advanced stages treatment with polychemotherapy and mitotane was recommended.

Results: The OS rate was 64.8%, the EFS rate 43%. Most patients had signs of hormonal excess [malignant disease (MD) = 83.3%], stage Ib (N = 26) and stage IV tumors (N = 25) were predominant. Tumor biopsy, tumor spillage, incomplete tumor resection, local recurrence, age and tumor size were correlated with outcome. Seven patients received additional percutaneous radiation in salvage situations with 40 to 56 Gy.

Conclusion: Pre- and perioperative management as well as systemic treatment in higher stages is important for outcome. Most of the tumors are hormonally active and can be diagnosed preoperatively. The need of a tumor biopsy has to be discussed critically. All patients should be registered in national or international trials and treated according to the current recommendations.

O162

AN INTERNATIONAL COLLABORATION REVEALS NOVEL CLINICAL AND GENETIC DETERMINATES OF THE BIALLELIC MISMATCH REPAIR SYNDROME

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1Division of Hematology/Oncology, Sick Kids Hospital; 2University of Toronto; 3The Farber/SIOP Gynecologic Cancer Research Registry on the chromosomal remodeling complex, in primary tumors and cancer cells. We have previously reported that reexpression of hSNF5 in MRT cell lines causes a G1 arrest via p21 mRNA induction, and hSNF5 binds to the p21 promoter. In this study, we assessed whether hSNF5 regulates the transcription of representative p53 target genes and then we clarified how hSNF5 regulates its target genes and verified the functions of hSNF5.

Results: We show hSNF5 can regulate a subset of p53 target genes such as p21 and NOXA in MRT cell lines. Furthermore, our results demonstrate lower NOXA expression in MRT cell lines compared to other human tumor cell lines suggesting that hSNF5 loss may alter the expression of this important apoptotic gene. We also examined how hSNF5 regulates transcription of the NOXA and p21 genes and find maximal binding within 1 kb of the transcription start site (TSS) at both promoters in MRT cell lines. Our results show that hSNF5 reexpression in MRT cell lines increases the SWI/SNF complex activity at the TSS at both loci and leads to activation of transcription initiation through recruitment of RNA polymerase II (RNPPII) accompanied by H3K4 and H3K36 modifications.

Conclusion: Our results show that hSNF5 reexpression in MRT cells increases both p21 and NOXA expression. Because MRT cells display repressed NOXA transcription activity due to loss of hSNF5, targeting reexpression of the NOXA pathway might be a promising new paradigm to treat MRT in near future.

References:


O163

HSNF5 REEXPRESSSION IN MALIGNANT Rhabdoid TUMORS REGULATES THE TRANSCRIPTION OF NOXA AND P21(CDKN1A) BY RECRUITMENT OF SWI/SNF COMPLEXES AND RNAPII TO THEIR PROMOTERS

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Purpose: Malignant rhabdoid tumor (MRT), a highly aggressive tumor of young children, is characterized by loss or mutation of CHD7, a core subunit of the SWI/SNF chromatin remodeling complex, in primary tumors and cancer cells. We have previously reported that reexpression of hSNF5 in MRT cell lines causes a G1 arrest via p21 mRNA induction, and hSNF5 binds to the p21 promoter. In this study, we assessed whether hSNF5 regulates the transcription of representative p53 target genes and then we clarified how hSNF5 regulates its target genes and verified the functions of hSNF5.

Methods: To assess whether hSNF5 regulates the transcription of representative p53 target genes, we use Q-RT-PCR and Western blotting. To clarify how hSNF5 regulates its target genes, we performed ChIP assays for hSNF5, histone modifications and SWI/SNF complexes.

Results: We show hSNF5 can regulate a subset of p53 target genes such as p21 and NOXA in MRT cell lines. Furthermore, our results demonstrate lower NOXA expression in MRT cell lines compared to other human tumor cell lines suggesting that hSNF5 loss may alter the expression of this important apoptotic gene. We also examined how hSNF5 regulates transcription of the NOXA and p21 genes and find maximal binding within 1 kb of the transcription start site (TSS) at both promoters in MRT cell lines. Our results show that hSNF5 reexpression in MRT cell lines increases the SWI/SNF complex activity at the TSS at both loci and leads to activation of transcription initiation through recruitment of RNA polymerase II (RNPPII) accompanied by H3K4 and H3K36 modifications.

Conclusion: Our results show that hSNF5 reexpression in MRT cells increases both p21 and NOXA expression. Because MRT cells display repressed NOXA transcription activity due to loss of hSNF5, targeting reexpression of the NOXA pathway might be a promising new paradigm to treat MRT in near future.

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Pediatric Blood Cancer DOI 10.1002/pbc
onset gastrointestinal (GI) cancers. These patients usually succumb to their cancers and rarely reach adulthood. We have initiated an international collaboration to improve diagnosis and treatment, and offer early detection to these patients and their at-risk family members.

**Methods:** We established a central clinical database and tissue bank, including blood and tumor samples. Review of pathology is conducted, tumors are stained for all four MMR genes (PMS2, MSH2, MLH1, MSH2) and tested for microsatellite instability. Germline DNA is sequenced and genetic counseling and surveillance are offered to these families accordingly.

**Results:** Twenty-two children from 14 families developed 29 tumors. Seventeen brain tumors developed in sixteen patients of the twenty two patients (72%) and 74% of the brain tumors were high grade gliomas. All patients with brain tumors (including 4 with multiple malignancies) had pre-existing Café-au-lait spots. Out of all genetic alterations detected in our group one novel deletion and one novel missense somatic mutation in PMS2, two novel deletion mutation in MSH6 and one complex genetic alteration were found. Germline mutations were detected in all patients whose tumor samples stained negative for the specific gene. A comparison between microsatellite instability and immunostaining is currently being performed. Pre- and post-test genetic counseling was conducted and clinical surveillance protocol was able to detect two brain tumors, multiple GI malignancies, and premalignant lesions.

**Conclusion:** We demonstrate the feasibility and efficacy of an international consortium for bMMR carriers.

Brain tumors are by far the most common cancer in this syndrome. Immunostaining of these tumors is a simple and reliable method to screen for MMR in suspected patients. Finally, surveillance may improve survival for at-risk family members once a germline mutation is discovered.

**NEUROBLASTOMA 2**

**O163**

**NEURAL CREST-SPECIFIC EXPRESSION OF LIN28 INDUCES NEUROBLASTOMA IN MICE**

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**Purpose:** Overexpression of Lin28 in tumors has been reported in neuroblastomas (NB) and other malignancies. Lin28 is known to repress expression of let-7 miRNAs, which target MYCN, but Lin28 tumor-initiating capacity and oncogenicity has not yet been investigated in vivo. We overexpressed Lin28 in the murine neural crest to determine if Lin28 can drive neuroblastomagenesis.

**Methods:** Lin28 was conditionally expressed by knock-in of the CAG-LSL-Lin28-iresLuciferase vector (LSL-Lin28) into the ROSACL6 locus. Mice were crossed back with DBH-Cre mice to target expression to the neural crest. Aiming tumors were characterized using histology, immunohistochemistry, PCR and western blotting, and maintained via serial transplantation.

**Results:** Abdominal tumors developed in 4 of 16 DBHCremLSL-Lin28 transgenic mice at 36–56 days of age. Autosomal recessive hereditary neural crest tumors in all mice, reflecting the most frequent localization of human NB. Thoracic tumors and tumors originating from the superior cervical or celiac ganglia were also observed. Tumors consisted of small round blue cells and expressed the NB markers, DBH, TH and Phox2b. The macroscopic tumor appearance, primary tumor site, tumor histology and marker gene expression confirmed these tumors as NB. Successful serial transplantation in immunocompromised mice supported that the primary tumors from this model system were fully transformed malignant tumors. Both the Lin28 and MYCN proteins were strongly expressed in all tumors and members of the let-7 miRNA family were significantly downregulated.

**Conclusion:** We demonstrate that overexpressing Lin28 in the neural crest can drive NB tumor formation in mice, supporting LIN28 as an important oncogene for NB and potentially for other malignancies. Our results suggest that, similar to human NB, MYCN is accordingly.

**NEUROBLASTOMA 2**

**O165**

**GENETIC EVOLUTION OF NEUROBLASTOMA IS CHARACTERIZED BY NEW CHROMOSOME BREAKPOINTS**

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**Purpose:** In neuroblastoma (NB), relapse can be associated with new chromosome breakpoints (BPs), but few data precisely describe relapse-specific genetic alterations. **Methods:** To characterize relapse-specific genetic events, SNPs (Affymetrix®) analysis of 22 paired diagnostict and relapse NB samples was performed. For one patient, genetic evolution was studied by whole-genome paired-end sequencing of constitutional (C), diagnostic (D) and relapse (R) tumor material (30× haploid coverage).

**Results:** SNPs analysis revealed new small interstitial alterations, extensive segmental alterations, or both, at relapse for 6, 11 and 12 cases, respectively (median: 12 new BPs). In 11 cases, BPs observed at diagnosis were not found at relapse. Gene ontology analysis of the smallest regions of overlap at relapse identified the histone-methyltransferase pathway as most frequently targeted by these alterations. In the deep-sequenced C/D/R case, among predicted structural variants, 21% were D-specific, 16% were common to D and R, and 63% were R-specific, most concerning small interstitial deletions. Three R-specific inter-/intron-chromosomal rearrangements could be experimentally validated: a 5q34/1p24.3, a 2q37/1p13.1 and a 11q23/1q13 to 1q13.23/3q13.23 translocation; breakpoints in the XAX77212, SCNA13 and PDGFD and OPCML genes, respectively. Among single nucleotide variants (SNVs), 30% were D-specific, 50% common to D and R, and 20% observed only in R. Non-synonymous SNVs predicted to be deleterious were, amongst others, the ALK Y1278S mutation in D and R, and one R-specific mutation in the GRIK2 gene. Interestingly, allele ratios indicated 12 isodisomic chromosomes at diagnosis, with three additional chromosome arms showing copy-neutral LOH at relapse. The heterozygous allele ratio for some mutations showed that they occurred after isodisomy.

**Conclusion:** These data support the hypothesis of an abnormality in DNA maintenance/repair leading to variable chromosome BPs in NB evolution. The observation that some genetic alterations of D were not observed in R support the hypothesis that relapse occurred from a more ancestral clone.

**O166**

**ANAPLASTIC LYMPHOMA KINASE (ALK) EXPRESSION IS AN INDEPENDENT PROGNOSTIC FACTOR IN NEUROBLASTOMA PATIENTS AND CORRELATES WELL WITH ALK INHIBITOR RESPONSE IN VITRO**

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**Purpose:** ALK mutations are one of the most common genetic aberrations occurring in 3–11% of the neuroblastoma (NB) patients. We determined the role of ALK protein levels
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SIOP ABSTRACTS

on survival of NB1 patients. Secondly, we tested in vitro responsiveness to ALK inhibitors in NB1 cell lines with and without ALK mutation.

Methods: Immunohistochemistry (IHC) for ALK protein on Paraffin-Embedded material of 71 NBL, 12 ganglioneuroblastoma (GNBL) and 20 ganglioneuroma (GN) patients. Cell viability assays (MTS-based) with ALK inhibitor (TAE684).

Results: ALK mutations were identified by sequencing in 2/63 NBL (3.2%) and 2/11 NBL patients. Cell viability assays (MTS-based) with ALK inhibitor (TAE684).

Conclusion: ALK protein expression is an independent predictor of overall survival in NB1 patients and ALK inhibitor response in vitro. ALK inhibitor response in patients is not mutation dependent, but also level dependent. For future patient stratification, ALK expression can be easily tested by IHC.

References

0167

HAPLOIDENTICAL NATURAL KILLER CELLS PLUS MONOCONAL ANTIBODY 3F8 FOR RESISTANT HIGH-RISK NEUROBLASTOMA: PRELIMINARY RESULTS OF AN ONGOING PHASE I STUDY

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Purpose: Natural killer (NK) cell-mediated antibody-dependent cellular cytotoxicity (ADCC) is a potent mechanism of 3F8 activity against neuroblastoma (NB). KIR and HLA genotypes define NK activity and are key prognostic markers in 3F8-treated patients. NK-cells are depleted by standard NB chemotherapy, but when rescued by autologenic NK transfusions, can be optimized for anti-NB cytotoxicity by selecting NK donors for maximum NK ADCC: from either licensed NK-cells responding to “missing self” or from unlicensed NK-cells responding to “missing ligand”.

Methods: We initiated a phase I study of the combination of haploidentical NK-cells and anti-GD2 antibody 3F8 for the treatment of refractory or recurrent high-risk NB (www.clinicaltrials.gov NCT00877110). The primary objective was to determine the maximum tolerated NK-cell dose (MTD). Secondary objectives included assessing donor ADCC activity and its relationship to KIR/HLA genotypes, NK function, and NK chimeraism. Eligibility criteria included availability of ≥ 2 x 10^5CD34+ autologous cells/kg. Patients received a lymphodepleting regimen of high-dose cyclophosphamide, topotecan and vincristine (days 1-3) prior to infusion (day 5) of NK-cells isolated from donor leukophereses using a process of CD3-depletion (to < 2 x 10^5CD3+ cells/kg) followed by CD56-enrichment. 3F8 (20 mg/m2/day) was administered on days 8-12. NK-cell dose-escalation occurred in the absence of dose-limiting toxicity (DLT). Cytoreduction-related side effects were not considered DLT.

Results: Ten patients have been treated thus far: 8 at dose-level 1 (1.49 x 10^6CD56+ cells/kg) and 2 at dose-level 2 (5.99 x 10^5CD56+ cells/kg). MTD has not yet been reached. One patient at dose level 1 developed DLT: grade 3 vomiting and hypertension. No other grade 2 or higher side effects were encountered. Neither GVHD nor myelosuppression requiring stem cell rescue was observed. 2 patients achieved complete response. Conclusion: Preliminary results from this first-in-human trial of NK-cells plus antibody against solid tumors suggest that the combination is safe following cytoreduction and may be effective for some patients with high-risk NB.

0168

SERUM CHROMOGRAIN A LEVELS AT DIAGNOSIS IN PATIENTS WITH NEUROBLASTOMA

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Purpose: Chromogranin A (CgA) is a secretory glycoprotein which is co-stored and co-released with neurotransmitters and peptide hormones by neuroendocrine cells. Serum CgA levels are often increased in patients with neuroendocrine tumours, and can be used to diagnose and monitor disease progression. In this study, serum CgA was measured at diagnosis in patients with neuroblastoma, and its possible associations with clinicopathological features were investigated.

Methods: 150 untreated patients (78M, 72 F), aged 3 days to 199 months (median, 32 months), were included. Primary site was adrenal in 84 and non-adrenal in 66; 19 patients were stage 1, 22 stage 2; 21 stage 3, 5 stage 4S, and 83 stage 4; 122 tumours were neuroblastomas and 28 ganglioneuroblastomas; Shimada grading was favourable in 74 cases and unfavourable in 76; 39/150 tumours (26%) were MYCN-amplified; urinary HVA/VMMA were increased in 138/150 cases (92%). As controls, serum samples were obtained at diagnosis from 45 children affected with non-neuroendocrine tumours. Serum CgA levels were determined by using radioimmunoassay. Written informed consent and ethical approval were obtained according to local institutional guidelines.

Results: Serum CgA was increased (> 98 ng/ml) in 147/150 patients with neuroblastoma, but in none of 45 children with other tumours (sensitivity 98%, specificity 100%). Higher mean serum CgA levels were associated with age at diagnosis >15 months (p < 0.001), advanced stage (p < 0.001), adrenal primary (p = 0.002), neuroblastoma histology (p = 0.011), unfavourable Shimada grading (p < 0.001), MYCN amplification (p < 0.001), increased urinary HVA/VMMA (p < 0.001). Higher serum CgA levels were also associated with a shorter 10-year overall survival probability in the 150 patients (p = 0.001) as well as in the 83 patients at stage 4 (p = 0.015).

Conclusion: Serum CgA at diagnosis is a highly reliable diagnostic and prognostic marker in patients with neuroblastoma. The role of serum CgA for monitoring disease response to treatment requires further investigation.

IPSO

IPSO001

FACTORS INFLUENCING THE RISK OF FAILURE OF SURGERY IN CHILDREN TREATED FOR NEUROBLASTOMA

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The SIOP Nephroblastoma Trial and Study Committee, Wroclaw, Poland

Purpose: Reasonably less aggressive treatment offers children with neuroblastoma (WT) great chance for cure with minimal sequels. Surgery, however, becomes even more important. Aim: Identify the risk factors for failure of surgery (FS); assess the relationship with survival.

Methods: Patients: 2092 localized (1763) and metastatic (329) WT (SIOP9301). Treatment: preoperative chemotherapy, surgery, postoperative chemotherapy ± radiotherapy. FS = incomplete resection of any invaded/suspicious area and/or an intraoperative rupture and occurred in 113 (5%) of cases. Factors evaluated for influence on FS: age, sex, tumor side, localized vs. metastatic disease, high (HR), intermediate (IR), low (LR) risk pathology, tumor volume and its change under pretreatment.

Results: Risk of FS was higher for right-sided tumors (p = 0.00931, rr = 1.65) and HR (p = 0.0356, rr = 1.96); diffuse anaplasia (p = 0.0269, rr = 2.16) > blastemal predominant (trend: p = 0.08). Median tumor volume was greater (at diagnosis 576 vs.402, p < 0.001; at surgery 308 vs. 150, p < 0.001) and its decrease smaller 38% vs. 61%, p = 0.006) in FS group. Children with FS were also older (median age 51 vs. 46 months, p < 0.001). There was no sex difference. In the univariate analysis, EFS (60 months) were lower in FS group than in non-FS (for EFS localized:80.5% vs. 90.5% p = 0.001; EFS metastatic: 45.0% vs. 74.4% p = 0.001) and pathology (EFS LR: 73.3% vs. 94.5% p = 0.004, EFS IR 80.1% vs. 88.3% p = 0.02; EFS HR 33.3% vs. 73.0% p = 0.002) but not in the multivariate analysis. FS was not associated with type (local/systemic) of relapse: p = 0.4/localized and p = 0.129/metastatic WT.

Conclusion: FS are rare in the reported study and are more likely in right sided tumors, larger volume tumors, HR pathology and older children. Surgeon shall pay special attention when operating such patients.

IPSO002

ONCOLOGICAL AND NEPHROLOGICAL OUTCOMES OF NEPHRON-SPARING SURGERY FOR UNILATERAL RENAL TUMORS: A 12-YEAR MEAN FOLLOW-UP STUDY OF 12 CHILDREN

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Purpose: To prevent renal failure, the Children’s Oncology Group recommends the use of nephron-sparing surgery (NSS) in children with unilateral Wilms tumor (WT) at risk for

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developing metachronous tumors. However, even minor post-uninephrectomy renal dysfunctions may be harbinger of late morbidity and mortality. The aim of the present study was to evaluate our institutional experience with NSS for unilateral renal tumor in children with or without predisposition to bilateral kidney tumors.

Methods: Between 1992 and 2011, 44 children with unilateral renal tumor underwent ablative renal surgery at a single academic centre (overall EFS: 87%). NSS was feasible in 13 children (six and two with stage I and II WT, respectively; two with hyperplastic multiloculated nephroblastomatosis and stage I WT; one with aniridia and stage I WT; one with cystic nephroma and one with oncocytoma). The KDQOI guidelines were used to classify the surviving patients into chronic kidney disease (CKD), stages based on their estimated glomerular filtration rate (eGFR).

Results: One child underwent an unnecessary nephrectomy elsewhere. At a median follow-up of 13 years (1–20), event free survival of 12 patients treated by NSS was 100%. Only one patient who underwent bilateral NSS for a metachronous WT was classified as stage 2 CKD (eGFR = 89 ml/min/1.73 m2). Both the B/L recurrences presented a renal function not different from subjects with two healthy kidneys (mean eGFR = 110.6 ± 17.5 ml/min/1.73 m2).

Conclusion: Present findings suggest that NSS is feasible in about 30% of children with unilateral renal tumor and may provide an opportunity to prevent post-uninephrectomy minor renal dysfunctions, while maintaining an excellent long-term oncologic outcome.

IPS0003
MANAGEMENT AND OUTCOMES IN MASSIVE BILATERAL WILMS TUMORS
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Purpose: To evaluate the outcome of children with bilateral wilms tumor (BWT) treated on ADMS-WT-99 protocol.

Methods: All children with bilateral WT registered in our solid tumor clinic from August 1999 through December 2010 were included. All received pre-resection chemotherapy of 6-10 weeks consisting of Actinomycin D, Cisplatin and Doxorubicin. This was followed by radiological re-evaluation and then either partial nephrectomy or tumorectomy depending on the tumor anatomy and location. Kaplan Meier survival estimates for overall survival(OS) and recurrence free survival(RFS) was calculated.

Results: Of the 178 fresh cases of WT treated during this period, 11 (6.2%) had bilateral involvement. All patients except one (12 cm and 3 cm) had massive bilateral tumors of more than 10 cm. There were 8 boys and 3 girls in the age range 6–30 months (5 < 12 months; 6 were 13–30 months). One patient had Denys Drash syndrome. Eighteen renal units were operated upon (10 tumorectomy; 5 partial nephrectomy and 3 nephrectomies) while one patient with IVC thrombus died of renal failure prior to resection. Tumor spill occurred in 3 patients (6 of 18 renal units (33%) two bilateral and 2 unilateral). Both the B/L resections refrused further treatment whereas the unilateral resections were treated with nephrectomy in one and tumorectomy in the other. There was one recurrence in the liver that was treated with radiofrequency ablation. All patients had low but acceptable GFR post-operatively. One patient developed post-operative peripheric infection for which a PCN drainage was required. One patient underwent laparotomy for adhesion obstruction. The 5-year OS was 90% [95CI 50.8–96.6] and the RFS was 38% [95CI 6.1–71.6].

Conclusion: Massive B/L renal tumors respond poorly to preoperative chemotherapy, are often not amenable to partial nephrectomy/tumorectomy and have a higher local recurrence rate giving a poor RFS.

IPS0004
LYMPH NODE SAMPLING IN WILMS TUMORS: SINGLE CENTRE EXPERIENCE
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Purpose: Lymph node evaluation (LN) in Wilms tumour (WT) is essential for accurate staging and the presence of nodal disease alters treatment and may affect survival.

Aim: To evaluate the frequency and pattern of LN sampling in children with WT and how it may affect prognosis.


Results: Over the study period 162 patients (67 boys and 95 girls), were treated for a total of 192 WT’s. The median age at diagnosis was 38 months. Thirty-three (20%) patients had bilateral WT, 26 synchronous and 7 metachronous. The majority received preoperative chemotherapy, in accordance with the SIOP protocol. A total of 106 patients had LN sampling, taken by the surgeon. An additional 12 patients had LN’s identified coincidentally in the nephrectomy specimen by the pathologist. We noted an upward trend in LN sampling, from 48% in the first 50 patients, to 79% in the last 50. When 3 or more LN’s were sampled, the likelihood of finding a tumour-positive node was 28% (10/35) compared with only 9% (8/94) if ≤2 nodes were sampled. The para-aortic region and renal hilum are the commonest sites for LN involvement. There was significant difference in the frequency of LN sampling between individual surgeons.

Conclusion: Failure to sample regional LN’s at the time of WT nephrectomy remains common in our practice. A minimum of 3 LN’s should be sampled, ideally from the renal hilum and para-aortic regions.

SOFT TISSUE TUMOURS

IPS0005
REVIEW OF LOCAL TREATMENT IN 145 CHILDREN WITH RMS AND RMS-LIKE TUMORS TREATED ACROSS TO CWS 2002 PROTOCOL
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Purpose: Aim of the report is to evaluate surgical treatment in children with RMS and RMS-like soft tissue sarcomas (STS).

Methods: 181 patients were registered in Polish Paediatric Solid Tumour Study Group, 145 children were treated according to CWS 2002 protocol for stage I-VW RMS and RMS-like sarcomas (girls 34/boys 80), 29 pts < 3, 117 pts > 3 years old. Pathology variants: RMI/E3, RMA/19, RME/RMA7, PNET/EII3/8S/19. Locations of primary tumours: non-BP/14, bladder & prostate/6, others/46, extremities/35, orbit/6, parameningeal/25, non-parameningeal head & neck/12, 1 pts with disseminated disease. T-status was: T1a-31, T1b-14, T2a-28, T2b-72; N: 0/107, N1-18, N2-43, N3-38, N: M0-101, M1-44. Treatment consisted of primary or secondary surgery, chemotherapy & radiotherapy.

Results: 79/145 patients are alive in 1st CR (55%), 2 pts died of progression of disease (DOD) (36%), 14 pts are alive in 2nd CR after relapse (10%). Regarding primary R0, 13 pts are alive in 1st CR (81%) and 3 pts in 2nd CR after relapse (10%), 20/9 pts after R1 are alive in 1st CR (72%), 7 pts died (DOD) (18%), 4 pts are alive in 2nd CR after relapse (10%). 15/28 pts after R2 are alive in 1st CR (81%) and 3 pts in 2nd CR after relapse (10%). 23 of 62 pts after initial biopsy are alive in 1st CR (37%), 34 pts died (DOD) (55%), 5 pts alive in 2nd CR after relapse (8%). Regarding localization of primary tumor the best outcome was noticed in pts with GU non-BP (85%), The worse outcome was in “other” localizations (thorax,abdomen) 41% and extremities (35%). Patients under or above 3 years with STS have similar chance for control of the disease (55.13% vs 53.84%).

Conclusion: Surprisingly, primary biopsied nonresectable tumors had worse outcome (33% in 1st CR and 8% in 2nd CR) than those after primary R2 resection (54% in 1st CR and 7% in 2nd CR) and weak chance for a long term CR. Special attention must be paid to surgical local control in extremity tumours (only 35% alive in 1st CR) and so called other locations (41%).

IPS0006
CLINICAL ASPECTS OF THORACIC NON-RHABDO SOFT-TISSUE SARCOMAS (NRSTS): THE ITALIAN EXPERIENCE
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Purpose: Among pediatric Soft Tissues Sarcomas (STS), Rhabdomyosarcoma and Ewing Sarcoma/pNET are well investigated entities in all sites of the body. NRSTS, represents a heterogeneous and less defined group. We report the experience of the Italian STS Committee on NRSTS of the thorax.

Methods: We analyzed retrospectively data on 41 patients with thoracic NRSTS enrolled in Italian Protocols for localized and for metastatic STS between 1979–2005.

Results: Patients ≥10 years were 18(41%) Primary site: 25 thoracic wall, 9 paraspinal, 7 intracavitary.

Sarcoma, 5 Fibrosarcoma, 18 other histotypes. Initial resection was attempted in 31/41: 15 initial complete surgery (partial cystectomy), 45 received conservative surgery with brachytherapy is required to confirm whether this approach results in lower morbidity in the future.

Conclusion: Prognosis of thoracic NRSTS is severe, although improvements have been registered in the last years. Small non invasive tumors show the best results, but if local control is inadequate, relapses are frequent. Surgery represents the keystone of treatment.

IPS0007

IMPROVEMENT IN LOCAL TREATMENT FOR BLADDER AND/OR PROSTATE RHABDOMYOSARCOMA THROUGH 3 CONSECUTIVE SIOP STUDIES (MALIGNANT MESENCHYMAL TUMOURS: MMT 84, 89 AND 95)

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Purpose: To report on local treatment of 172 children (138 boys–34 girls) with bladder and/or prostate rhabdomyosarcoma treated in 3 consecutive SIOP studies (MMT 84, 89 and 95).

Methods: Most patients were treated by chemotherapy after initial biopsy (IRS III group) and downstaging treatment for a residual mass after chemotherapy. Local treatment consisted in surgery (radical e.g. total cystectomy and/or total prostatectomy, or conservative e.g. partial cystectomy and/or partial prostatectomy) and/or radiotherapy (external beam (ERT) or brachytherapy). An attempt was made to reduce significant therapy (ERT and/or radical surgery) without jeopardizing survival.

Results: One hundred-seventy two patients were included in the studies. The 5-year EFS and OS were 65% (95% CI: 57–71%) and 77% (95% CI: 70–83%) respectively, with no significant difference between the 3 studies in univariate analysis. Among 119 survivors (100 in first complete remission and 19 in second or subsequent CR after relapse) with more than 5 years of follow-up, 59 (50%) were cured without significant local procedures: 10 had had only biopsy and no further local treatment, 1 patient received limited chemotherapy after initial complete surgery (partial cystectomy), 45 received conservative surgery with additional brachytherapy for 14 of them and 3 were treated with brachytherapy without surgery. Sixty received significant local therapy; 18 received ERT after conservative surgery for 14 of them, 42 underwent radical surgery (13 total cystectomy, 11 total prostatectomy and 18 total cysto-prostatectomy). Eighteen of those 42 patients received additional ERT. Bladder preservation improved from 60% to 76% through the 3 studies and ERT of the preserved bladder decreased from 44% to 15%.

Conclusion: The burden of local therapy decreased in the MMT studies whilst maintaining survival rates. Further assessment of the late effects of local therapy and especially of brachytherapy is required to confirm whether this approach results in lower morbidity in the long term.

IPS0008

EXTRAESKELETAL EWING SARCOMA IN CHILDREN: ANALYSIS OF OUTCOME FROM A SINGLE INSTITUTION

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Purpose: The aim of the present study was to evaluate the outcome of children with extraskelatal Ewing sarcoma (EES) treated with multi-modality at a single institution.

Methods: The clinical features, treatment and outcome of children with EES treated between March 2006 and March 2011 were evaluated.

Results: There were 24 patients (19 boys and 5 girls) with a median age of 10 years (range 11 months – 17 years). Disease sites were the extremity (14), trunk (3), intra-abdominal (3), head and neck (3) and perineum (1). Upfront surgery was performed in 10 patients. Fourteen patients received prior chemotherapy including one patient who also received radiation therapy. In these 14 patients local therapy included surgery in 13 and definitive radiotherapy in one. Tumor free margins were achieved in 21/23 patients; both patients with positive margins had intra-abdominal disease. In patients with negative margins the smallest 3 dimensional margin was less than 1 cm in 16 and more than 1 cm in 5 patients. Fourteen patients received postoperative radiotherapy. There were six (25%) relapses (local: 1, distant: 3, local and distant: 2). Patient with isolated local relapse had received definitive radiotherapy and was salvaged with surgery and brachytherapy. With a median follow-up of 38 months (range 12– 79 months), 18 (75%) patients are alive and disease-free, two (8%) are alive with evidence of disease; three (12%) have died of disease and one (4%) died of treatment related toxicity. The 5-year relapse free survival and overall survival rates are 68% and 78% respectively. There was no difference in outcomes of patients with a negative margin of more or less than 1 cm (p = NS).

Conclusion: Optimal outcome could be achieved in children with EES with multimodal therapy, although disease relapses remain a cause of concern. Achieving a three dimensional tumor free margin should be the goal of surgical resection.

IPS0009

OUTCOMES OF NONRHABDOMYOSARCOMA SOFT TISSUE SARCOMAS IN CHILDREN TREATED AT A SINGLE INSTITUTION

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Purpose: To describe the outcome of pediatric patients with nonrhabdomyosarcoma soft tissue sarcoma (NRSTS) treated at a single institute.

Methods: Of the 250 patients with pediatric soft tissue tumors treated between January 2006 and December 2011 the records of 65 patients (44 boys and 21 girls) with NRSTS were reviewed.

Results: The median age was 11 years (range, 3 months to 18 years). The common histological subtypes were synovial sarcoma (n = 28), alveolar soft part sarcoma (n = 6), spindle cell sarcoma (n = 5) and fibrosarcoma (n = 4). Majority of the tumors were localized to the extremities (37) followed by the trunk (10), abdomen (9), and head and neck (8). Tumor size were T1a/b in 30 and T2a/b in 35 patients. More than 80% (54/65) tumors were grade 3. Regional lymph node and/or pulmonary metastases were present in nine patients. Upfront surgery was performed in 48 patients (33 were primary re-excision). Delayed surgery was performed in the remaining 17 patients after neoadjuvant chemotherapy. Cut margins were positive in five patients and negative in 57 patients. In patients with a negative margin, the smallest margin was more than 1 cm in 19 patients and less than 1 cm in 38 patients. Adjuvant radiotherapy was used in 39 patients and chemotherapy was offered to 28 patients. At a median follow-up of 31 months (range 1–73 months), the projected 5-year overall survival and disease-free survival is 78% and 60% respectively. Tumor size, presence of metastatic disease, and margin status were predictive of overall and disease-free survival. Although there was a trend toward better survival in patients with a margin of more than 1 cm, it was not statistically significant.

Conclusion: Complete surgical excision with tumor negative margins is essential in management of NRSTS. T-size and metastatic disease are important predictors of prognosis.

IPS00010

OPTIMIZED IN VIVO IMAGING OF DISSEMINATED RHABDOMYOSARCOMA IN MICE BY PET-MRI

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Purpose: Assessment of suspicious structures after therapy in metastatic rhabdomyosarcoma (RMS) is often difficult using conventional imaging. Therefore, novel imaging modalities such as PET/MRI need to be evaluated in order to combine functional and anatomical information. The aim of this study was to develop an animal model of metastatic RMS and to evaluate PET/MRI as a novel imaging technology.

Methods: Embryonal or alveolar RMS cells were stably transfected with mCherry and stauas luciferase. 106E5 cells were injected i.p. into NOD/LtSz-scid IL2Rnull mice.

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NEUROBLASTOMA

IPS00011

STAGE 4 NEUROBLASTOMA: OUTCOME OVER A 14 YEAR PERIOD FROM AIIMS NB 96 PROTOCOL

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Purpose: To evaluate the outcome of children with stage 4 neuroblastoma (NB).

Methods: All children with stage 4 (NB) registered from October 1996 through July 2009 were included. INSS was used for staging. All received chemotherapy and radiation therapy. Results: Of the 148 NB cases registered in this period, 71 (48%) were stage 4. The age ranged of 3–137 months (median 36) with only 12 (17%) children being below 12-months. Fifty-eight (82%) of the primary tumours were abdominal with neuroblastoma staging. Amplification) reports. In two cases (1 'open/1 'needle biopsy) MYCN status was not confirmed in MLPA (Multiplex Ligation-dependent Probe Amplification) reports. In two cases (1 'open' or 'needle' biopsy) had 1p and 11q confirmed in MLPA (Multiplex Ligation-dependent Probe Amplification) and complete remission was achieved in 17.6%. Large proportion (48%) of our NB cases are stage 4 disease at presentation. Though a large number of these respond to chemotherapy, the 3 year OS is dismal 38% with only 17.6% achieving disease free status.

IPS00012

INFANTILE NEUROBLASTOMA – 5 YEARS POST SURGICAL OUTCOME

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Purpose: Treatment of Infantile neuroblastomas regarding the extent of surgery is controversial. We present here the outcome of children with infantile neuroblastomas where the implications of extent of surgical resection on long term overall survival has been analysed.

Methods: From 1996 to 2007, all children with neuroblastoma of age upto 365 days and completed therapy were included in the study. INSS, surgical extent of resection were tabulated and analysed, though no thorough risk stratification could be performed. All children were reviewed up to 5 years post therapy till 2011, and overall survival in relation to extent of surgical excision was evaluated.

Results: 34 infants presented to the departments of pediatric surgery and hematology-oncology with neuroblastoma. 9 who abandoned treatment were excluded. Of the 25 children who completed therapy, stage I were 5/25 (20%), Stage 3–8/25 (32%), stage 4–7/25 (28%), stage 4s–5/25 (20%). Depending on the extent of the disease, surgical intervention was pursued in 20 patients, either upfront (n = 12 [60%]) or post-chemotherapy (n = 8 [40%]). Total excision (n = 8) was done in all stage 1 tumors (5), and 3 of the stage 3 tumors post neoadjuvant chemotherapy, 12 had residual tumor after resection. On evaluation of the 5 year survival, 16 (64%) of the children are alive and well. 6/9 succumbed to progressive disease/reoccurrence(PR/DR) and 3 to chemotherapy related complications. On evaluation of the cause of PDR, 4/6 had unfavorable histology, and 5/6 had incomplete resection of the tumor.

Conclusion: Unfavorable histology and incomplete resection was found to be main causes of progressive disease/reoccurrence in infantile neuroblastomas amounting to 24% of mortality. Since the extent of surgical resection can be influenced by the surgeon, especially in the third world countries, with lack of infrastructure and resources, a complete surgical excision should be the focus of treatment of infantile neuroblastomas.

IPS00013

UTILITY OF OPEN VERSUS NEEDLE BIOPSY IN DIAGNOSING NEUROBLASTOMA – A PRELIMINARY REPORT

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Purpose: Open surgical biopsy is traditionally advocated prior to initiating therapy in neuroblastoma therapy protocols. We report the utility (Shimada classification, MYCN expression, Cyto genetics – 1 p, 11 q) and value of open vs image guided ‘needle’ biopsy in aiding diagnosis and risk stratification of neuroblastoma.

Methods: Medical records of all new cases of neuroblastoma presenting to a single centre during January 2002–January 2012 were examined.

Results: Twenty six patients [median age 30 months: range 1.2–73 months] underwent ‘open’ or ‘needle’ biopsy for tumour diagnosis. Twenty had ‘open’ and six cases ‘needle’ biopsy procedures. Neuroblastoma disease classification was stage 4 (n = 17), stage 3 (n = 6), stage 2 (n = 2) and stage 4S in a single infant. Site of primary tumour included adrenal gland (n = 12), abdomen (n = 9), thorax (n = 2), abdominothoracic (n = 2) and abdomino pelvic regions (n = 1). In all patients ‘open’ vs ‘needle’ adequate tissue was retrieved for histological confirmation of neuroblastoma. Eleven patients (10 ‘open’ and 1 ‘needle’ biopsy) had lp and 1q confirmed in MLPA (Multiplex Ligation-dependent Probe Amplification) reports. In two cases (1 ‘open’ needle biopsy) MYCN status was not assessed despite adequate tissue sampling. No single patient required a second tumour biopsy procedure.

Conclusion: Open and image guided needle biopsy appear to yield adequate tissue sampling for diagnosis, risk classification and staging of neuroblastoma. Larger co-operative studies may support the wider practice of deploying needle biopsy in future protocols and neuroblastoma staging.

IPS00014

DOES “AGGRESSIVE SURGICAL RESSECTION” IMPROVE SURVIVAL FOR ADVANCED STAGE III AND IV NEUROBLASTOMA? – A SYSTEMATIC REVIEW AND META-ANALYSIS

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Purpose: The defining role of surgery in the management of advanced staged childhood neuroblastoma (NBL) is conflicting. Against this background we report a systematic review and meta-analysis of published studies to address the evidence for curative ‘gross total tumour resection’ (GTR) in stage III and IV neuroblastoma.

Methods: Studies were identified using Medline (1950–), Embase (1980–) and Cochrane database(s). Search strategy included terms – ‘neuroblastoma ’, ‘surgery’ ‘gross total resection’, ‘limited or partial resection’. Studies were required to report 2 or 5 year survival after GTR and partial resection (PR) for stage III or IV NBL. Data were analysed for – treatment era, chemotherapeutic(s), radiotheray, extent of surgery, MYCN status, INSS stage, and surgical morbidity. Primary outcomes were 2 and 5-year overall (OS) and disease free survival (DFS). Data were analysed using Review Manager. Categorial data with the Mantel-Haenszel method for a random effects model. Odds ratios (95% CI) were calculated for dichotomous variables. Heterogeneity was calculated using X²and I². Results: Twenty studies (total patients = 2,336) yielded robust data for inclusion in the meta-analysis. No RCTs defined the role of surgery. All published data analysed included the era(s) 1952–2005 where a variety of cancer therapy protocols were deployed. Conclusion: This study provides strong evidence to support the role of GTR in children with Stage III NBL to improve survival (5 yrs DFS). However the heroic and painstaking efforts by surgeons to achieve GTR in stage IV NBL appears to offer no survival benefits.

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IMPACT OF LOCAL CONTROL IN METASTATIC NEUROBLASTOMA
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Purpose: Surgery on primary tumor plays an important role in the treatment of metastatic neuroblastoma. The aim of this study is to evaluate the impact of radical surgery on survival in patients treated with conventional and high-dose chemotherapy, with or without radiotherapy.

Methods: Fifty-six patients older than 1 year of age with metastatic neuroblastoma were enrolled in two consecutive local protocols based on conventional plus high dose chemotherapy and autologous peripheral stem cell rescue. Thirty-five, received also local radiotherapy (RT) plus cis-retinoic acid. Surgery was performed by the same surgical team. Surgery was classified as complete, with macroscopic residual or with microscopic residual.

The Kaplan–Meier method and the Cox proportional hazard model were used to calculate the probability of overall and progression-free survival (OS and PFS) and to perform a multivariate analysis on factors influencing prognosis.

Results: The 5-year PFS and OS for complete surgery patients were 22% (95% CI 10–37%) and 34% (95% CI 19–49%); 33% (95% CI 5–70%) and 47% (95% CI 11–76%) for microscopic residual and 33% (95% CI 8–62%) for both in macroscopic residual. The difference was not statistically significant. In multivariate analysis, the presence of MYCN amplification predicted a higher risk of death with an hazard ratio (HR) of 2.9 (p < 0.01); patients transplanted in partial response before high dose chemotherapy had an increased risk of recurrence as compared to patients in complete response/very good partial response, the HR being 2.8 (p < 0.08). Neither radical surgery nor RT represented prognostic factors for OS or PFS in multivariate analysis. The local PFS probability at 5 years in patients who did or did not receive RT was 91% (95% CI 75–97%) and 52% (95% CI 26–72%), respectively (p = 0.24).

Conclusion: Our data suggest that the quality of resection did not impact on survival in patients treated with high-dose chemotherapy; local radiotherapy may marginally contribute to local disease control.

SURGICAL APPROACHES FOR TUMORS OF THE UPPER APERTURE AREA OF THE CHEST IN CHILDREN
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Purpose: Surgery of tumors of the aperture area is a difficult section of thoracic surgery. For planning a surgical intervention it’s necessary to know: the topography of the tumor in the chest, the relationship of the tumor with interscalene spaces at the neck and its morphology.

Methods: In our clinic 15 children (2006–March 2012) were operated on for: neuroblastoma – 7, ganglioneuroma – 4, embryonic carcinoma – 1, mature teratoma – 2 and cavernous hemangioma – 1. Median age was 32 months (18–63). There were approaches: thoracotomy (in the 5 th intercostals space) – 3; thoracoscopic – 3; sternotomy – 3, Masaoka’s approach – 1, hemiclamshell/trapdoor incision – 1, L-shaped – 2 and two combined approaches, when cervical transclavicular access combined with thoracotomy or thoracoscopy.

Results: Time of operation – 65–360 min (M = 130 min). Blood loss – 30–350 ml (M = 90 ml). Complete removal of the tumor was assessed in 11 pts (73%). There were no severe intraoperative complications. Horner’s syndrome after surgery was in 4 pts. 13 alive patients are without relapses. Median follow up was 38.5 months (2–56). Two deaths: 1 girl with embryonic carcinoma (Masoka’s approach) died of disease progression and 1 boy with NB (intermediate risk group) died at 62 days after surgery (serotonin) of lung complications.

Conclusion: Our philosophy in choosing of surgical access for tumors located in the thoracic intercostal area is to maintain the sternum and hence to maintain the frame of the chest and also based on an understanding of tumor biology. We believe that the L-shaped access may be advantageous for tumors with a small intrathoracic component. It’s important to preserve the clavicle, and most importantly sterno-clavicular junction.

THE FIRST EXPERIENCE WITH NEPHRON SPARING SURGERY (NSS) FOR UNILATERAL WILMS TUMOR (UWT) WITHIN WT SIOP 2001

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Purpose: Although total nephrectomy (TN) remains the standard in uWT, the SIOP WT 2001 protocol allowed NSS for polar or peripherally non- infiltrating tumors. Aim: Inventory of the current SIOP NSS-experience.

Methods: Patients (stage I–IV) with an unequivocal surgical technique recorded, were included (n = 2664, 84%). All had received adjuvant chemotherapy and delayed surgery. In 97 (3%) NSS was performed and in 2567 TN. Results regarding local recurrence and survival were compared and stratified for stage and histopathology.

Results: The NSS group contained more stage I tumors than the TN group: 60% vs 57% respectively. Within stage III, after NSS, 41/17 (65%) had positive margins (M+), of whom 8/17 (47%) had tumor negative lymph node (N-) 1. After TN, 3326/65 (50%) had M+ of whom 2422/65 (36%) had LN+ 2. The LN – M+ status was regarded as ‘surgical failures’. Treatment of M+ in the NSS group resulted besides intensified chemotherapy (VAD) in 4 conversions to TN, i.e. combined with radiotherapy, 3 patients were given radiotherapy only, and in 4 patients local therapy, if given, was not recorded (1 margin positive for nephroblastomatosis). After NSS, 3 recurrences occurred. The 3- and 5-years OS (94% vs 95% CI 93.3–100%) and 92.5% (95% CI 86.9–98.5), respectively and did not significantly differ from OS/EFS after TN: OS 92.0% (95% CI 90.7–93.2), EFS 83.8% (95% CI 82.2–85.4). Stratification for localized versus metastatic disease, stage or histology did not show significant differences in outcome after NSS or TN.

Conclusion: NSS was only performed in 3% of uWT patients, concordant with the intention to allocate NSS to small tumors. Despite good long term survival with few relapses, the gain of nephrons still carefully needs to be weighed against the risk to induce stage 3 with the consequence of intensified therapy including irradiation.

RENAL FUNCTION OUTCOME OF SURGERY FOR UNILATERAL RENAL TUMOR IN CHILDHOOD: A CROSS-SECTIONAL AND LONGITUDINAL STUDY UP TO THE AGE OF 50 YEARS

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Purpose: Many cohort studies have suggested that even mild and moderate renal dysfunctions may be associated with an increased risk of cardiovascular diseases and overall mortality. The present study was designed to assess the prevalence of renal dysfunctions in children with unilateral renal tumor and a normal contralateral kidney, over a long period of time after nephrectomy or nephron-sparing surgery.

Methods: At a single academic pediatric surgery unit, 55 children treated by nephrectomy and 12 treated by nephron-sparing surgery were enrolled. Glomerular filtration rate was estimated (eGFR) with the Modification of Diet in renal disease Study equation and Schwartz equation in patients older or younger than 17 years, respectively. Cross-sectional data analysis was performed in 14 patients aged ≥30 years a significant difference in mean eGFR between 12 children treated by nephron-sparing surgery and 41 treated by nephrectomy (109.8 vs 96.2 ml/min/1.73 m²; p = 0.03). In patients treated by nephrectomy there was a significant difference in mean eGFR between 41 patients aged ≤30 year and 14 patients aged >30 year (96.2 vs 73.0 ml/min/1.73 m²; p = 0.001). Eighteen of the 41 ≤30 year old patients and eleven of the 14 >30 year old patient who had undergone nephrectomy had a mean eGFR between 86 and 98 ml/min/1.73 m² (p = 0.03). The longitudinal study of serial eGFR measurement in individual patients confirmed the positive correlation between aging and renal dysfunction.

Conclusion: Children with unilateral renal tumor who have undergone nephrectomy may present during adulthood a progressive decline of renal function associated with a high prevalence of mild and moderate renal dysfunctions. Nephron-sparing surgery might have a renal function advantage over nephrectomy.

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IS A HEMISCROTECTOMY AFTER PRIMARY TRANSSCROTAL APPROACH IN PATIENTS WITH PARATESTICULAR RHABDOMYOSARCOMA NECESSARY?

RESULTS FROM THE “COOPERATIVE WEICHTEILSARKOM STUDIENGRUPPE” TRIALS CWS-86, -91, -96 AND -2002P

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Purpose: Patients suffering from paratesticular rhabdomyosarcoma (RMS) treated within the CWS trials have a very good prognosis. Complete surgical tumor resections are often possible due to early diagnosis and the site specificity of the tumors. A major surgical treatment problem is inadequate primary surgical procedures (e.g. transscrotal approach) and the necessity of secondary hemiscrotectomy. The aim of this study was to evaluate the necessity of hemiscrotectomy regarding local relapse and outcome. 

Methods: One-hundred-seventy-three patients with diagnosis of paratesticular RMS were enrolled into the trials between 1986 and 2008. Nine patients were excluded due to an incomplete data set. One-hundred-sixty-four patients were finally analyzed. All patients were treated according to the treatment protocols including multiagent chemotherapy, tumor resection and/or radiation therapy.

Results: One-hundred-fifty six patients had embryonal histology. Eight patients had alveolar RMS. The five year overall survival rate was 91.9% ± 2.2 for the whole group. Thirty-two patients underwent transscrotal approaches initially (RM: n = 30; RMA: n = 2). Fourteen of these patients were treated with hemiscrotectomy. One of them relapsed locally and survived. One of the patients died of metastatic relapse. Patients without hemiscrotectomy had no local relapse and 1/18 received radiotherapy at primary site. One of eighteen patients treated without hemiscrotectomy died due to metastatic relapse.

Conclusion: Hemiscrotectomy seems not to be mandatory in patients after transscrotal approaches regarding outcome and local relapse.

IMPACT OF POSTOPERATIVE COMPLICATIONS ON THE OVERALL SURVIVAL OF PATIENTS WITH HEPATOBLASTOMA

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Purpose: The resection of hepatoblastoma is in many cases a demanding operation and may result in postoperative complications. We evaluated how these complications influence the whole course of disease and weather complications influence the overall survival of these patients.

Methods: Patients with high-risk (HR) hepatoblastoma and standard-risk (SR) hepatoblastoma treated in the German prospective multi-centre study HB99 of the GPOH in the years 1999 to 2008 were evaluated concerning postoperative complications, further operations and therapy, overall survival (OS). Possible reasons for complication as size, location (PRETEXT) and vessel involvement were also evaluated.

Results: Surgical Information were available for 126 patients out of 141 patients, 48 of these HR and 78 SR. Postoperative complications as biloma (9), cholestasia (4), failure of liver perfusion (5) and others (7) occurred in 20% (25) of the operated patients, 19 (76%) required a second operation. In the HR-group the ratio of complications was higher (27%) compared to the SR-group (15%). Patients with PRETEXT II/III tumour had the same rate of complications as patients with PRETEXT III/IV tumour (19% vs. 20%). Patients with vessel involvement had significantly more complications than patients without (54% vs. 17%, p = 0.01). The postoperative treatment started more often delayed (> 20 days) in patients with postoperative complications (87% vs. 57%, n.s.) 5-year OS for patients in the HR-group was significantly lower with complications than without (46% vs. 75%, p = 0.009). There was no difference in the SR-group. In multivariate analysis postoperative complication was an independent negative prognostic factor (HR 3.5 < p < 0.05).

Conclusion: Postoperative complications and inevitable second operations worsen the overall survival of patients with HR-hepatoblastoma. Possible reasons are the high rate of complications in patients with tumour in the big vessels or the delayed further treatment of these patients. This makes it all the more important to treat these patients in experienced centres.

GERM CELL TUMOURS

TESTICULAR TUMOR IN UNDESCENDED TESTIS IN CHILDREN BELOW 5 YEARS OF AGE

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Purpose: To evaluate the presentation, treatment and outcome of testicular tumor in undescended testis (UDT) in boys below 5 years of age.

Methods: Case records of boys below 5 years of age, presenting to the above two hospitals in the period 2008–2011, and diagnosed to have germ cell tumors (GCT), both benign and malignant, in the UDT were reviewed for presentation, treatment and outcome.

Results: Seven children in the age range of 18–54 months (mean 31 months) were included. While 5 of these 7 (71%) presented with an abdominal mass (one antenatally detected), 2 (28%) were detected to have a GCT during orchiopexy for UDT. Ultrasound and contrast enhanced CT scans showed a heterogenous solid and cystic mass in all patients with abdominal mass. In 3 of these 5 with an abdominal mass, the TFp was markedly elevated. Two of these three with elevated TFp were endodermal sinus tumors while the third was embryonal carcinoma. The 4th patient with an abdominal mass was diagnosed to have an immature teratoma (ITM) while the patient with antenatally diagnosed mass had a mature cystic teratoma (MT). Both these had a normal TFp. Both the patients with incidentally detected mass during the orchiopexy had mature teratoma (MT). The three with raised TFp received 2 courses of neoadjuvant chemotherapy (Cisplatin + Etoposide + Bleomycin-PEB) followed by resection and one course of adjuvant PEI. The children with ITM and MT did not receive any chemotherapy. All the seven children are alive and disease free at last follow-up ranging from 48 months to 2 months. Two of these 7 patients had a testicular pathosis placed subsequently.

Conclusion: Though rare, boys with impalpable undescended testis may develop germ cell tumors early in childhood. These can be managed with chemotherapy (for malignant ones) and resection and have a good disease free outcome.

SURGICAL TECHNIQUES OF OVARIAN TRANSPOSITION IN CHILDREN UNDERGOING RADIOTHERAPY OR BRACHYTHERAPY FOR CANCER

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Purpose: Ovarian transposition (OT) out of the radiation field reduces the ovarian exposure. The aim of this study is to describe surgical techniques of OT in children according to radiotherapy techniques.
Methods: 28 patients underwent OT for brachytherapy or external beam radiotherapy (ERT) between November 1998 and December 2011. For patients undergoing brachytherapy, the ovaries were unjured, while for those undergoing ERT, the ovaries were removed. Laparoscopic technique was used for the ovarian mobilization. They were then attached to the abdominal wall. Ultrasound or MRI were used to confirm the ovarian position in cases of ERT. The median age of the patients was 5 years (1–18).

Results: OT was performed at median age of 5 years (1–18). Fifteen patients had OT without dissection of the ovaries and 13 had OT to the paracolic gaures. Surgery was performed by laparoscopy in 20 patients and by laparotomy in 8 patients. OT was unilateral in 6 patients and bilateral in 22 patients. The calculated median ovarian radiation dose was 1.4 Gy (0.4–2.1) for brachytherapy and 60 Gy (45–60) and 5 Gy (0.4–23.7) for ERT with a median dose to the tumor of 42 Gy (36–55).

Conclusion: These 2 techniques lead to an acceptable ovarian irradiation consistent with future normal function. Longer follow-up is required to assess the ovarian function.

RARE TUMOURS/MISCELLANEOUS

IPSO0024

PATTERNS OF COMPLICATIONS AND THE EFFICACY OF ANTIBIOTIC LOCK IN SALVAGE OF HICKMAN CATHETERS IN PEDIATRIC PATIENTS UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANT: EXPERIENCE FROM A TERTIARY CARE CENTRE IN INDIA

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Purpose: To evaluate the complications and the role of antibiotic lock system in salvage of hickman catheters in children undergoing hematopoietic stem cell transplant (HSCT).

Methods: The records of children who underwent HSCT from November 2007 to May 2011 were analyzed. Hickman insertions were performed in the operation theatre under general anesthesia and catheter tip position confirmed with X-ray. Post insertion surveillance blood cultures were drawn from all lumina. Colonisation was defined as growth of an organism from any lumina in absence of fever (i.e. temperature > 100 F). Catheter-related blood stream infection (CRBSI) was defined as growth of an organism from any lumina in presence of fever. Antibiotic locks were used for both colonization and CRBSI (if not removed due to persistent fever or hemodynamic instability) for 14 hours. Urokinase was instilled in catheters which were blocked and patency checked after 24 hours.

Results: 45 children (29 boys and 16 girls) with a median age at transplant of 12.5 (1.94–19) yrs underwent 52 (29 autologous and 23 allogeneic) hickman insertions. There were no insertion related complications like pneumothorax, hemoptysis, arterial perforation or air embolism. Colonisation of hickman lumina was seen in 7 (13%), with all catheters salvaged with antibiotic lock. CRBSI was seen in 9 of which 4 were salvaged. Organisms grown from surveillance cultures or CRBSIs were Pseudomonas spp (5), S aureus (2), Streptococcus (1), Stenotrophomonas (1), Candida spp (2), Enterococci (2), acinetobacter (2), gram positive bacilli (1) and coagulase-negative S aureus (1). Two catheters were removed due to blockage and tip migration. The median duration of catheter stay was 123 (11–1091) days with total catheter days 910.

Conclusion: Most common complications in our study were hickman lumina colonisation and CRBSIs. However majority of catheters were salvaged with antibiotic lock.

IPSO0025

ADDITIONAL EPIDURAL ANALGESIA FOR MAJOR ABDOMINAL TUMOR SURGERY IN CHILDREN

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Purpose: To analyse the effects of additional epidural anaesthesia using a tunneled permanent catheter in children undergoing major abdominal tumor surgery.

Methods: We retrospectively analyzed 40 children undergoing major abdominal tumor surgery with additional perioperative conduction anesthesia using an epidural catheter (0.2% ropivacain ± sufentanil). The study group was compared to a historical control group (n = 44) undergoing abdominal tumor surgery without conduction anesthesia. Surgical procedures were scored according to complexity and surgical trauma. Demographic data and postoperative courses were assessed. Pain scores were monitored at 24 and 48 hours postoperatively.

Results: There were no statistically significant differences between the 2 groups regarding demographic data. Surgical scores (grade EBI/E BS) were significantly higher in the study group (1/10/20) compared to control group (9/22/13, p = 0.02). Accordingly, mean operation times were longer in the study group (4.7 hours, range 4.11–5.39) compared to control patients (2.8 hours, range 2.56–3.32, p < 0.001). Median time for placement of the catheter was 10.0 minutes (8.8–11.5); catheters were removed after mean 3.9 days (3.14–4.85). Pain scores were lower in the study group after 24 hours (mean 2.9, 2.22–3.58) and 48 hours (mean 0.97, 0.47–1.48) compared to controls (3.57, 2.94–4.2 and 1.65, 1.06–2.24) but did not reach statistical significance (p = 0.15 and 0.09). Despite the higher complexity and trauma of surgical procedures in the study group, there were no significant differences between the two groups with regard to postoperative ventilation time, time on intensive care unit, time to completed oral intake, time to full mobilization, and time to discharge from hospital. No adverse effects related to epidural anaesthesia were noted.

Conclusion: Children undergoing major abdominal tumor surgery benefit from additional conduction anesthesia using an epidural catheter. This tool provides better pain control and positively influences the general early postoperative course.

IPSO0026

PERIPHERALLY INSERTED CENTRAL CATHETERIZATION IN ACUTE LEUKEMIA PATIENTS: A SINGLE TERTIARY CARE CENTRE EXPERIENCE FROM EASTERN INDIA

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Purpose: PICC is a well known central venous access device that plays important role in successful administration of chemotherapy agents and other supportive medications. Due to low incidence of procedure related infection, it is now becoming method of choice in dealing patients with hematopoietic- oncological conditions. Considering all merits and demerits we did a prospective study to compare beneficial effects versus complications in our patient pool.

Methods: We analysed a total no of 94 PICC in 88 acute leukemia patients (age range 1.5–65 years) during January, 2006 to December, 2010. We have selected PICC from one reputed company, with traditional peel-away cannula insertion technique and placed only in vein in ante-cubital fossa under strict aseptic condition and performed by doctors & trained nurses in our study team.

Results: We evaluated these 94 PICC with a total of 7520 access days. Rates of catheter related sepsis was 0.079/100 days, Coagulase negative Staphylococcus was the most common organism. Rate of non infectious complication was 0.100/100 catheter days. The most common reason for PICC removal were blockage 8 (8.5%) and infection 6 (6.3%). We studied and observed that role of complications, cost of PICC insertion, care and maintenance were comparatively low as compared to the Hickman catheter.

Conclusion: Our study revealed that 74% patients did not face any complications, 10% developed catheter induced sepsis, 8% developed erosion from insertion site. PICC is method of choice for long term accessing of central venous system for cancer patients having merits like minimum discomfort, easy to implant, well tolerated, fewer complications, low rate and without any need for repeated venipuncture.

SURGICAL CHARACTERISTICS OF MALIGNANT PERIPHERAL NERVE SHEATH TUMOUR (MPNST) – EXPERIENCE OF THE POLISH PAEDIATRIC SOLID TUMOUR STUDY GROUP

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Purpose: Aim of the report is to evaluate characteristics and surgical treatment of malignant peripheral nerve sheath tumour (MPNST) in Polish Paediatric Solid Tumour Study Group (PSTSG).

Methods: Patients: 381 patients (pts) with soft tissue sarcoma (STS) staged I–IV were registered and treated in PSTSG according to CWS 1996 and 2002 protocols. Twelve of 49 STS (64%, 18/28) were diagnosed as MPNST and treated according to the non- rhabdomyosarcoma arm in CWS protocols (7 pts/CWS 2002, 5 pts/CWS 96). Primary tumours were located in: extremities/1, thorax/4, abdominal cavity/3, non-parameningeal headneck/3, parameningeal headneck/1. T-status was T1a/T1b, T2a/T2b, T2a/T2b-5. distant mets were detected in 3. Treatment consisted of chemotherapy and primary or secondary
resection of tumors/R0-0, R1-3, R2-5, biopsy-4/and radiotherapy/8 pts/. The risk groups
were later administered sunitinib or other TKR (tyrosine kinase receptor) inhibitors.

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**SIOP ABSTRACTS**

**IPSO0028**

**EXPRESSON OF A NOVEL GENE IN AN ANIMAL MODEL OF DESMOPLASTIC SMALL ROUND CELL TUMOR**
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**Purpose:** Desmoplasic small round cell tumor(DSRCT) is a rare abdominal sarcoma for which no effective treatment has been proven. Lack of progress in the treatment of DSRCT, has been hindered by the absence of commercially available cell lines and lack of animal models. Here we describe a human xenograft model of DSRCT.

**Methods:** After approval from the institutional review board, abdominal tumor tissue from patients with DSRCT undergoing surgical resection, were minced and directly implanted into nude mice, and NOD-SCID mice. Subcutaneous, intra-abdominal and perinephric transplants were evaluated. In addition, immunohistochemistry with fresh frozen patient tissue was done to confirm the expression of the novel gene TOX-4.

**Results:** Human DSRCT tissue from peritoneal and omental implants in 3 different patients, were found to be very hypovascular. Zero to 1 CD31 positive vessels were identified per high powered field, indicating very little angiogenic activity despite many small round blue cells present. Subcutaneous and intraabdominal DSRCT transplanted tissue did not grow in nude or NOD-SCID mice. Subcutaneous, intra-abdominal and perinephric transplants were evaluated. In addition, immunohistochemistry with fresh frozen patient tissue was done to confirm the expression of the novel gene TOX-4.

**Conclusion:** We have demonstrated successful engraftment and growth of human DSRCT in a murine model. To our knowledge, this is the first description of an orthotopic xenograft model of DSRCT. Hypovascularity in these tumors may explain consistent partial response only to intravenous chemotherapy. In addition, Tox-4 was found to be highly expressed in DSRCT and may be a novel target.

**IPSO0003**

**OBATOCLAX PREVENTS TUMOR GROWTH IN AN ORTHOTOPIC MOUSE MODEL OF HB**
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**Purpose:** Drug resistance and metastatic diseases remain major challenges in the treatment of high-risk HB (hepatoblastoma) requiring development of alternative therapeutic strategies. The aim of this study was to investigate the impact of apoptosis sensitizers, obatoclax and ABT-737, on the interaction between host and HB to reduce tumor growth, dissemination and to enhance immunity.

**Methods:** Induction of apoptosis mediated by TRAIL and TNF-α in combination with obatoclax and/or ABT-737 was detected using Caspase-Glo® 3/7 and JC-1 staining. To define cytotoxic activity of peripheral blood mononuclear cells (PBMCs) a MTT assay was performed. Migration of HB cells was investigated in scratch assays. Incidence of HBsAg in NOD/IL-2rg-/- mice was assessed in different mouse lines to develop orthotopic tumors was monitored by serum AFP and histology (1).

**Results:** HB13 mimetic obatoclax and ABT-737 led to a decrease of viability in HB cells at high concentrations above 1μM. BH3 mimetics enhanced the effect of cytokines secreted from Kupfer cells such as TNF-α or TRAIL on resistant HB cells shown as an increase of active caspases 3 and 7. Treatment of HB cells with BH3 mimetic drugs in a co-culture with PBMCs led to a significant decrease of tumor cell viability (p < 0.05, two-way ANOVA). Furthermore, tumor cell migration was inhibited by ABT-737 and more markedly by obatoclax. In an orthotopic model of HB tumor growth was reduced when cells were treated with low concentrations of obatoclax prior injection. Only 1 of 6 mice developed HB in the liver compared to an incidence of 0.8 in the control group (p < 0.005).

**Conclusion:** The apoptosis sensitizers obatoclax and ABT-737 showed broader effects on HB cells than expected including drug sensitization (2), migration and susceptibility to TNF mediated cell death. Sensitizing HB to apoptosis may also render resistant HB to immune cells such as Kupfer cells and prevents tumor cell dissemination.
References

IPSO0032
TREATMENT OF PRETEXT IV HEPATOBLASTOMA
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Purpose: Unresectable hepatoblastoma without extrahepatic disease is generally considered to be an indication for liver transplantation. PRETEXT IV hepatoblastoma was initially considered to be unresectable; however, a decrease in the tumor size after initial chemotherapy sometimes allows complete macroscopic resection. Therefore, liver transplantation is not always necessary. This report summarizes cases of PRETEXT IV hepatoblastoma to consider the therapeutic strategy for PRETEXT IV hepatoblastoma.

Methods: Six children with PRETEXT IV hepatoblastoma were treated between 2000 and 2011 after induction of living donor liver transplantation. The patients included 5 males and 1 female ranging from 1 month to 6 years of age. Two of them had lung metastasis at the time of diagnosis. Serum AFP was markedly elevated in all cases. All children received initial chemotherapy and four children received high-dose chemotherapy (HDC) with hematopoietic stem cell rescue before surgery.

Results: Lung metastases were still viable in two cases, and were completely resected before the hepatectomy. Preoperative chemotherapy was effective in the 3 cases, and the liver tumors had regressed sufficiently to perform tumor excision. Hepatic lobectomy and enucleation of the residual nodules could achieve the complete macroscopic tumor excision. Total hepatectomy with living donor liver transplantation was necessary to achieve complete tumor removal in the remaining 3 cases. Postoperative chemotherapy was performed and all of the patients were alive without disease 3 months to 11 years (Median: 5 years) after surgery.

Conclusion: Half of the initially unresectable PRETEXT IV hepatoblastoma become resectable after preoperative chemotherapy including HDC. The utmost effort should be made to achieve complete tumor resection of initially unresectable hepatoblastoma, with conservative surgery before the indication of liver transplantation to improve the QOL of these patients.

ICCCPO ORAL ABSTRACTS
ICCCPO0001
GUIDELINES FOR ESTABLISHING A SURVIVORS GROUP AND KEEPING IT GOING
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1Austrian Childhood Cancer Organisation, Survivors Group, Wien, 2Austrian Childhood Cancer Organisation, Survivors Group, Innsbruck, Austria

Purpose: The aim of the guidelines is the support of people who either want to establish a survivors’ group or already lead one. It is a clearly structured and solid guide to get necessary information what has to be considered in establishing a survivors’ group or leading it. It is written from survivors for survivors, parents’ representatives, psychologists, nursing staff and pediatric oncologists.

Methods: The first step for creating these guidelines was a workshop at the ICCSN conference in Auckland 2011 to get as many ideas as possible from experienced international survivors. The workshop was held in small groups which were organized in a way that a lot of ideas were written down in a short period of time, because everyone was influenced by the notes of others and so it was possible to encourage each other to get new concepts.

Results: Establishing a survivor group within a country has a very high importance for survivors themselves. It is a possible tool to empower survivors. Within a network or group survivors themselves can focus on their needs and they can create necessary and important activities for other survivors in their region or country. The guidelines show what has to be considered and examples of existing survivors’ groups’ activities, needs and ideas. These guidelines shall support new survivors and be compared with their individual national or regional situation and adapt one or more concepts for their individual purpose.

Conclusion: The guidelines shall encourage survivors from high income countries and low income countries to establish new groups or to get ideas for existing groups. It is important to provide such information, because survivors have made a lot of experience within their course of mainly voluntary work with other survivors or childhood cancer patients and this could make it easier for new ones.

ICCCPO0002
HOW TO STRUCTURE A SURVIVORS’ GROUP?
Pediatr Blood Cancer DOI 10.1002/pbc

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1Austrian Childhood Cancer Organisation, Survivors Group, Innsbruck, 2Austrian Childhood Cancer Organisation, Survivors Group, Wien, Austria

Purpose: The aim of this presentation is providing an overview of existing structures of survivors’ networks, groups or organisations and how they work. This shall support encouraged people who want to establish or restructure their survivors group to get ideas how working structures look like and how it is possible to adapt them for their individual needs.

Methods: For collecting information we prepared questions which we sent via email to representatives of survivors’ groups we know. Additionally, we made an internet search to find out more about other survivors groups and organisations around the world.

Results: There is a growing number of survivors’ groups around the world. For survivors it is more and more important to form a network, group or organisation in their country. There is a lot of existing survivors’ groups and most of them have different organisational structures. The main organisational level is that Survivors groups can be a part of a parents’ organisation, completely independent or a mixture of both. An additional organisational structure which has to be considered is the hierarchy within the survivors’ groups of a country. The organisational structure is very important for a successful sustainable work, but it depends on the situation in the country, which includes for instance the financial situation, the support of parents’ organizations, the population structure and the number of survivors who are encouraged to work.

Conclusion: There are different organisational structures of survivors’ networks or groups which show the different situation in the country—quite similar to the structure of the state or cultural conditions. If these are considered there will be a sustainable and stable structure developed. This leads to the conclusion that everyone has to adapt the organisational structure to its own needs.

ICCCPO0003
ART, HEALING AND SURVIVING 3
Sean Nurcombe
BC Children’s Hospital, Vancouver, BC, Canada

Purpose: To continue with Art, Healing and Surviving 3 as a follow up to the SIOP conferences in Berlin and Boston where I presented art as a form of healing for survivors of childhood cancer. I plan on giving a presentation to survivors and then creating a collaborative art piece with the help of all survivors attending the conference. I would complete the art piece back in Canada and send a copy of the finished piece to the participants via mail or email. I will also post “our” collaborative artwork on my website so other survivors can see the piece online and are encouraged to use art as a form of healing.

Methods: My presentation to the survivors would be oral/video using the theme “The Long and Winding Road” to describe my cancer experience. I would distribute art paper for them to sketch an image of their “winding road.” I will transfer these sketches onto a glass art piece through a technique I have learned once I am back in Canada. Then I will make cards or email the finished piece to survivors. I would have assistance with my presentation from another survivor from Vancouver with handouts and collection of the sketches.

Results: The result is that we will have created a collaborative memory through art of SIOP 2012 in London using all the survivor’s sketches. This process was a success from the Berlin conference.

Conclusion: Art is a way to connect with other survivors and the collaborative art piece will be a reason to keep in touch and share our experiences. This will allow continuation of networking throughout the world with other survivors.

References: Dan Mornar, Parent Advocate BC Children’s Hospital Dr. Karen Goddard, BC Cancer Agency.

ICCCPO0004
OUR BROTHERS AND SISTERS- UNDERSTANDING SIBLING ADAPTATION TO CHILDHOOD CANCER
Lena Cadogan
BC Children’s Hospital, Vancouver, BC, Canada

Purpose: To demonstrate that siblings of pediatric cancer patients can be at risk for developing emotional, behavioral, and social problems.

Methods: Discussion of child development in relation to understanding sibling adaptation with the childhood cancer experience. Exploring different ways that cancer impacted on the lives of children with cancer and their families Will explore/search medical journals & studies for evidence that young children feel deprived of parental attention when one sibling becomes ill, demonstrate sibling rivalry behaviors, have trouble developing emotional bonds with others, experience emotional and social problems.

Results: Description of adjustment difficulties healthy siblings face when they have a brother or sister with childhood cancer. Studies have shown that siblings of children with cancer do not experience elevated mean rates of psychiatric disorders, but a significant number have
shown post-traumatic stress symptoms, negative emotional reactions and poor quality of life in emotional, family, and social domains.

Conclusion: It is evident that more needs to be done to help siblings in coping with childhood cancer. An understanding of sibling adaption to childhood cancer from a developmental perspective is lacking. This lack of theoretical understanding may contribute to inadequate care of siblings of children with cancer. Siblings of children who have cancer or have had cancer are at-risk on a psychosocial level and need to be provided with appropriate family support.

References:

ICCCPO0005

20 YEARS BICYCLE TOUR FOR YOUNG CANCER PATIENTS IN GERMANY

Dorothee Schmid
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Purpose: The German Childhood Cancer Foundation champions young cancer patients. Since 1993 it offers a bicycle tour for young adults after cancer. Purposes are: - to be active in a group of other young cancer patients - to reassure other young cancer patients and their parents - to show that even after a cancer treatment you are still able to cycle in a sportive way

Methods: Once a year about 40 young adults after cancer cycle together for one week in August. During this bicycle tour - called “bicycle tour on the rainbow - for hope to heal cancer” - they visit young cancer patients in different hospitals on the way. In the visits on the wards they talk to young cancer patients and their parents who are still in therapy. They tell about their own cancer diseases and their strenuous therapies. They also tell about the bicycle tour and their “normal life” after therapy.

Result: Since 1993 the young adults after cancer visited more than 90 hospitals for children with cancer throughout Germany. Altogether they cycled more than 8,000 km. This year we celebrate a jubilee, the twentieth tour! It goes from Bielefeld over Münster, Datteln, Dortmund, Herdecke, Essen, Duisburg, Krefeld, Düsseldorf, Wuppertal, Sankt Augustin and Köln to Bonn. In more than 600 km the young adults want to visit 13 hospitals on the way.

Conclusion: 20 years bicycle tour for young cancer patients Germany shows its importance. Some of the visited children with cancer are now adults, members of the bicycle tour and demonstrate other their own fitness. To cycle in a group of other young cancer patients helps to overcome the experience of having cancer at young ages. I for myself was member of the bicycle tour in 1996, 1997, 1998 and 2008.

References:
www.regenbogenfahrt.de

ICCCPO0006

EMOTIONAL DYNAMIC SUPPORT GROUP FOR PARENTS OF CHILDREN WITH A MALIGNANT BRAIN TUMOR

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Purpose: Medulloblastoma and Ependymoma are both malignant brain tumors often occurring in the posterior fossa. These tumors can spread within the brain, the spinal cord and meninges. Treatment includes surgery, chemotherapy and radiation which cause short and long term side effects impairing hormonal, developmental, cognitive, neurological and emotional functions. These affect the child and his family throughout their lives and represent a continuous stress. Support is essential and in our experience, parent support groups can fulfill this need effectively.

Goals:
1) Providing parents with techniques for coping with chronic disability.
2) Establishing a support network for parents undergoing similar experiences.
3) Providing information about changes in physiological, emotional and social issues after treatment ends.

Methods: Emotional Dynamic Group Intervention method, led by a nurse and social worker. We held 12 meetings, and the group included 9 parents of children that had completed treatment.

Results: Group members described emotional experiences from the period of the active treatment and the follow-up. During the process, feelings of guilt, denial and acceptance along with fear of relapse, death and uncertainty in their child’s developmental future arose. Intervention techniques such as holding and containing provided opportunity for sharing mutual pain and difficulties. Different ways of adaptation and coping with daily challenges arose and we discussed dilemmas and difficulties regarding the healthy siblings, extended family and friends.

Conclusion: Parents reported emotional and personal empowerment as a result of participating in the group. Information about changes resulting from treatment and illness, contributed to their understanding and ability to cope with their child’s problems. A change occurred in their emotional approach to the child and their own feelings, while strengthening and supporting other members of the group. Parents also raised the need for emotional and professional preparation at the end of treatment for the next stage in life.

ICCCPO0007

EXPANDING ACCESS AND ENSURING AVAILABILITY OF AFFORDABLE ESSENTIAL MEDICINES FOR CHILDHOOD CANCER

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Purpose: In the Philippines, poverty and childhood cancer survival is inextricably linked. The Intellectual Property Code prohibited parallel importation of patented medicines from other countries where they are cheaper and price regulatory mechanisms were weak. The Philippines has one of the highest costs of medicines in Asia. This served as a major deterrent to families wanting to seek treatment for kids with cancer as well as a key factor for abandonment of treatment. Out of 500 kids diagnosed with cancer annually, it is estimated that less than 30 per cent survive; 1 every hour; 8 every day. Experts believe that with a population of 88 M and limited registry, there are many more unreported and undiagnosed cases of childhood cancer. This study documents the best practices and lessons learned from this successful policy advocacy and public private partnership.

Methods: Interviews with key stakeholders involved in the initiative as well as collation and analysis of data on key result areas.

Results: Key results were: 50-75% price reduction for 10 essential childhood cancer drugs included in the priority list of drugs included in the priority list of drugs covered by the Cheaper Medicines Law; government partnered with CWFI to provide free medicine for 300 kids with ALL and also provided free medicine for leukaemia patients in 14 public hospitals. These has led to: Increased survivorship rates; more families seeking treatment for kids with cancer; substantial decrease in abandonment rates; parents energized, actively engaged in monitoring the program and in supporting other families.

Conclusion: In low resource countries, the policy environment often serves as a major constraint for improving early diagnosis, timely treatment and completion of care for kids with cancer. Multi-stakeholder policy advocacy and social mobilization can be an effective strategy for creating a more supportive environment and improving survivorship in childhood cancer.

ICCCPO0008

THE ROLE OF CHILDHOOD CANCER SURVIVOR IN SUPPORTING MEDICAL TREATMENT FOR CANCER PATIENTS IN INDONESIA (AN EXPERIENCE FROM INDONESIAN CHILDHOOD CANCER SURVIVOR SOCIETY)

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Purpose: Children psychological level is very susceptible; they need full support in their struggle against cancer. Therefore, the attendance of supporting group is an essential. There are two objective of this paper. Firstly, to point the role of Cancer Survivors as a supporting actors in motivating cancer patients and provide assistance to giving spirit alive. Secondly, to prove that cancer survivors have an important role in support the successful of the medical treatment being undertaken.

Methods: The study undertaken is by longitudinal observation and auto-ethnographic method, this study explores how the initiative of the cancer survivor in supporting the cancer patients. The study is conducted in Indonesian Childhood Cancer survivor society by using qualitative research methods that applied to the ten cancer survivors.

Results: The study showed that the cancer survivor has an important role in four areas in supporting the medical treatment, which is; (1) Act someone who knows how the patients are feeling; (2) Provides an example of success for the patients; (3) Convince that chemotherapy could cure cancer and have no negative effects; and (4) Provide psychological-assistants during the treatment.

Conclusion: Childhood cancer survivor society should be attached to the medical-treatment that is given to the patients. Chemotherapy will be more effective if the patients believe that they will be totally cured and can gain their normal life afterwards. The attendance of survivors society in every country or even in every city will be hugely advantageous in supporting patients fight against cancer.

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ICCCPO0009
THE SIBLING PROJECT
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Purpose: When a child suffers from cancer, the entire family is affected and the siblings often feel neglected. One or both parents will spend a lot of time at the hospital with the sick child, while the sibling is expected to live a normal life with schooling and leisure activities. The idea of having a designated person work especially with the siblings came from parents, who had struggled with the task to be at hand both for the sick child and their siblings. Sibling supporters were first introduced at three of the six national children’s oncology departments. To provide equal care for all families, Barncancerfonden decided to establish sibling supporters at the remaining three oncology departments.

Presentation: We will introduce the work and organization of sibling supporters. The presentation also refers to Margareta Nobris thesis, Being a sibling of a child or young person with cancer - Thoughts, needs, problems and support, 2009.

Methods: Describe how the sibling supporters work both individually and in close cooperation with the rest of the staff at the different children’s oncology departments. Given that the oncology department’s work under different conditions, activities will vary, there will be both individual and group activities. Since there are large geographical distances, other “meetings” than in person will occur, e.g. Skype, chat and Facebook.

Conclusion: Children suffering from cancer may be sick for several years. Any siblings’ childhood will be affected during that period. Siblings could end up lacking socialization with both their sick sibling and parents. This affects their path towards independence and their feeling of being loved and cared for. Sibling support can help them understand their situation. This can ease communication between family members and help create understanding of how the illness not only affects the sick child, but also the physically healthy ones.

ICCCPO0010
INSPIRATION, EDUCATION AND AWARENESS THROUGH STORY TELLING OF CHILDHOOD CANCER SURVIVORS AND YOUNG ADULT CANCER SURVIVORS
Vikram Bubber
BC Children’s Hospital, Surrey, BC, Canada

Purpose: Set against the dramatic backdrop of the Owyhee River gorge deep in the Southeast Oregon desert, a group of ordinary Canadians embark on a journey of a lifetime down the one of the most remote rivers in the United States. This incredible river journey is all the more remarkable as the core expedition members are all young adults and survivors of cancer. In our modern age of technology, advanced medical care and support, many people from all countries are surprised to learn that young adults with cancer face many challenges unique to their age group. With 25 year old Mike Lang, who finished treatments just a few months before the expedition, this inspirational group of young adult survivors share their personal stories and apply the lessons they learned from their cancer struggle as together they battle a mental challenge of the disease, but a far more subtle fight for acceptance and recognition in a health system that has largely forgotten them.

Methods: Led by 25 year old Mike Lang, who finished treatments just a few months before the expedition, this inspirational group of young adult survivors share their personal stories and apply the lessons they learned from their cancer struggle as together they battle a mental challenge of the disease, but a far more subtle fight for acceptance and recognition in a health system that has largely forgotten them.

Conclusion: “meetings” than in person will occur, e.g. Skype, chat and Facebook.

Results: We collected 254 surveys (response rate 79%). Median patient age was 9.5 years (IQR 4.5-14) and median time from diagnosis was 19.2 months (IQR 5-28). Most common diagnoses were Leukemias (n = 105, 42%), Lymphomas (n = 32, 12.6%), and CNS tumors (n = 31, 12.2%). Of the respondents, 20% were considered “rural” with 38% and 23% reporting > 1 and > 2 hours travel times, respectively. Mean time from initial symptoms to diagnosis was 7.6 and 11.4 weeks for urban and rural patients. (p = 0.08). Caregivers from > 2 hrs away missed a mean of 17.4 and 12.7 days of work monthly (p = 0.21) and 37% measures of financial burden (travel costs/time, relocations, missed work/school), time from first symptoms to diagnosis, and clinical trial enrollment.

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Purpose: Children with cancer often suffer from considerable symptoms and psychological distress. Yet children do not have the same verbal skills as adults to communicate about distressing symptoms, leaving them at risk that problems remain unrecognized. Sisom is an interactive communication tool that takes children on a journey through an island world where they can express how they feel, which in turn can help parents and care providers to better understand and support the child. We tested effects of Sisom when children used it in preparation to a consultation with their physician on consultation content and quality, especially symptoms/problems addressed, physicians’ responses, and how much the child actively participated in the consultation.

Methods: We videotaped 26 consultations, 10 for the “usual care” control group; 16 for the Sisom group. The resulting assessment summary was available to the child, parent and the physician in the subsequent consultation, using it as they wished.

Results: Six boys and seven girls age 8–12 undergoing cancer treatment participated in control or intervention consultations, 1–3 times each; fifteen physicians in 1–5 consultations each. In those consultations where physicians chose to use the assessment summary, twice as many symptoms or problems were addressed (p < 0.01) without increasing consultation time. Also, physicians significantly more often acknowledged the child’s problems, directly addressed her when talking, asked more probing questions, provided more explanations and expressed more empathy. Children in the Sisom group actively participated twice as much in the conversation compared to the control group.

Conclusion: While small, this study demonstrated that Sisom can significantly improve communication and care for children with cancer. Study results were repeatedly reported in children with heart disease. Available in English, Spanish and Norwegian on web-based or tablet platforms, Sisom could help many care providers and parents to better understand, communicate about and support their children during their illness.

DCAN FARBER/CHILDREN’S HOSPITAL CANCER CARE PEDIATRIC PATIENT AND FAMILY ADVISORY COUNCIL “WEEKEND INITIATIVE”; HOW WE HEAR THE VOICE OF PEDIATRIC PATIENTS AND FAMILIES WHO ARE CURRENTLY RECEIVING CANCER TREATMENT

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1Dana Farber/Children’s Hospital Cancer Care, 2Dana Farber/Children’s Hospital Cancer Center, Boston, MA, USA

Purpose: The Pediatric Patient and Family Advisory Council of Dana-Farber/Children’s Hospital Cancer Care is a partnership of patients, family members, and professional caregivers. We are dedicated to improving hospital programs, policies, and the overall quality of cancer care provided to children, teens, and their families while in treatment. The “Weekend Initiative” is led by trained Pediatric Patient and Family Advisory council members who facilitate inpatient groups where pediatric patients and families can share their thoughts, questions, and ideas. These groups are led in an objective manner so that all pediatric patients and families can feel free to raise their questions and input, reinforcing that their voice is heard and will be acted upon. Real time patient and family input is translated into tangible actions and outcomes. DF/CHCC prides itself on its patient and family centered approach, as well as conduct question and answer session. In attendance/presenting will be current members of the PPFAC, who facilitate the “Weekend Initiative.”

Results: We will provide a framework, resource support and specific examples for those looking to launch a Pediatric Patient and Family Advisory Council “Weekend Initiative” effort to solicit real-time feedback from current pediatric oncology patients and their families, currently receiving cancer care.

Conclusion: Pediatric Cancer Care Institutes can learn how a “Weekend Initiative” can support patient and family centered care and facilitate real time feedback and dialogue with current patients and families. It is important for Institutions to utilize parents who can speak for those who cannot speak for themselves. The volunteers who facilitate the “Weekend Initiative” have the common bond of also being the parent of a pediatric cancer patient and, together with current families and patients, can forge ahead to improve the experience for future patients.

NEW PROJECT GIVE NEW HOPES FOR THE SICK CHILDREN

G Petrosyan

NGO Friends of Children with Cancer, Yerevan, Armenia

Purpose: In connection with world economic crisis Pediatric Oncology in Armenia has had lots of financial difficulties connected 2008. Our NGO was unable to reduce them, in particular to provide the patients with the necessary medicines, as far as the donations were minimized. Our mission was to modify the Pediatric Oncology service in Armenia. Methods: We realized that the problem can only be solved on a high governmental level. Our chairman suggested the high-ranking officials that a contemporary Children’s Oncology Centre should be constructed in our country.

Results: On the initiative of First Lady creation of a new Children’s Oncology & Hematology Centre has been started and will be constructed by 2014. The first fundraising concert took under her patronage in State Opera and Ballet Theatre of Yerevan.

Conclusion: According to the project the new centre will be unique in our region with its up-to-date equipment and bone-marrow transplantation unit. As far as the resources of the state are limited the World Bank will initially subsidize the project. And further implementation depends on large-scale fundraising projects. Our NGO also is planning to contribute to this project and carry out fundraising through ICCCPo.

THE COWS - PEOPLE WITH A PASSION FOR LIFE, WANTING TO MAKE A DIFFERENCE

Kerrin Bain

Head Office, CHOC Childhood Cancer Foundation South Africa, Randburg, South Africa

Purpose: The massive fundraising project all started with a 20-month-old little girl named Jessica Madison Bain. In April 2007, Jessica was diagnosed with Neuroblastoma Stage 4 at the tender age of 10 months. CHOC played a significant role in the Bain family’s life in the last few weeks of life, specifically with palliative care and emotional support. In 2008, Kerrin and Grant, Jessica’s parents, decided to cycle the 94.7 Challenge in memory of Jess and to raise money for CHOC. Kerrin’s colleague and friend, Cordi van Niekerk, heard about her fundraising project and he and a group of friends got together and decided to raise money by cycling the race in cow suits.

Methods: The CHOC Cow initiative was born by a group of 6 enthusiastic cyclists keen to make a difference and raise money for a much needed cause.

Results: What started in 2008 as a challenge to raise R60,000 resulted in the group raising more than R230,000 that same year for CHOC. With the word spreading about Cow initiative, 2009 turned into another spectacular success. The energy of the herd was infectious and the fundraising challenge, which took a mere two weeks, went on an upward trajectory. With more than 140 cyclists riding in varying state of cow gear and a fundraising target of R1 million, the Cows successfully closed the year with more than R2.2 million raised for CHOC.

Conclusion: In 2011, the 300 strong herd went on to raise R3.6 million bring total fundraising to more than R6 million since inception. And as for 2011 . . . the sky is the limit!

ACUTE LYMPHOBLASTIC LEUKAEMIA

PA001

GENE EXPRESSION-BASED IN SILICO SCREENING FOR GLUCOCORTICOID-SENSITIZING THERAPEUTICS IN MLL-REARRANGED ALL IDENTIFIES PI3K INHIBITORS AS POTENTIAL MODULATORS OF PREDNISOLONE RESISTANCE

Jill Spijkers-Hagelstein, Sandra Mimoso Pinhancos, Pauline Schneider, Rob Pieters, Ronald Stam

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Purpose: Obtaining successful treatment results for MLL-rearranged acute lymphoblastic leukemia (ALL) remains challenging, to some extent due to poor glucocorticoid (e.g. prednisone and dexamethasone) responses. Thus, overcoming resistance to these drugs may be a crucial step towards improving prognosis. However, despite intensive research, little is known about the mechanisms of resistance. Therefore we aimed to produce a gene expression signature associated with in vitro prednisolone resistance in MLL-rearranged infant ALL, and identify therapeutic agents that reverse the profile and induce prednisolone sensitivity.

Methods: By comparing gene expression profiles (Affymetrix Hu133plus3.0 GeneChips) from MLL-rearranged infant ALL patients either sensitive or resistant to prednisolone in vitro, we defined a gene signature associated with prednisolone resistance. Using this signature, we applied Connectivity Map analysis to perform an in silico screen for agents potentially capable of reversing the prednisolone-resistance profile and induce sensitivity.

Results: Connectivity map analyses revealed that LY29402, a PI3K inhibitor, would potentially fulfill this task. Subsequent validation demonstrated that indeed LY29402, as well as other known PI3K inhibitors, markedly sensitized otherwise resistant MLL-rearranged ALL cell to prednisolone in vitro. Using quantitative real-time PCR analyses, we validated the modulating effects of LY29402 on the expression of the genes present in our prednisolone-resistance profile. This showed that prednisolone-sensitizing actions of LY29402 are indeed mediated by inhibition of PI3K, as two of the genes down-regulated in response to LY29402, i.e. PAK2 and FGR1, represent known PI3K targets. Another gene affected by LY29402 treatment, i.e. TLR2 (encoding Toll-like receptor 2), a connection with PI3K have been reported. Moreover, Toll-like receptor 2 physically interacts with PI3K.
with the glucocorticoid receptor and plays a critical role in downstream glucocorticoid effects.

Conclusion: We conclude that implementing FDA-approved P3K inhibitors in current treatments may potentially improve the GC-response, as well as the prognosis, for patients with MLL-rearranged ALL.

PA002

SRC KINASE-INDUCED PHOSPHORylation OF ANNEXIN A2 MEDIATES glucocorticoid resistance in MLL-REARRANGED INFANT ACUTE LYMPHOBLASTIC LEUKEMIA

Jill Spijkers-Hagebein, Sandra Mimoso Pinhanos, Pauline Schneider, Rob Pieters, Ronald Stam

Pediatric Oncology, Erasmus MC/Sophia’s Children’s Hospital, Rotterdam, The Netherlands

Purpose: Glucocorticoids (e.g., prednisone and dexamethasone) are commonly used in the treatment of childhood acute lymphoblastic leukemia (ALL). Unfortunately, infants with ALL (< 1 year of age) characterized by translocations of the MLL gene are frequently resistant to these drugs. As poor glucocorticoid responses are firmly associated with therapy failure, overcoming glucocorticoid resistance may be a crucial step towards improving prognosis. In search of insights into glucocorticoid resistance mechanisms, we generated a gene expression signature associated with in vitro prednisolone resistance in MLL-rearranged infant ALL. One of the genes strongly discriminating between resistant and sensitive patients appeared to be annexin A2, encoding a ubiquitous membrane-associated protein. Here we functionally studied to role of annexin A2 in prednisolone-resistant MLL-rearranged ALL.

Methods: ANXA2 expression was validated by quantitative RT-PCR and immunoblotting in MLL-rearranged cells. To study the role of annexin A2, Src kinases or p11 in prednisolone resistance, we performed RNAi experiments using lentiviral constructs expressing either a non-targeting shRNA or shRNAs directed against ANXA2, Src kinases or S100A10. In vitro prednisolone response was determined byMT assays.

Results: MLL-rearranged cells resistant to prednisolone in vitro expressed elevated levels of annexin A2 and its phosphorylated form (active). Further investigation demonstrated that the underlying factor of annexin A2 phosphorylation is dependent upon Src kinase-biding, initiated by the adapter protein p11. shRNA-mediated knock-down of ANXA2, the Src kinases FYNK,C or S100A10, all led to inhibition of annexin A2 phosphorylation and resulted in marked prednisolone sensitization. Likewise, exposure of prednisolone-resistant MLL-rearranged ALL cells to different Src kinase inhibitors exerting high specificity towards FYN and/or LCK had similar prednisolone-sensitizing effects.

Conclusion: In conclusion, we here present a novel mechanism of prednisolone resistance in MLL-rearranged ALL, and propose that inhibition of annexin A2 phosphorylation embodies an attractive therapeutic strategy for overcoming resistance to glucocorticoids in this highly aggressive type of leukemia.

PA003

PROGNOSTIC SIGNIFICANCE OF MLL FUSION GENE TRANSSCRIPTS (FGT) monitoring as marker of minimal residual disease (MRD) in infant acute lymphoblastic leukemia (ALL)

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Purpose: To evaluate prognostic significance of MRD monitoring by quantitative and qualitative detection of FGT in infants with ALL-rearranged ALL treated by MLL-Baby protocol.

Methods: 39 infants (12 boys, 27 girls) with defined MLL rearrangements were included in the current study. Median age was 4.37 months (range 0.03–11.80). MRD detection was performed by nested RT-PCR and real-time quantitative PCR (RQ-PCR) in bone marrow samples, obtained at the time of diagnosis, on day 15 and at the end of remission induction (time point (TP) 1 and TP2) and then after each course of ATRA administration (TP3-TP9). Median of follow-up period was 32 months (range 0.03–11.89).

Results: We estimated prognostic significance on risk of relapse in the univariate and multivariate analysis of the initial patients characteristics (age, sex, WBC count, Immunophenotype, CNS-status, type of MLL partner gene) and treatment response parameters (day 8 peripheral blood blast cell count, day 15 bone marrow status, day 36 remission achievement, MRD level at TP1 and MRD status at TP4). Among them age less than 6 months, MRD value at TP3 higher than 0.1% and any MRD-positivity at TP4 showed prognostic significance on relapse risk in the univariate analysis (p = 0.001, p = 0.003 and 0.003, respectively). In multivariate model MRD-positivity at TP4 and MRD level at TP3 higher than 0.1% remained significant prognostic factors (HR 3.771, 95% CI 1.033–13.674, p = 0.044 and HR 4.250, 95% CI 1.159–15.585, p = 0.029, correspondingly). Comparison between presence of MRD-positivity at TP4 and MRD level higher than 0.1% at TP3 did not allow us to determine the best discriminative factor. MRD data obtained at later TPs did not bring additional prognostic information.

Conclusion: In our series MRD level at TP3 higher than 0.1% and any MRD-positivity at TP4 were associated with unfavorable outcome.

PA004

EXCELLENT OUTCOME IN MLL-NEGATIVE INFANTS WITH ALL TREATED BY ATRA CONTAINING MLL-BABY PROTOCOL

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Purpose: Our prior reports have shown that ATRA based MLL-Baby Protocol, developed for infants with ALL demonstrates better survival rate in patients with infant ALL, and particularly the MLL positive group. It is also of interest to evaluate the outcome in MLL-negative patients who were treated by MLL-Baby, intermediate risk-group arm.

Methods: Intermediate risk-group schedule includes 1 - 2 weeks consecutive courses at the dose 25 mg/m2/day adjusted to age and started immediately after induction, simultaneously applied with standard chemotherapy during reinduction courses. Among 75 infants with primary ALL enrolled onto MLL-Baby Protocol since September 2003, 22 (29%) were confirmed by FISH, PCR and conventional cytogenetics as MLL-negative patients. Three of them were diagnosed with other genetic abnormalities: one with hypodiploid karyotype; one with (t(11;19)(p23;q13)TCF3-PBX1 and one with SCL-TAL1/microdeletion 1p. More than half of MLL-negative cohort 13 patients had BII immunophenotype; 5-BII, 2-B1; I1-TIV respectively. One patient was not examined. The median of age is 8 months (range 1–11 months). Median leukocytes number is 65.6 × 109/L (range 1.6–418.0). Initial CNS involvement was registered in 4 (18%) cases.

Results: Three patients with the above noted genetic abnormalities had a dismal outcome: one with TIV-ALL and SCL-TAL1 did not respond to the treatment and died in progression; two other infants: one with BII-ALL and hypodiploid karyotype and one with BII-ALL and TCF3-PBX1 relapsed within 8 and 15 months after treatment start and both died. One more patient died in complete remission from severe infection. The rest 18 babies (81.8%) have perfect treatment results. All of them are in complete continuous remission with median time of follow-up 36 months. 7-year EFS is 0.80 ± 0.08 and RFS is 0.89 ± 0.07.

Conclusion: MLL-negative ALL in infants can be successfully cured by ATRA-containing MLL-Baby Protocol in vast majority of cases. Perhaps, molecular mechanisms of ATRA are influencing alternative MLL-dependent pathways.

PA005

MOTOR PERFORMANCE AND FUNCTIONAL EXERCISE CAPACITY IN SURVIVORS OF PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA

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Purpose: Cross-sectional studies have shown impaired motor performance after cessation of treatment of acute lymphoblastic leukemia (ALL). However, no longitudinal study monitoring motor performance after cessation of treatment has been published. Whether functional sub-maximal exercise capacity is reduced has not yet been investigated.

Methods: Motor performance of ALL survivors, treated with ALL-9 protocol of the Dutch Childhood Oncology Group was measured with the movement-ABC at cessation of treatment and 7 years later. At the latter time functional exercise capacity was also investigated, using the Six Minute Walk Test (6MWT).

Results: Nineteen boys and 14 girls, median age 12.3 years (range 9.0 – 17.8), median age at diagnosis 4.7 years (1.3 – 11.5), median time since cessation of treatment 5.2 years (5.0 – 7.1), participated in the study. Mean height/age did not differ from the norm nor did mean weight/ age, whereas mean BMI/age was significantly increased (mean SDS 0.38, SDM 0.17).
survival was 70% for patients with less than 1% at day 28 and 0% for 6 patients. 28 was negative in 87%; 57 male, 44 female; 99 had Pre B, 1 T-cell and 1 B cell. Fifteen were standard risk, 86 Kaplan Meier test and compared with log rank test.

sensitivity of PCR. Tandem application of FC at early time-points and FGt detection by PCR achieved 86.41%. Larger number of PCR-positive samples could be explained by higher outcome of childhood ALL.

monitoring during early treatment phases, when precise MRD value is essential while PCR by PCR is more appropriate for qualitative MRD assessment. FC is more applicable for MRD consolidation/intensification was significantly different (78.26 and 91.20% respectively, high-risk. MRD at day 14 was negative in 73.5%; 57 male, 44 female; 99 had Pre B, 1 T-cell and 1 B cell. Fifteen were standard risk, 86 Kaplan Meier test and compared with log rank test.

MINIMAL RESIDUAL DISEASE AT DAY 14 AND 28 OF REMISSION INDUCTION AS A PROGNOSTIC FACTOR OF SURVIVAL IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA TREATED AT HOSPITAL CIVIL DE GUADALAJARA DR. JUAN I. MENCHACA

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To define the prognostic value of minimal residual disease at day 14 and 28 of induction remission treatment on survival of patients with ALL treated at Hospital Civil de Guadalajara from August 2007 to December 2009.

Methods: We performed a descriptive clinical prospective study in children with ALL MRD was measured by immunophenotype by flow cytometry at day 14 and 28 of induction remission. It was considered negative with 0.00% of leukemic cells and positive divided in three groups: A > 0.00% to < 1%; B > 1% to 5% and C > 5%. Survival was analyzed with a Kaplan Meier test and compared with log rank test.

Results: There were 113 patients with ALL, 102 were evaluable. A mean age of 6.2 years (1–15); 57 male, 44 female; 99 had Pre B, 1 T-cell and 1 B cell. Fifteen were standard risk, 86 high-risk. MRD at day 14 was negative in 73.5%; > 0.1% in 9.8%; > 1–5% in 9.8% and > 5% in 6.9%. Event-free survival according to day 14 MRD was 76.4; 30, 50 and 14.3%, respectively (p < 0.001); and relapse-free survival was 88.9; 70, 70 and 42.9%. MRD at day 28 was negative in 87%; > 0–1% in 6.9%; 1–5% in 2.9% and > 5% in 2.9%. Event-free survival was 70% for patients with less than 1% at day 28 and 0% for patients > 1% at day 28 of induction. Relapse-free survival was 84.9 and 50%. Standard-risk had 80% event-free survival and high-risk had 67.6% with negative MRD at day 28.

Conclusion: MRD status at day 14 and 28 was a prognostic factor for survival in children with ALL.

MOLECULAR ANALYSIS OF FUSION GENES AMONG PAEDIATRIC B-LINEAGE ACUTE LYMPHOBLASTIC LEUKAEMIA IN KERALA, SOUTH INDIA AND THEIR EFFECT ON EARLY TREATMENT OUTCOME

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Purpose: Acute lymphoblastic leukaemia (ALL) is the most common paediatric malignancy. Identification of oncogene fusion transcripts like ETv6-RUNX1, BCR-ABL, MLL-AF4, and E2A-PBX1, is essential for risk stratification and tailored therapy. ETv6-RUNX1 is the commonest (25%) fusion gene in the West. This 3 year study, funded by Kerala State Council for Science Technology and Environment was initiated in December 2008 to characterize the molecular genetic profile of paediatric B-lineage ALL in Kerala by estimating the frequency of ETv6-RUNX1, BCR-ABL, E2A-PBX1 and MLL-AF4 fusion genes.

Methods: In this 3 year prospective study (16th December 2008 –15th December 2011) 216 bone marrow/narrow blood samples were collected from Keralite children (0–14 years) with newly diagnosed, B-lineage ALL treated at Regional Cancer Centre (RCC) Trivandrum, Kerala. Fusion genes were estimated by RT-PCR and confirmed by Real-time PCR analysis in Molecular Medicine Division of RCC. Chemotherapy protocol was BFM-95. Early treatment outcome was analysed and survival calculated by Kaplan –Meir Method. Results: 111 samples yielded analyzable cDNA. (5 infants and 106 older children) Mean age 6.75 years (range 0–14 years). M:F ratio was 1.7. 21 children (19.09%) tested positive for one of the fusion gene transcripts. Nine (8.18%) had ETv6-RUNX1, six (5.45%) had BCR-ABL, four (3.63%) had E2A-PBX1 & two infants (1.92%) had MLL-AF4. In ETv6-RUNX1 group no one relapsed but 1 child died during induction. 3 children relapsed in BCR-ABL & 1 child each in MLL-AF4 & E2A-PBX1. 3 year Overall Survival probability was 88.89% in ETv6-RUNX1, 62.50% in BCR-ABL, 66.67% in E2A-PBX1 & 50% in MLL-AF4 subgroups. Conclusion: 19.09% of Keralite children were positive for fusion genes. Early treatment outcome was favourable in ETv6-RUNX1 subgroup. ETv6-RUNX1 frequency is low (8.18%) in our study indicating that this favourable fusion gene is underrepresented in Kerala and this could be contributing to the reduced survival in our patients.
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2 g/m² and HR: 9 blocks of chemotherapy + RT. Accrual: 993 pts, CR: 93.9%, CIR: 32% (SR: 27%, IR: 33%, HR: 38%) CNS-R: 7%. ’96 Study (3 risk groups); SR decreased.

anthracyclines, IR randomized MTX 2 g/m² vs. MTX 3 g/m² + cytarabine, HR: 6 blocks + Prot-II Accrual: 975 pts, CR: 92.8%, CIR: 32% (SR: 17%, IR: 27%, HR: 37%) CNS-R: 5%, anthracycline reduction no increase relapses, randomization had not significantly differences, HR improve results with Prot-II. ’02 Study (3 risk groups): MTX 5 g/m²/for T-ALL. Every risk randomized to combinations of Prot-I and Prot-II, HR used also 3 blocks. Accrual: 1520 pts, CR: 97%, CIR: 24% (SR: 20%, IR: 25%, HR: 27%) CNS-R: 3.8%.

Conclusion: The GATLA treatment used BFM protocol standardized the treatment of pediatric ALL in Argentina. CIR was decreased; CNS protection achieved considerable results to international protocols. According the results is possible to emphasize the importance of correct stratification, effectiveness of Prot-II and reducing toxicity in SR.

PA010 IMPROVED OUTCOME FOR CHILDREN WITH HIGH RISK (HR) ACUTE LYMPHOBLASTIC LEUKAEMIA (ALL) IN ARGENTINA: A GATLA REPORT

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Purpose: From 1996 to 2009, 2769 evaluable patients (pts) were treated according BFM based protocol. We analyzed the results of ALLGAC-02 compared to ALLGAC-06, PA011 EXCELLENT OUTCOME WITH CONTEMPORARY THERAPY FOR PEDIATRIC ACUTE LYMPHOBLASTIC LEUKAEMIA (ALL) IN SAUDI ARABIA

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Purpose: Background: Approximately 85% of North American and Western European children with ALL are cured with contemporary therapies, but data are limited regarding outcome for children with ALL from Arab countries. Here we describe the outcome of treatment of Saudi children with ALL using Children’s Cancer Group (CCG)-based treatment regimens and aggressive supportive care.

Methods: Patients: From August 2006-August 2011 (median follow up 31.7 months), 99 consecutive children (1–14 years; median 4.3 years) at KFMC with ALL were classified into risk groups based on age and WBC count. High-risk patients (HR: n = 43) received treatment based on the CCG 1961 augmented regimen, with intensification of Peg-asparaginase (PEG: 2500 units/m²) given every fortnight (total of 10–12 doses). Standard-risk (SR: n = 56) patients received 2 doses of PEG during both induction and delayed intensification. Patients with PEG reactions received Erwinia asparaginase.

Results: Twelve patients (12%) were diagnosed with T-cell and 87 (89.7%) with precursor B-ALL. Remission was achieved at end induction in 97/99 (98%) patients, with one death during induction from pseudomonas sepsis. To date, 11 (11.1%) patients have relapsed including 2 isolated CNS and 9 marrow relapses. Characteristic abnormalities that were observed included 2 with T-ALL, 3 with 9p deletion and 1 with hypodiploidy. Six patients (6%) developed mild to moderate systemic PEG reactions. There was 1 patient with dorsal sinus thrombosis, 1 with mild veno-occlusive disease associated with thioquanine therapy and two patients developed hyperglycemia during induction. There were no cases of pancreatitis.

Four (4%) of 99 patients died; one while in remission; the 4-year overall survival and event-free survival are 94 and 80% respectively.

Conclusion: We obtained excellent early results for Saudi children treated with CCG based therapy. While numbers are small, patients with 9p abnormalities did poorly and may require more intensive treatment.

PA012 DISTINCT GENETICS OF TEENAGE AND YOUNG ADULT ACUTE LYMPHOBLASTIC LEUKAEMIA

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Purpose: The outcomes for Teenagers and Young Adults (TYA) with T-cell Acute Lymphoblastic Leukaemia (T-ALL) has improved significantly using paediatric based chemotherapy protocols, although it remains poorly understood why their outlook remains inferior to children aged 1–9 years. This study aims to characterise the genetic events leading to TYA-T-ALL and establish whether T-ALL in Teenagers and Young Adults is a distinct disease entity.

Methods: DNA and RNA were extracted from TYA-T-ALL (10–25 years) samples. The DNA was examined at high resolution for Copy Number Alterations (CNAs) and Loss of Heterozygosity (LOH) using the Affymetrix SNP 6.0 platform. The most frequent CNAs were confirmed by MLPA (P-383-T-ALL). The DNA was screened for mutations in NRAS, KRAS, CBL, FLT3 and SH2P2 using denaturing high performance liquid chromatography. The RNA was subjected to real-time PCR for CDKN2A. Promoter methylation was performed by SaBiolosciences EpTect Methyl qPCR Arrays and Methylation Specific PCR.

Results: The most frequent CNA was deletion of CDKN2A in 72.7% of patient samples (91.6% homozygous deletions). Other frequent CNAs were loss of MLF1 (31%), STIL (27%), PFTN (21%), LELF (15%) and gain of MYB (12%) These CNA's were confirmed by MLPA. The only recurrent region of Copy Number Neutral LOH encompassed p9243-p13.3, including the gene CDKN2A (27%). Two mutations have been identified: 1 NRAS and 1 CBL mutation (known variants). We demonstrated CDKN2A promoter methylation in cases without gene deletion by MSF, but not Epitected Methyl Arrays.

Conclusion: Genomic analysis to date has not shown significant differences between T-ALL in children versus teenagers and young adults. We are in the process of analysing additional cases for CNAs, LOH, including NOTCH1/FBXW7/PFTN gene mutations. To be able to appreciate potential cooperation between genetic abnormalities, we are measuring aberrant expression of the oncogenes TAL1, LYL1, LMO1, LMO2, TILX, TLX3, NX2, ERG and MEF2C.
exact etiology of these insults is largely undetermined. Role of intrathecal methotrexate versus unidentified viral encephalitis contributing to leuencephalopathy and intratable seizures needs research. Decreasing therapy related toxicity and infections are essential to improve survival.

References

PA014
DECREASING TREATMENT RELATED MORTALITY IN ACUTE LYMPHOBLASTIC LEUKEMIA IN A DEVELOPING COUNTRY
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Purpose: Treatment related mortality (TRM) in our unit in acute lymphoblastic leukemia (ALL) has been 25–30% for the last decade. The 20 bedded unit treating around 300 patients yearly has: 3 consultants, 1 registrar, 4 pediatric trainees and 1–2 nurses. A concerted effort according to the national TRM and improvement guidelines was made.


Results: (1) Children treated: 2007–2009: 191, 2010/2011:189. (2) No remission on Day 28: 1 in 0.7–1.3% of patients. (3) TRM was 31.36% and 33.9% in 2007, 2008 and 2009. In 2010–2011: TRM was 17 and 13.9%. (4) Death was related to an infective process in 91.5% cases. (5) Induction deaths with change in protocol remained similar [9.6 & 8.4%; p = 0.74].

Deaths during intensive phases of therapy decreased from 12% to 2.6% (p < 0.001). Deaths during maintenance decreased from 12% to 3.7% (p = 0.001). (5) The difference in mortality between 2007 and 2009 and 2010/2011 was significant. (p < 0.001).

Conclusion: Decreasing protocol intensity and addition of dedicated personnel have made a substantial decline to TRM. The chance of dying decreased by 2.84 times. (1) Developing countries by and large function with insufficient staff. (2) International protocols are probably not appropriate in view of inadequate facilities. (3) Decreasing TRM is an essential step to improve survival.

PA015
TREATMENT RESULTS AND RELAPSE ANALYSIS IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA IN THE SLOVAK REPUBLIC TREATED ACCORDING TO ALLIC BFM 2002 PROTOCOL
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Purpose: To evaluate the outcome and analyze the relapses in children and adolescents with ALL in Slovakia who were treated with protocol ALLIC BFM 2002, to compare with treatment results according to ALLIC BFM 95.

Methods: Diagnostic and therapy was done according to the guidelines of protocol. Patients were classified in the groups of standard, intermediate, or high risk (SRG, IRG and HRG) according to age, initial leukocytes count, early treatment response and genotype of leukemia. Relapses were very early, early, and late (18, more than 18, and more than 24 months after diagnosis). Survival at 31.12.2011 was done according to Kaplan–Meier in all patients included in the study to 31.12.2010.

Results: 2007–2009, 2010–2011: 227 patients (149 boys, 78 girls) aging from 13 to 225 months were included in this analysis. According to the risk groups: SRG 31.3% / IRG 56.4% / HRG 12.3%. As for immunophenotype: T-ALL 13.6% / B-ALL 85.9%.

Conclusion: In comparison with ALLIC BFM 95 5-years EFS has improved from 0.70 to 0.77; the occurrence of relapse has decreased from 20% to 14%; and death in the 1st CR has also decreased from 10.8% to 6.7%. We saw fewer deaths in patients if SCT was included in treatment of relapse.

PEDIATRIC BLOOD CANCER DOI 10.1002/pbc

PA016
ABSOLUTE LYMPHOCYTE COUNT RECOVERY AS PROGNOSTIC MARKER OF SURVIVAL IN PEDIATRIC PRECURSOR B ACUTE LYMPHOBLASTIC LEUKEMIA
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Purpose: To determine if absolute lymphocyte count (ALC) is a prognostic marker of event free survival or overall survival in children with ALL independent of MRD.

Methods: Retrospective analysis of 261 children with pre B ALL treated from Jan 2004 to Dec 2009. ALC was measured at days 8, 15 and 29 of Induction, start of maintenance and at 6 months of maintenance. Children were treated with different POG/COG protocols as per risk stratification. Children with very high risk ALL and infant ALL were excluded.

Results: As expected detectable MRD at D29 was predictive of lower event free survival (EFS) (p = 0.034). ALC at all studied time points did not correlate with relapse. ALC at day 8 (p = 0.002) and day 15 (p = 0.001) correlated with OS and EFS. A high ALC > 1.5 correlated with higher EFS (p = 0.034) and higher overall survival (OS) (p = 0.009).

Conclusion: ALC at 6 months into maintenance correlated with MRD at D29 (p = 0.046) and EFS (p = 0.012) and OS (p = 0.011). Actuarial survival at 4 years was 100% for those with higher ALC at D29 vs 94% for those with ALC < 1.5 (p = 0.001). Amongst patients who were MRD-negative, ALC count at D29 did not differentiate EFS. It was 95.7% for those with high ALC on D29 vs 91.6% for patients with lower ALC (p = ns). This data has a remarkably small number of deaths or relapses and MRD information was available only for 139 patients.

Conclusion: ALC was not independent of risk status at diagnosis by neither NCI criteria nor MRD in estimating EFS. Absolute lymphocyte count recovery at end of induction and at 6 months maintenance was an important prognostic variable statistically but was not significant clinically. Moreover, ALC was not predictive of relapse.

PA017
COAGULATION FACTOR XIII IS A NEW PROGNOSTIC FACTOR IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA
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Purpose: Recently we have identified B-cell progenitor (BCP) lymphoblasts as a new expression site of coagulation factor XIII subunit A (FXIIIa). Detection of FXIIIa by flow cytometry (FC) allows a more accurate definition of the leukemia-associated immunophenotype and for quantitation of minimal residual disease (MRD). Here we have evaluated, for the first time, the possible impact of FXIIIa expression on overall survival (OS) in children with BCP acute lymphoblastic leukemia (ALL).

Methods: MRD detection was performed on day 15 using four color FC analysis with a FACScan flow cytometer. Three yrs OS of 62 leukemic children with a BCP ALL phenotype treated according to the antileukemic protocols BFM 95 (No. 8) and BFM ALL-IC 2002 (No. 54) were studied retrospectively.

Results: Three-yrs OS of patients with FXIIIa expressing lymphoblasts (No. 59) was 87%, significantly higher (p = 0.025; Chi square test) than 3-yrs OS (65%) of patients with FXIIIa-negative lymphoblasts (No 23). Unfavorable genetic conditions were significantly more frequent among FXIIIa-negative vs. positive cases. Distribution of other conventional prognostic factors was similar between the two groups. Day 15 FC MRD successfully separated patients into 3 well defined groups: standard-risk (SR) patients (FC MRD = 0.1%); intermediate-risk (IR) patients (0.1% ≤ FC MRD < 10%) and high-risk (HR) patients (FC MRD ≥ 10%) with a 3-yrs OS of 92%, 72 and 43%, respectively. FXIIIa positivity selected a subpopulation of FXIIIa-positive, FC MRD SR patients (No. 14) with a 100% 3-yrs OS. Three-yrs OS of FXIIIa-negative, FC MRD SR patients (No. 6) was 74%.

Conclusion: Retrospective analysis of a limited number of patients indicated an important prognostic role of FXIIIa expression in childhood BCP ALL. Preliminary data suggest that FXIIIa expression may define a new subgroup of childhood ALL. Exact impact of FXIIIa expression in childhood ALL should be evaluated within the frames of prospective multi-center studies.

References

PA018
CONSUMPTION OF FRUITS, VEGETABLES AND MILK PRODUCTS IN CHILDHOOD DECREASES THE RISK OF PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA
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1030 SIOP ABSTRACTS

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Purpose: Cancer causation is known to be the interplay between genetic factors and environmental influences. Food consumption is an important environmental factor which may play either a protective or a contributory role in malignancy. The causative risk factors for acute lymphoblastic leukemia (ALL) are still largely unknown. There are few studies that attempt to demonstrate the protective or harmful nature of food groups with relation to childhood ALL. We studied the type and frequency of foods consumed by children with ALL and the maternal diet during pregnancy.

Methods: A pretested Food Frequency Questionnaire was administered to all children with ALL and their mothers, and to age and sex matched controls at our institution. The frequency of consumption of various food groups (cereals and pulses, vegetables, fruits, meat and fish, processed foods and milk/milk products), infant feeding practices and duration of breast feeding was recorded. The time period addressed was pregnancy and a period of 6 months prior to the diagnosis of leukemia. Pearson’s chi-square test and likelihood ratios were used to compare cases and controls.

Results: There were 48 cases and 64 controls studied. Milk and milk product consumption in pregnancy was significantly lower in mothers of cases as compared to mothers of controls (p = 0.16). Among children with ALL, there was a significantly lower consumption of fruits (0.01), vegetables (0.01) and milk and milk products(0.06) in comparison to controls. There was no significant difference between duration and frequency of breast feeding or age of initiation of complementary foods among case and controls.

Conclusion: Consumption of fruits, vegetables, milk and milk products may have a protective role in ALL causation in children. Milk consumption during pregnancy may also have a protective role. Larger epidemiological surveys are needed to confirm these preliminary observations.

PA019

A COMPREHENSIVE STRATEGY REDUCES TREATMENT MORTALITY AND ABANDONMENT RATES IN POOR CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA TREATED AT INSTITUTO NACIONAL DE CANCEROLOGIA, BOGOTA, COLOMBIA

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Purpose: We previously found high toxic death and abandonment rates in poor children with acute lymphoblastic leukemia (ALL) treated at Instituto Nacional de Cancerologia (INC) in Bogota, Colombia. Here, we report results of a comprehensive strategy to improve outcomes for these patients.

Methods: The ACHOP 2006 protocol, a BFM-based regimen modified to reduce toxicity, was devised and implemented. A twinning program was undertaken between INC and Dana-Farber/Children’s Hospital Boston (CHB), Harvard University, Boston, MA, USA.

Results: The rate of DH during induction chemotherapy improved from 9.6% in historic controls to 3.4% in the study population. Remission rates after induction chemotherapy improved from 85 to 95%. The rate of deaths in remission improved from 38 to 13%. The rate of abandonment decreased from 35% to 18%. However, the rate of relapse increased from 22% to 29%. Estimated 5-year event-free survival (EFS) and overall survival (OS) rates are currently 46% EFS and 59% OS for the study population, versus 43% EFS and 55% OS in historic controls, but the twinning program interventions were not fully implemented until 2009.

Conclusion: Toxicity and abandonment rates markedly improved in the study population, and we are hopeful that these improvements will eventually translate into improved long-term outcomes. Major remaining challenges include the increased rate of relapse, and the difficulty in delivering therapy without administrative delays within the Colombian public health insurance system.

PA020

CENTRAL NERVOUS SYSTEM COMPLICATIONS IN CHILDREN UNDERGOING TREATMENT FOR HEMATOLOGICAL MALIGNANCIES: A DEVELOPING WORLD EXPERIENCE

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Purpose: Survival of children with haematological malignancies in developing countries remains suboptimal. Survival can be improved further by managing treatment related complications well. Central nervous system (CNS) complications are known to occur in these patients and can be fatal. We analysed the CNS complications in children undergoing treatment for haematological malignancies focussing on clinical presentation, etiology, radiological findings and outcome.

Results: Of 403 pediatric haematological malignancies diagnosed between 2005 and 2012 we reviewed 27 patients with 28 neurological complications (6.9%). These included posterior reversible encephalopathy syndrome (PRES, n = 3), stroke (n = 11), intracranial infections (n = 4), intracranial haemorrhage (ICH, n = 3), pseudotumor cerebri (n = 2), SIADH (n = 1), abdominal epilepsy (n = 1), neurothetics neuropathy (n = 1), unclassified (n = 2). Neuro-imaging (CT/MRI) was performed in all cases. Patients with PRES showed complete neurological recovery. Radiological findings in cases of stroke were suggestive of superior sagital sinus thrombosis in 4 cases and infarcts in 7. All three cases of ICH had acute myocardial lesion and DIC. SIADH-developed in 1 child of Juvenile Myelomonocytic leukemia post-unrelated cord blood transplant secondary to drug interactions. Abdominal epilepsy was diagnosed after EEG in 1 child with persistent abdominal pain who had previously presented with seizures. Seizures were the commonest presenting complaint seen in 85% of patients and 17.3% had recurrent episodes in follow-up. Mortality was 17.4% as 5 children expired from progressive CNS insult.

Conclusion: Neurological complications lead to morbidity and mortality in children with haematological malignancies. Prompt recognition and intervention maximize favourable outcomes. Long-term follow-up is essential to exclude persistent neurological sequelae.

PA021

SYMPTOM DIAGNOSIS INTERVAL IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA: PROGNOSTIC IMPACT AND ASSOCIATION WITH CLINICO-DEMOGRAPHIC FACTORS

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Purpose: Outcome of childhood ALL in developing nations remains inferior. Despite therapeutic advances diluting the importance of traditional prognostic-factors in developed nations, these factors are still important in developing world. No study from developing nations has assessed the impact of symptom diagnosis interval (SDI) on ALL. This study was planned to determine the association of SDI with clinic-demographic variables and its impact on outcome.

Methods: Data of ALL patients managed at PGIMER, Chandigarh between 1990 and 2006 (followed till 2009) was analysed. SDI was defined as period between onset of symptoms and establishment of diagnosis.

Results: The SDI (mean: 59.9 ± 54 days) was < 8 weeks, 8–24 weeks and > 24 weeks in 448 (335 male, 113 female), 298 (231 male, 67 female) and 16 (13 male, 3 female) patients respectively. There was no significant temporal change in mean SDI over the study period. SDI was significantly associated with age at diagnosis (p = 0.017) and splenomegaly (p = 0.011), WCC (0.01), Gender (p = 0.011), disease-bulk (p = 0.415), hepatomegaly (p = 0.271), lymphadenopathy (p = 0.07), veno cava obstruction (p = 0.711), medastinal-adenopathy (p = 0.672), platelet count (p = 0.138), CNS-disease at presentation were not associated with SDI. The median survival outcome for patients with SDI < 8, 8–4 > 24 weeks was 59.08 ± 5, 36 ± 7 and 19.06 ± 12 months respectively (p = 0.005 by log-rank test). In multivariate analysis, SDI wasn’t an independent predictor of outcome (p = 0.08). Relapse was documented in 77, 43 and 5 patients of the patients with SDI < 8, 8–24 and > 24 weeks respectively.

Conclusion: This is the first study depicting the significant association of SDI with NCI-risk-category factors (age, WCC) and its impact on survival outcome of childhood ALL. Prolonged SDI adversely impacted survival. These observations are critically important in resource constraint nations where delayed presentation of ALL is common. Further studies including analysis of cytogenetic and molecular data are necessary to determine the ultimate impact of SDI on childhood ALL.
Purpose: A recent study reviewing 171 patients treated on COG protocols reported that absolute lymphocyte count (ALC) at end of induction is a powerful prognostic factor in pediatric acute lymphoblastic leukemia (ALL) and it can refine minimal residual disease (MRD) risk stratification. We aimed to investigate prognostic significance of ALC in our pediatric ALL patients who were treated with SIOP protocol of total study XV for low and standard/high risk ALL.

Methods: 408 pediatric ALL patients treated at the Children’s Cancer Hospital in Egypt, CCHL, from 1st October 2007-end of September 2009 and followed till end of December 2011, were reviewed for ALC at day15 and end of induction (day42), age, initial WBC, cytogenetics, risk group, MRD day42 and survival.

Results: ALC day2 < 1500/mL, was found to be significantly associated with age ≥10 years (p = 0.001), standard (SR) and high (HR) groups (p = 0.025), T-cell phenotype (p < 0.001), induction remission failure (p = 0.013), high MRD day42 (0.048) and a trend with Ph +/− t(11;22) (p = 0.07). ALC day42 was ninefold higher in relation to gender, initial WBC, t(1;19), and t(12;21) did not show statistically significant differences. ALC day15 and day42 did not have impact neither on 3-year relapse free survival (RFS) (p = 0.308, p = 0.46; respectively) nor on event free survival (EFS) (p = 0.106, p = 0.26; respectively). Patients who were MRD day42 positive (≥0.01%) with ALC day42 < 1500 had 3-year RFS 80.7 ± 5.2% versus 92.2 ± 4.4% for ALC ≥1500 (p = 0.08) and 3-year EFS of 77.6 ± 5.5% and 81.5 ± 5.9% respectively (p = 0.54).

Conclusion: Our study showed significant association of ALC day2 < 1500 with unfavorable age, SR and HR groups, T-cell phenotype, induction failure and high MRD day42 but did notconfirm its prognostic significance on survival or refining MRD-risk based stratification at cut-off 0.01%. Intensifying treatment for patients having MRD day42 ≥0.01% in St Jude protocol might have abrogated the prognostic significance of ALC day42 on survival.

PA023

SERUM VASCULAR ENDOTHELIAL GROWTH FACTOR-A LEVELS DURING THERAPY AND AT RELAPSE IN PEDIATRIC ACUTE LYMPHOCYTIC LEUKEMIA

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Purpose: The role of angiogenesis in acute lymphoblastic leukemia (ALL) is not fully elucidated. Data on the dynamics of serum Vascular Endothelial Growth Factor-A (s-VEGF) during treatment are conflicting. We prospectively evaluated s-VEGF in children with ALL at different time points, and compared s-VEGF with risk stratification and response to treatment.

Methods: Fifty-one children with newly diagnosed ALL were enrolled between January 2009 and October 2011 to assess s-VEGF by double sandwich ELISA (Assay Designs, USA) at diagnosis, end of induction chemotherapy with UKALL-XL or BFM-95 protocols (n = 51), and at the end of treatment (n = 7). In addition, s-VEGF samples were taken from children outside the study cohort at the end of ALL therapy (n = 6) or at relapse (n = 3). Twenty-seven healthy age- and sex-matched controls were selected for s-VEGF comparison. All experiments were run in duplicates, and the mean value was calculated.

Results: Median s-VEGF was significantly lower in patients with newly diagnosed ALL (14.2 pg/mL, interquartile range 5.7–33.2) as compared with controls (53.9 pg/mL, 33.3–79.8, p < 0.001). s-VEGF showed no difference in 7-risk ALL, unfavorable age group, or T-cell immunophenotype. Initial s-VEGF displayed a fair inverse correlation with absolute TLC (r = −0.5, p < 0.001) and LDH (r = −0.4, p = 0.016). S-VEGF rose significantly in 50 patients who achieved remission at the end of induction (38.7 pg/mL [16.1–71.9], p = 0.001). Post-remission therapy (n = 13), median s-VEGF was 39.5 pg/mL [27.0–57.3], not significantly different from controls (p = 0.21). Including one relapse in the initial cohort, s-VEGF levels at relapse (n = 4) were lower than in controls (16.6 pg/mL [10.6–29.8], p = 0.008).

Conclusion: Children with newly diagnosed or relapsed ALL have significantly lower s-VEGF levels in comparison with healthy controls. S-VEGF levels increase to near normal levels of therapy, with a partial recovery 12–24 months after diagnosis. Levels of serum creatinine, a surrogate measure of SMM, were mainly unchanged. The extent of the drop in SMM during early therapy was associated with the duration of hospitalisation (r = 0.31, p < 0.05).

Conclusion: Children with ALL experience a notable reduction in SMM early in treatment, with incomplete recovery. The degree of loss is associated with the burden of illness. These findings provide a target for a therapeutic intervention and a measure to determine its efficacy.

PA026

PREDICTORS OF COMPLICATIONS IN FEBRILE NEUTROPENIA IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA

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Purpose: Febrile neutropenia [FN] patients are at risk of developing complications during the course of their illness. Our aim was to determine risk factors at admission which independently predict complications during an episode of FN in children with acute lymphoblastic leukemia (ALL).

Methods: All children of ALL (age < 14 years) presenting with FN were evaluated for clinical, laboratory parameters and complications of illness till discharge or death. Complications studied included: encephalopathy, severe mucosal bleeds, severe sepsis, multi-organ dysfunction, metabolic disturbances, pneumonia during ventilator support, renal failure or neutropenic enterocolitis [NEC].

Results: There were 320 episodes of FN (176 patients). Seventy three (22.8%) developed complications. Metabolic disturbances, pneumonia, severe sepsis, severe mucosal bleeds, NEC, encephalopathy and renal failure were seen in 16, 12, 6, 3, 2 and 0.3%. Nine risk factors found to be significant on univariate analysis were then entered onto multivariate logistic regression. The best fitted model identified five independent risk predictors [adjusted OR (95% CI)] times last chemotherapy ≤7 days [2.2 (1.4–4.5)], focus of infection at admission [2.7 (1.3–5.5)], undifferentiated [2.5 (1.1–5.3)], absolute neutrophil count (ANC) at admission ≤100x10^6/L [2.8 (1.3–5.9)] and C-reactive protein (CRP) > 60 mg/L at admission [13.3 (5.2–33.8)]. Internal prediction accuracy was 79.8%. Regression coefficients were converted into scores of 2, 2, 2, and 5. A score of ≥7 had a sensitivity (95% CI) of 88% (78.2%–93.8%) and specificity of 72.5% (69.7%–78.4%) in predicting complications.
Risk scoring would help in identifying the subgroup of patients at risk of problematic FN during an episode of FN. A multicentric study for validation of this risk scoring is needed. Risk scoring would help in identifying the subgroup of patients at risk of problematic FN.

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HUMAN HEMATOPOIETIC STEM CELL KINETICS AFTER CHEMOTHERAPY: AN ANALYSIS OF MUTANT ERYTHROCYTES AFTER TREATMENT FOR ACUTE LYMPHOBLASTIC LEUKAEMIA

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Purpose: Intensification of treatment for paediatric malignancies over recent years has led to vastly improved survival. However, the incidence of second malignancies in survivors of childhood cancer is higher than expected. Evidence of increased somatic mutations has been documented in childhood cancer survivors [1] and, although the relationship between mutagenesis and carcinogenesis remains to be fully elucidated, the increase in secondary malignancies is (at least partly) thought to be due to exposure to mutagenic therapy. To further understand the development of secondary cancer it is crucial to know the number and turnover rate of stem cells, particularly those that have mutated due to chemotherapy. Previously, we have shown that, with serial measurements of mutant erythrocytes, we are able to delineate the progeny of individual haematopoietic stem cells (HSC) [2].

Methods: Somatic mutations at the selectively neutral glycophorin A (GPA) locus in red cells can be measured using flow cytometry in individuals who are heterozygous for the two GPA alleles, M and N. We performed serial measurements of mutant erythrocytes in 18 informative children after treatment for acute lymphoblastic leukaemia for a period of up to 25 months on left-over blood from clinically indicated blood samples.

Results: The number of mutant erythrocytes from 5/18 patients varied in a way that is compatible with 13 individual HSC differentiation events. From these data we deduce that chemotherapy is highly toxic to healthy HSCs, with only 1–5,000 remaining at the end of treatment. Recovery then occurs over a period of at least 2 years to > 100,000 HSCs.

Conclusion: We present a technique that enables the assessment of HSCs kinetics after chemotherapy. From our data we estimate the fractional cell kill rate of HSCs to chemotherapy and subsequent recovery kinetics.

References

PA028
CYTOMEGALOVIRUS RETINITIS IN CHILDREN AND YOUTH ADULTS WITH ACUTE LYMPHOBLASTIC LEUKAEMIA IN LEBANON

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Purpose: Cytomegalovirus (CMV) retinitis is a severe intraocular infection that results in retinal destruction and loss of visual acuity in immunocompromised patients. Characteristics of CMV retinitis infection in children and young adults with acute lymphoblastic leukaemia (ALL) are not well described.

Methods: We reviewed the medical records of all children with ALL treated at our center between April 2002 and May 2011 (n = 131) using St. Jude Total XV protocol with minor modifications. Data from patients presenting with symptoms and signs consistent with CMV retinitis on ophthalmological examination were retrieved.

Results: A total of four patients were identified (3%). Their median age was 18 years (range, 15–23) including three males and one female. Two had T cell and two had precursor-B lineage ALL, all treated on the intermediate risk arm. The four patients were diagnosed with CMV retinitis using macular OCT. Three patients presented with macular vision while the fourth was asymptomatic (screened due to CMV lung involvement and viremia). All patients had viremia affecting the area surrounding the fovea and the optic nerve head (zone 1). CD4 counts were lower than 50 cell/mm³ in three patients. CMV viremia was present in three patients, with one patient having concurrent lung involvement. Intravenous ganciclovir followed by oral valganciclovir were used in all patients. Three patients had recurrent disease. Two patients required intravitreal ganciclovir while one patient required foscarnet and another foscarnet and cidofovir to achieve response. Two patients maintained vision of 20/20 in both eyes while two suffered irreversible visual impairment.

Conclusion: CMV retinitis may occur in children and young adults with ALL treated with an intensive protocol. Early detection and management are vital as the disease course may be severe and associated with visual impairment.

PA029
THE TIMING OF CENTRAL VENOUS CATHETER INSERTION AND RISK OF VENOUS THROMBOEMBOLISM IN PATIENTS WITH ACUTE LYMPHOPROLIFERATIVE LEUKAEMIA

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Purpose: Current CCLG guidance is that all children receiving chemotherapy for acute lymphoblastic leukaemia (ALL) receive induction chemotherapy via a peripheral cannula and that central venous catheter (CVC) insertion is delayed until after day 28 of treatment (the end of induction chemotherapy). Children being treated on the current trial for ALL (UKALL 2003) have an overall incidence of VTE of 3.2% (Qureshi et al. Br J Haematol 2010;149(3):410–3).

The aim was to audit our practise against national guidelines and ascertain whether early CVC placement is safe by looking at the VTE incidence as well as need for line removal due to VTE or infection.

Methods: We retrospectively evaluated the timing of CVC placements, type of CVC placed and incidence of VTE as well as need for urgent line removal in children with ALL treated on UKALL 03 between August 2007 and June 2011 at the Royal Marsden Hospital.

Results: One hundred and seventy seven patients were studied. A total of 199 CVCs were inserted, 161 during the first week and prior to the first dose of PEG-asparaginase, 8 during induction and 30 were inserted after induction. 165 Portacaths, 5 Hickman lines and 29 PICC lines were inserted. There were 5 episodes of VTE, 3 with a port and 2 with a PICC. The incidence of VTE associated with lines inserted prior D28 was 2.96% (95% CI 1.11–6.93%). Using a chi-square test, the association between risk of VTE and timing of CVC insertion is not statistically significant (p = 0.317). Using a Fisher’s Exact test, the association between risk of VTE and timing of CVC insertion is not statistically significant (p = 0.218). The proportion of patients with lines inserted prior D28 that needed urgent line removal was 4.73% (95% CI 2.27–21.9%)

Conclusion: Early CVC placement was not associated with an increased risk of thrombosis.

References

PA030
VITAMIN D MODULATES OSTEOCYTE RESPONSE TO DEXAMETHASONE IN VITRO: A POTENTIAL THERAPEUTIC STRATEGY FOR GLUCOCORTICOID-INDUCED OSTEONECROSIS?

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Purpose: Osteonecrosis is a disabling side effect of dexamethasone used to treat childhood acute lymphoblastic leukaemia (ALL). 10–20% of patients develop symptomatic osteonecrosis and asymptomatic disease occurs in up to 70%. Pathogenesis involves interruption of blood supply, ischaemia and bone collapse. High levels of VEGF are present in osteocortic bones, where it couples angiogenesis and osteogenesis during bone repair. Vitamin D has multiple effects on bone biology and is used during the treatment of many osteonecrosis and asymptomatic disease occurs in up to 70%. Pathogenesis involves interruption of blood supply, ischaemia and bone collapse. High levels of VEGF are present in osteocortic bones, where it couples angiogenesis and osteogenesis during bone repair. Vitamin D has multiple effects on bone biology and is used during the treatment of many patients with ALL. Vitamin D modulates the effects of dexamethasone alone. Vitamin D reduced IL-6 production by 18.2% (p = 0.002) and 24.2% (p = 0.001) respectively when compared to vitamin D alone. Vitamin D increased VEGF and IL-6 secretion. We hypothesised that vitamin D may influence osteocyte function and may modulate the effects of dexamethasone.

Methods: MLO-Y4 osteocytes were treated with 1α-25-dihydroxyvitamin D (10−11–10−7 M) alone or in combination with dexamethasone (10−6 and 10−5 M). Media and RNA were collected after 24 h and VEGF and IL-6 secretion and expression measured. Results were analysed using SPSS by one way ANOVA.

Results: Vitamin D (10−5 M) increased VEGF production by MLO-Y4 osteocytes with 41.8% ± 10% (mean ± SE; p = 0.007). Other concentrations appear to show a dose-dependent effect. qRT-PCR revealed upregulation (1.93-fold; p = 0.020) of VEGF gene expression following vitamin D treatment. Dexamethasone reduced VEGF secretion (10−7 M, 48% ± 2.2%, p < 0.001; 10−5 M, 37% ± 1.1%, p = 0.001). Vitamin D (10−8 M) significantly modulated the effects of dexamethasone (10−5 and 10−7 M) on VEGF secretion -22.7% and 2.9% and 31.5 ± 2.3% increase (both p < 0.001) respectively when compared to dexamethasone alone. Vitamin D reduced IL-6 production by 18.2 ± 1.8% (p = 0.002) and 24.2 ± 4.4% (p = 0.027) at 10−5 M respectively.

Conclusion: These novel findings reveal that vitamin D upregulates VEGF and downregulates IL-6 production by MLO-Y4 osteocytes, as well as modulating the adverse effects of dexamethasone in vitro. This identifies a potential role for vitamin D in the prevention and/or treatment of corticosteroid induced osteonecrosis.

References
PA031

PROSPECTIVE STUDY ON INCIDENCE, RISK FACTORS, AND LONG-TERM OUTCOME OF OSTEONECROSIS IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA


Purpose: To identify if current guidelines for prevention of pneumocystis pneumonia are being investigated, all of which were negative for G6PD deficiency. The first 5 patients did not tolerate co-trimoxazole, with 20 cases of intolerance secondary to cytopenia. Of the 22 patients who completed treatment for Acute Lymphoblastic Leukaemia, on the UKALL2003 protocol, cumulative incidence, risk factors, therapeutic strategies, and outcome were described.

Results: Cumulative incidence of osteonecrosis was assessed prospectively in 694 patients treated with the dexamethasone-based Dutch Child Oncology Group-ALL9 protocol. Osteonecrosis was defined by development of symptoms (National Cancer Institute grade 2–4) during treatment or within 1 year after treatment discontinuation, confirmed by magnetic resonance imaging. We evaluated risk factors for osteonecrosis using logistic multivariate regression. To describe outcome, we reviewed clinical and radiologic information after antileukemic treatment 1 year or more after osteonecrosis diagnosis.

Conclusion: Six percent of pediatric patients with ALL developed symptomatic osteonecrosis during or shortly after treatment. Older age and female sex were risk factors. After a median follow-up of 5 years, 60% of patients had persistent symptoms.

PA032

PNEUMOCYSTIS CARINII PNEUMONITIS (PCP) PROPHYLAXIS IN PEDIATRIC PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKAEMIA

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Purpose: To identify current guidelines for prevention of pneumocystis pneumonia are effective and tolerated in children undergoing treatment for Acute Lymphoblastic Leukemia.

Methods: This is a retrospective review of PCP prophylaxis in 165 paediatric patients who completed treatment for Acute Lymphoblastic Leukaemia, on the UKALL2003 protocol.

Results: 164 patients were commenced on co-trimoxazole, and one was commenced on dapsone due to concerns regarding a prior trimethoprim allergy. Of the 22 patients who discontinued co-trimoxazole, 20 patients (87%) have documentation of G6PD status being investigated, all of which were negative for G6PD deficiency. The first 5 patients to require 2nd line therapy were commenced on pentamidine, with ‘cytopenia’ cited as the cause of co-trimoxazole intolerance for all of these patients. One patient was subsequently suspected of developing pneumocystis pneumonia, and retrospectively this patient was found to be non-compliant with co-trimoxazole.

Conclusion: This review demonstrates that current PCP prophylaxis treatments are effective, and for the majority of patients, co-trimoxazole is well tolerated.

PA033

MANAGEMENT OF HYPERLEUCOCYTOSIS AND PREVENTION OF TUMOR LYSIS SYNDROME BY ADMINISTRATION OF L-ASPARGINASE IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKAEMIA

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Purpose: Acute lymphoblastic leukemias (ALL) may present with high blast counts. Cytoreductive therapies including chemotherapy, transfusion, and leucapheresis, need expensive equipment and trained staff, while steroid administration, is associated with tumor lysis syndrome (TLS). The efficacy of other induction chemotherapeutic drugs to bring about cytoreduction without precipitating TLS is not known. In this study, the patients with hyperleucocytic ALL were treated with single chemotherapeutic agent L-Asparaginase along with supportive treatment and its effect on white blood cell (WBC) count and precipitation of TLS was assessed.

Methods: Between April 2010 and February 2012, all children of ALL ≤12y age, presenting with WBC count > 100x10^9/L were included. All the patients were administered intravenous fluids (3L/h/72h), and allopurinol on admission. One dose of L-Asparaginase (6000U/m², intramuscular) was administered after confirmation of morphological diagnosis and drawing samples for cytochemical and genetic testing. A second dose of L-Asparaginase was administered 48h later if WBC count was > 100 x10^9/L. Complete hemogram, and blood chemistry (serum electrolytes, creatinine, urea, uric acid, calcium and phosphorus) were performed every 12h for the first 72h and daily thereafter.

Results: Seven children (3 boys and 4 girls) with hyperleucocytic ALL were treated with L-Asparaginase. Six children received one dose of L-Asparaginase. The median age of children was 5y (3–8 years). The median WBC counts at presentation was 251 x10^9/L (151–428 x10^9/L). The mean reduction in WBC count achieved by treatment was 5.4, 35.5, 52.4, 70.6, 85.2, 88.1% at 12, 24, 36, 48, 60 and 72h respectively. None of the patients developed life-threatening metabolic disorders or required dialysis. Serum uric acid, creatinine, and potassium stayed within normal limits. One patient had hyperphosphatemia (6mg/dl, managed with oral sevelamer) and hypocalcemia (6.9 mg/dl, managed with calcium supplementation) on day 3 of treatment.

Conclusion: Among patients with hyperleucocytic ALL, L-Asparaginase reduces WBC counts without precipitating TLS.

PA034

NO EVIDENCE OF INCREASED ASPARAGINE LEVELS IN THE BONE MARROW NICHE OF PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKAEMIA DURING ASPARAGINASE THERAPY

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Purpose: Mesenchymal cells in bone marrow (BM) may produce asparagine and form ‘protective niches’ for leukemic cells. In vitro, this led to high levels of asparagine and asparaginase resistance of acute lymphoblastic leukemia (ALL) cells. The aim of our study is to analyse whether mesenchymal cells indeed produce significant amounts of asparagine in vivo that may lead to clinical asparaginase resistance.

Methods: Twenty-six de novo ALL patients were enrolled. All children received induction chemotherapy according to the Dutch Childhood Oncology Group (DCOG) ALL10 protocol. Asparaginase was administered from days 12 to 33. Asparaginase, asparagine, aspartic acid, glutamine and glutamic acid levels were measured in BM and peripheral blood at diagnosis, days 15, 33 and 79.

Results: In both compartments, the median asparaginase trough levels were not significantly different at days 15 and 33. Only at diagnosis, asparagine level was significantly higher in BM than in blood (p = 0.001). Asparaginase levels were all below the lower limit of quantification in both BM and blood at days 15 and 33. However, the asparagine acid level in BM was significantly higher than in blood (p < 0.0001) already at diagnosis, and this significant difference was also found at days 15, 33 and day 79.

Conclusion: We demonstrate higher aspartic acid levels in BM compared to blood. In increased asparagine levels in BM compared to blood were seen during induction therapy containing asparaginase. Therefore, it is questionable whether production of asparagine in the BM microenvironment leads to clinical resistance to asparaginase.

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Between March 2005 and May 2007, a pilot study was conducted to investigate the variation in Cathepsin-B expression or activity may contribute to the large variation in serum ASNase levels in patients.

**Conclusion:** Together, these findings suggest that variation in Cathepsin-B expression or activity may contribute to the large variation in serum ASNase levels in patients.

**PA036**

**HIGH EARLY RESPONSE AND LOW INDUCTION DEATH RATES AND BETTER EFS WITH EARLY PEG ASPARAGINASE IN CHILDHOOD ALL – UPDATE OF A PILOT STUDY MB 2005**

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**Purpose:** A major problem of the treatment of ALL in Russia is the high rate of induction deaths (ID) due to severe infections and disease-related aplasia. To reduce the ID rate, the MB-group aims at achievement of an earliest possible remission leading to an earlier reconstitution of bone marrow and immunocompetence.

**Methods:** The induction treatment in ALL Moscow-Berlin (MB) Protocol 2002 employed a 6 week phase with dexamethason, vincristin, daunorubicin and triple intrathal cerebral therapy. Between March 2005 and May 2007, a pilot study was conducted to investigate the feasibility, safety and activity of a single dose of 1,000 U/m2 PEG-asparaginase in 151 patients on day 3 of induction treatment in 3 centers in Moscow: In SR patients daunorubicin was omitted at all. 255 patients treated with MB2002 in the same centers served as historical control.

**Results:** On day 15, significantly more patients with day-3-PEG-Asp showed a M1 marrow allowing for early regeneration of the blood counts. Remission rates on day 33 however were not different (247/255 (96.9%) vs. 153/155 (98.7%)). Induction death rates were 3.1% (8/255) in historical controls versus 1.3% (2/155) in “PEG” Group. 6-year EFS rates were 75% ± 3% in historical controls versus 84% ± 3% in “PEG” Group (p = 0.03). These differences in EFS rates was much more prominent in SHR (74 ± 3 vs 89 ± 3, p = 0.004) despite of DNR was omitted in “PEG” Group. Additionally, severe non fatal infections occurred less frequently in patients with day-3-PEG-Asp as compared to historical controls.

**Conclusion:** PEG-Asp on day 3 of induction leads to an earlier achievement of remission and allows earlier reconstitution of immunocompetence. The future ongoing randomised multicentric trial ALL – MB 2008 will prospectively investigate, whether early PEG-asp can improve remission and EFS rates and reduce induction death rates in SR and IM/R patients and may allow to omit daunorubicin in SR patients.

**PA037**

**SUB-CLONAL CYTOGENETIC HETEROGENEITY IN HIGH HYPERDIPLOID ACUTE LYMPHBLASTIC LEUKAEMIA**

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**Purpose:** Cytogenetic patterns in high hyperdiploid pediatric acute lymphoblastic leukaemia (HHD pALL) have been investigated using multicolour interphase fluorescence in situ hybridization (MI-FISH). Clonal evolution routes and sub-clonal architecture of leukaemic cell population have been revealed; furthermore results were compared to clinical data.

**Methods:** 67 bone marrow samples withdrawn from 63 patients at the time of diagnosis or relapse were selected. Investigating aneusomies of eight different chromosomes (X, 4, 6, 10, 14, 17, 18 and 21) at single cell level using MI-FISH and automated microscopy, we doubled the number of targets having ever been used for this purpose.

**Results:** Considering the ratio of various chromosomal abnormalities within the abnormal cell population of each patient, gains of chromosomes X and 21 were presented at the highest level referring to their early occurrence during the formation of HHD pattern, while aneusomy of chromosome 17 proved to be the latest event. Scrutinizing the combined (eight-target) signal pattern at single cell level, a high heterogeneity has been found. The most dominant clone was presented in a range of 28–85%. The count of non-dominant, but unambiguously abnormal MI-FISH patterns varied between 25 and 159 and the totalized rate of cells harboring these patterns proved to be 13–70%. Comparing paired samples withdrawn from the same patient at diagnosis and relapse, it has been found that not only the appearance of new aneusomies but also an increased rate of clonal heterogeneity is associated with disease progression.

**Conclusion:** While a certain level of sub-clonal genetic heterogeneity has been previously revealed in HHD pALL by other groups, it was only assumed so far that a real cell-to-cell variation characterizes its genetic profile. Comparing our cell-based results to clinical outcome of patients, we found that clonal heterogeneity may have significant prognostic value providing further stratification for this genetic subgroup of pALL.

**PA038**

**IMPROVEMENT IN RISK GROUPS CLASSIFICATION IN CHILDHOOD ACUTE LYMPHBLASTIC LEUKAEMIA: CRYPTIC DUPLICATIONS AND DELETIONS**

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**Purpose:** Acute lymphoblastic leukemia (B-ALL) is the most common pediatric malignancy and a major cause of death by disease in children. Survival has increased adapting therapy to risk groups, characterized by prognostic markers that include cytogenetic alterations.

However, some patients do not respond properly to treatment and have to be moved to higher risk groups. This means that the risk groups are not well defined, due in part to undetected cryptic alterations such as deletions and duplications. Therefore, in this study we wanted identify novel deletions and duplications that could allow a better risk-group classification.

**Methods:** We analyzed DNA samples from 23 patients diagnosed with B-ALL from the different risk groups. The alterations were analyzed with Cytogenetics Whole-Genome 2.7 M platform (Affymetrix) and Chromosome Analysis Suite program (ChAS).

**Results:** In total, 223 alterations were detected, with an average of 9.7 genomic abnormalities per case. Losses outnumbered gains. Some recurrent aberrations were present in patients from different risk groups and may be associated with the leukemic process (deletions at 1q23.1, 3q13.2, 3q26.3, 7p14.3, 12q11.2, 17p11.2, 17q21.3, 17q21.2). We detected recurrent aberrations that distinguish the standard risk group (1q41.2 and 1q42.4 deletions) and high risk patients (1q22.31 loss). We also detected alterations (1q23.1 and 1q25.1 gain, 3q33.3 gain or loss, 1q25.1 q25.2 and 1q21.2 loss) that distinguish standard-risk patients who remain in this group from those who were changed to high risk. On the other hand, we did not find any recurrent alternation to differentiate the high-risk patients who remain in this risk group from patients switching to very-high-risk.

**Conclusion:** Risk groups classification could be improved in patients with pediatric B-ALL through the analysis of new deletions and duplications. This project was supported by RETICS (RD06/060200304), Basque Government (GIC07/131, SA033/09 and 2006/11/15) and UPV/EHU (UIF11/35). Support by SGiker (UPV/EHU) is gratefully acknowledged.

**PA039**

**FREQUENCIES OF ETV6-RUNX1 GENE FUSION AND SECONDARY CHROMOSOMAL ABNORMALITIES IN PEDIATRIC LYMPHOBLASTIC LEUKAEMIA**

Pediatr Blood Cancer DOI 10.1002/pbc
Purpose: The translocation (12;21) / ETV6-RUNX1 is the most common chromosomal translocation in childhood acute lymphoblastic leukemia (ALL). We studied the frequencies of ETV6 / RUNX1 fusion gene and secondary chromosomal abnormalities involving ETV6 and RUNX1 by cytogenetics and FISH in 300 children with B precursor ALL.

Methods: Bone marrow samples were obtained from 300 pediatric B-lineage ALL patients who presented at Children's Cancer Hospital in Egypt from September 2007 till December 2011. Karyotyping and FISH using probes for ETV6 and RUNX1 were performed to detect the signal pattern. Results: In the current study, FISH for ETV6-RUNX1 gene fusion was detected in 55/300 cases (18.3%). Among the 55 cases of ETV6-RUNX1 fusion gene there were 41/55 (74.5%) cases with secondary chromosomal abnormalities involving the ETV6 and RUNX1 genes such as deletion of the nontranslocated allele of ETV6 in 38.2%, gain of der(12;21) in 21.8% and gain of normal chromosome 21 in 30.9%. These abnormalities corresponded to: lack of ETV6 signal, extra ETV6-RUNX1 fusion signal and extra RUNX1 signals, respectively as detected by FISH. There were also 6 cases with both extra der(12;21) and deletion of the nontranslocated allele of ETV6, and 3 cases with gain of normal chromosome 21 and deletion of the nontranslocated allele of ETV6. Complex variant translocation was detected in 4 cases involving 11q15, 6q21, and 14q11. Near tetraploidy was encountered in 2 cases, and trisomy 16 in two cases.

Conclusion: The frequency of ETV6/RUNX1 fusion in our series is in concordance with other publications. Secondary chromosomal abnormalities involving the ETV6 and RUNX1 genes are commonly detected.
Purpose: Acute Lymphoblastic Leukemia (ALL) is the most common type of cancer in children. Susceptibility to develop ALL is due, in part, to small variations in the genome. One of the most common genetic variations are single nucleotide polymorphisms (SNPs). Pediatric ALL develops in early life, so it could be expected to present a strong influence of the genetic variations of the individual. Recently, two genome-wide association studies (GWAS) in childhood ALL were carried out. From the 10 most significant SNPs in both studies, 3 were found between intron 2 and 3 of ARID5B gene (AF-rich interactive domain 5B). These SNPs are located in a small region of the gene ARID5B, of 52Kb approximately. Follow-up studies confirmed the association of these SNPs. None of the SNPs analyzed has a clear functional effect, so it is expected that others SNPs in this region will help to explain the cause of this association. Therefore, the aim of this study was to analyze the polymorphisms between intron 2 and 3 of ARID5B gene, to confirm the involvement of this region in susceptibility to pediatric ALL.

Methods: 238 childhood B-cell ALL patients during complete remission and 352 healthy controls were analyzed. We analyzed 10 SNP covering completely the region of 52 Kb of ARID5B gene. Taqman OpenArray platform was used.

Results: All the SNPs analyzed were significantly associated with susceptibility to childhood ALL (p < 0.05), supporting previous results.

Conclusion: Our results indicate that inherited variation in intron 2 and 3 of ARID5B gene contributes to the risk of developing childhood ALL.

This project was supported by RETICS (RD06/0022/0048), UPV/EHU (IFI 11/35) Basque Government (GIC10/71, SA11/03 and 2006111015) and Jesús de Gangoiti Barrera Foundation. Support by SIKERG (UPV/EHU) is gratefully acknowledged.

REGULATION OF XIAP-IRES ACTIVITY BY EIF4GI, P97 AND EIF4A IN AN IN VITRO TRANSLATION SYSTEM

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Purpose: Overexpression of X-linked inhibitor of apoptosis protein (XIAP), a key regulator of apoptosis, is associated with poor response to therapy and prognosis in several malignancies and therefore a promising target of novel therapeutic strategies. According to its central role in regulation of apoptosis, XIAP expression is controlled at multiple levels. Alternative translation initiation via an internal ribosomal entry site (IRES) located in the 5′-untranslated region of XIAP mRNA allows translational control of XIAP expression. XIAP overexpression in childhood ALL and neuroblastoma is caused by posttranscriptional regulation.

Methods: We used a cell-free in vitro translation system based on HeLa cells for molecular characterization of XIAP IRES function. We studied the role of different translation initiation factors in XIAP IRES-mediated translation by targeted siRNA-mediated silencing (previous to preparation of cytoplasmic extract from HeLa cells) or addition of the respective recombinant proteins.

Results: The HeLa-based cell-free translation system recapitulates XIAP IRES-mediated as well as cap-dependent translation in vitro. Depletion of eukaryotic initiation factor (eIF4GI abolished cap-dependend as well as XIAP IRES-mediated translation. As described before, the middle fragment of eIF4GI (m4G) is sufficient to support XIAP IRES-mediated but not cap-dependent translation. Surprisingly, the cellular protein p97, that harbors strong homologies with m4G in its N-terminal domain and is activated during apoptosis, stimulates XIAP IRES activity even stronger than m4G. This stimulatory effect of p97 is diminished after C-terminal truncation of p97. The RNA helicase activity of eIF4A is essential for XIAP IRES-mediated (as well as cap-dependent) translation.

Conclusion: The HeLa-based cell-free translation system can be used for molecular characterization of XIAP IRES-mediated translation. Our findings on the role of eIF4GI, p97 and eIF4A in XIAP IRES function may provide new insights in the understanding of XIAP overexpression in malignant diseases.

IGF-1R EXPRESSION AND EFFECT OF IGF-1 ON B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA CELLS

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Purpose: Insulin-like growth factor 1 (IGF-1) is known to be a major growth factor effecting on various cells including hematopoietic cells and is regulated by IGF binding proteins (IGFBPs). We demonstrated that IGF-1 and IGFBPs are important for differentiation and proliferation of B-cell precursors. IGF-1 also effects on growth of neoplasms. It is reported that IGF-1 increases in growth and survival of acute myeloid leukemia by an autocrine mechanism. In addition, IGF-1 receptor (IGF-1R) is investigated as therapeutic target for multiple myeloma, Ewing sarcoma, thymoma, neuroblastoma, medulloblastoma, and osteosarcoma. The objective of our research is whether IGF-1 and IGFBPs effect on B-cell precursor acute lymphoblastic leukemia (B-ALL) cells.

Methods: We detected the expression of IGF-1R by using the fluorescein-labeled specific antibody by flow cytometry (FC500, BECKMAN COULTER). We examined effects of IGF-1 and IGFBP-1,7 on growth and signaling of B-ALL cell lines expressing IGF-1R by WST assay, immunoblot analysis and flow cytometry.

Results: Expression of IGF-1R in clinical samples of B-ALL was approximately 20%, but IGF-1R was expressed in most of B-ALL cell lines. We observed that IGF-1 enhanced proliferation of RS4; 11 and NALM-16 cells expressing IGF-1R. On the other hand, IGFBP-1, 3 and 4 partially inhibited the proliferative effect of IGF-1. We also observed that IGF-1 enhanced the phosphorylation of IGF-1R, Akt, and p44/42 MAPK in NALM-16, whereas simultaneous addition of IGFBP-1, 3 and 4 inhibited the effect of IGF-1. Our data suggest that IGF-1 can enhance the proliferation of B-ALL cells expressing IGF1R that inhibited by some of IGFBP. Further investigations whether IGF1 affects pathogenesis of B-ALL or not are now underway.

Conclusion: It is considered that IGF-1/IGFBPs play important roles in B-ALL progression and response to therapy.

EXPORTIN 7: A NOVEL TARGET TO CHEMOTHERAPY SENSITIVITY IN ACUTE LYMPHOBLASTIC LEUKEMIA CELL LINES

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Purpose: The molecular mechanisms responsible for the chemotherapy resistance process in acute lymphoblastic leukemia (ALL) remain unclear. In a previous cDNA microarray study we found that XPO7 gene overexpression was observed in poor treatment responders and also related to lower event free survival when validated in diagnosis bone marrow samples from 86 childhood ALL patients, suggesting its correlation with poor prognosis. Thus, the present study was undertaken to address the possible involvement of XPO7 gene, a nuclear export receptor, in lymphoblastic leukemia chemotherapy resistance.

Methods: Lymphoblastic leukemia cell lines Jurkat and ReH were transfected with lentivirus containing shRNA for the target gene. Empty vectors were used as negative controls. The gene knockdown was confirmed by qRT-PCR and Western blotting. Responsiveness of leukemia cells to vincristine (1.0–20 μM), prednisolone (0.5–150 μg/mL) and daunorubicin (10–150 μM) was determined by 4-day XTT drug resistance assay. XPO7 effect on apoptosis induction was analyzed by Annexin V staining by flow cytometry. The IC50 value was calculated with CalcuSyn software and t-test was conducted to determine statistical significance (alpha was set at 5%).

Results: Compared to the non-transduced cell lines, XPO7 gene expression knockdown significantly reduced the ReH IC50 values to prednisolone and daunorubicin. The same was not observed for Jurkat cells, which remained expressively resistant to prednisolone. However, prednisolone treatment induced a significantly 7.0-fold higher apoptosis rate in XPO7 knockdown in both ReH and Jurkat cells. The cytotoxic effects of the chemotherapeutic agent vincristine were not significantly modified by XPO7 silencing in ReH cell line.

Conclusion: This data suggests that the XPO7 gene could play an important role in leukemic cells sensitivity to the glucocorticoid agent prednisolone and could be considered as a target for further investigations on new therapeutic interventions for ALL treatment. This is the first report of Exportin7 participation on ALL drug response.

KIRS GENE PROFILE IN PEDIATRIC B ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) GENE EXPRESSION

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Purpose: The aim of the study was to investigate the polymorphisms of activating and inhibitory Natural Killer cell Immunoglobulin-Like receptors (KIR) genes in children with...
SIOP ABSTRACTS

B-ALL and to correlate the expression frequencies with susceptibility or protection against B-ALL.

Methods: The genotyping was performed by polymerase chain reaction-sequence-specific primer (PCR-SSP) detecting simultaneously 14 KIR genes (2DL1, 2DL2, 3DL1, 2DL4, 2DL5, 2DS1,2DL2, 2DS2, 2DS3, 2DS4, 2DS5, 3DL1, 3DL2, 3DL3, 3DS1,3DS3,3DP1) and 2 pseudogenes. Study population was stratified according to the total number of activating/ inhibitory KIR expressed in 3 categories: high expression (> 4 activating genes, > 8 inhibitory genes), median (2-4 activating genes, 4-8 inhibitory genes), low (<1 activating gene, 1-3 inhibitory genes). Patients were additionally stratified according to BFM protocol in high versus median and low risk group. KIR gene distribution between patients and controls was compared with independent test, gene by gene logistic regression analysis was performed to detect odds ratio with 95% Confidence Intervals (CI). Two sided p < 0.05 was considered as statistically significant.

Results: Thirty two children diagnosed with B-ALL and 33 controls both of Greek origin were genotyped for inhibitory and activating KIR receptors. All six activating KIR genes were significantly higher expressed in the control group compared to the patient group (p < 0.05), while the inhibitory genes did not present significant differences between the two groups. The strongest association was observed for KIR2DS1, KIR2DS1 and KIR2DS5 (p = 0.01, p = 0.017 and p = 0.025, respectively). The number of inhibitory genes expressed in each participant has not been strongly associated with protection or susceptibility to B-ALL.

Conclusion: Our results are consistent with the only previous study in pediatric Canadian ALL patients reinforcing the hypothesis that the loss of expression in activating KIR genes may predispose to the development of pediatric B-ALL.

PA048
MICRORNAS AS POTENTIAL MARKERS OF TOXICITY IN CHILDHOOD ACUTE LYMPHOBlastic LEUKEMIA

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Purpose: Methotrexate (MTX) is a key component in the treatment of childhood Acute Lymphoblastic Leukemia (ALL). Treatment with high dose MTX often causes toxicity, thus dose reduction or cessation of treatment is needed. In the last years, several studies have investigated the relationship between genetic variation and MTX-related toxicity. One of the most common genetic variations are SNPs or single nucleotide polymorphisms. Recent studies have provided evidence that SNPs in miRNAs and in genes of the processing machinery of miRNAs may effect the expression of genes involved in drug response. However, there are few studies that show how SNPs in miRNAs or processing genes affect the response to treatment in childhood ALL. The aim of this study was to determine the potential role of variations in miRNAs or their processing genes as markers of toxicity induced by MTX in children with ALL.

Methods: 152 childhood B-cell ALL patients during complete remission treated with the LAL9402 protocol (intensive MTX plasma levels were used as an objective and quantifiable marker of toxicity. 126 SNPs in miRNAs and miRNA biogenesis pathway were studied. Taqman OpenArray platform was used.

Results: Of the 126 SNPs analyzed, 9 were significantly associated (p < 0.05) with clearance of MTX of above were located at miRNAs and six in miRNA biogenesis pathway genes.

Conclusion: Our results suggest that polymorphisms in both genes of miRNAs and processing machinery genes may affect the risk of MTX toxicity in childhood ALL. This project was supported by RETICS (RD/060020/0048), UPV/EHU (UPI 11/35 Basque Government (GIC10/71, SA10103 and 2006111015) Jesús de Gangotia Barrera Foundation. Support by SGiker (UPV/EHU) is gratefully acknowledged.

PA049
NEW MARKERS IN SUSCEPTIBILITY TO DEVELOP CHILDHOOD ACUTE LYMPHOBlastic LEUKEMIA: MIRNAS

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Purpose: Pediatric Acute Lymphoblastic Leukemia (ALL) develops in early life, so it could be expected to be strongly influenced by individual variations. Susceptibility to develop ALL is also in part, to small variations in the genome. One of the most common genetic variants are single nucleotide polymorphisms (SNPs). MicroRNAs (miRNAs) are non-coding RNAs that can block mRNA translation and influence mRNA stability. Up to 171 deregulated miRNAs have been reported in children with ALL, showing that this regulatory mechanism plays an important role in both the origin and evolution of the disease. Recent studies have provided evidence that SNPs in miRNAs and in genes of the processing machinery of miRNAs might be associated with risk of developing cancer. The aim of this study was to evaluate the role of single nucleotide polymorphisms in both precursor miRNA and in genes related to microRNAs in the susceptibility in ALL patients.

Methods: 238 childhood B-cell ALL patients during complete remission and 352 healthy controls were analyzed. 126 SNPs in miRNAs and miRNA biogenesis pathway were studied. Taqman OpenArray platform was used.

Results: Twelve polymorphisms were found to have significant associations (p < 0.05) with risk of childhood ALL.

Conclusion: Our results suggest that SNPs in miRNAs and miRNA biogenesis pathway may affect childhood ALL susceptibility. This project was supported by RETICS (RD/060020/0048), UPV/EHU (UPI 11/35 Basque Government (GIC10/71, SA10103 and 2006111015) Jesús de Gangotia Barrera Foundation. Support by SGiker (UPV/EHU) is gratefully acknowledged.

PA050
THE ROLE OF PHARMACOGENETICS IN THE TREATMENT OF LEUKEMIC PATIENTS WITH CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

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Purpose: Several investigators are highlighting the role of pharmacogenetics in acute lymphoblastic leukemia (ALL) treatment response; however, data remains controversial. Methods: We are currently measuring the frequencies of 1 SLC19A1, 1 ABC2C2, 3 ABC2B1, 2 MTHFR, 3 TPMT, 3 TYMS and 1 SLC01B1 genetic polymorphisms in 150 Lebanese children with ALL treated according to the St. Jude TOTAL XV protocol, and correlating the genotyping results with chemotherapy-related variables.

Results: During consolidation treatment, patients who carry the mutant allele for ABC2C2 showed a trend towards developing methotrexate toxicity since they required an increased dose of leucovorin, but this was not statistically significant. Furthermore, the TYMS 6-bp deletion polymorphism was statistically significantly associated with greater need for transfusion, indicating greater toxicity (P = 0.033), and ABC2B1 C3435T allele carriers were at a significantly higher risk for developing febrile neutropenia (OR = 5.813; 95% CI = 1.96 – 29.25; P = 0.029). A high inter-individual variability was noted in the measured methotrexate levels during the 4 consolidation cycles; nevertheless, the mean methotrexate AUC was significantly higher in ABC2B1 C3435T allele carriers indicating a lower methotrexate clearance and hence potentially higher toxicity. As for maintenance treatment, both TYMS 6-bp deletion polymorphism and 28-bp repeat polymorphism showed a significant association with reduction in both 6-mercaptopurine and methotrexate doses indicating greater toxicity (P = 0.024 and 0.001, respectively), and MTHFR C677T allele carriers were at a significantly higher risk for necessitating a decrease in 6-mercaptopurine dose (OR = 7.424; 95% CI = 1.026–53.537; P = 0.047). Note that, in case of toxicity, our practice was to gradually decrease the dose of 6-mercaptopurine until 50 mg/m2 followed by a gradual decrease in the methotrexate dose.

Conclusion: This is the first study that evaluates the frequencies of several candidate gene polymorphisms in a population of Lebanese children with ALL and the effect of these polymorphisms on toxic effects of chemotherapy. Further recruitment is ongoing to increase statistical power.

PA051
METHYLMIONETETRAHYDROFOLATE REDUCTASE (MTHFR) POLYMORPHISMS IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL), AND THE NEED FOR REDUCTION OR CESSATION OF METHOTREXATE DOSING DURING MAINTENANCE THERAPY: THE POLISH MULTICENTER ANALYSIS

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Conclusion: The results indicate that MTHFR genotype influences the safety and efficacy of therapy. A total of 211 ALL children (132 boys and 79 girls) were analysed. The control group consisted of 99 healthy volunteers (47 men and 52 women). The MTHFR polymorphisms were investigated using PCR-RFLP technique. Restriction analysis with two enzymes (Hinfl and Fnu4HI) of the enzymatically amplified products allowed identification of 677C > T and 1298A > C polymorphisms.

Results: Among the patients, 25/211 (11.8%) children had homozygous 677CC/1298AA genotype (wild type) at both the MTHFR 677 and 1298 loci. The C/A-C/C genotype was the most common, occurring in 50/211 (23.7%) children. The second most common was heterozygous C/C-T/A genotype detected in 42/211 (20.3%) children. 223/211 (10.4%) children had homozygous 677TT genotype. Homozygous alleles 1298CC were detected in 232/211 (10.9%) children with ALL. The genotype and allele distributions were similar in the ALL and control groups. The methtroxy reductase dose was reduced more frequently in patients with homozygous alleles AA at 1298 locus (p = 0.023). There was no association between variant allele at 677 locus and MTX dose adjustments. The presence of variant allele 1298C was associated with reduced risk of leukaemia (p = 0.03), gastrointestinal disorders (p = 0.05) and hepatotoxicity (p = 0.02).

Conclusion: The results indicate that MTHFR genotype influences the safety and efficacy of MTX therapy.

Methods: Retrospective analysis of all patients treated for Philadelphia positive CML at our institution between March 2006 and January 2011 was performed. Starting dose of Imatinib Mesylate was 600 mg/day. Response was evaluated by haematological, molecular and cytogenetic criteria. Progression-free and overall survival rates were calculated by standard methods.

Results: Fifty five children were included. Median age was 13 (range 4–18) years. Thirty three (60%) were male. Fifty two patients were in chronic phase, while three were in blast crisis at the time of presentation. A complete haematological response was seen in 45 (81%) patients at 3 months. Complete cytogenetic response (CCyR) was seen in 61% patients at 12 months. Major molecular response was present in 54% at 12 months and 67% at 18 months. Five patients developed blast crisis during therapy. Progression-free and overall survival rates at a median time of 31 (range: 13–72) months were 67 and 87% respectively. A second generation tyrosine kinase inhibitor (TKI) was used in 14.5% patients, mainly because of primary Imatinib resistance. The most common toxicities were seen in hematological and musculoskeletal systems.

Conclusion: Imatinib Mesylate is effective in paediatric CML, with response rates similar to those reported in adults with an acceptable toxicity profile. This data is useful for developing countries where facilities for allo-SCT are limited. Further studies are required to fully assess the long term impact.

A study of 55 patients from a tertiary care centre in Pakistan

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Purpose: Imatinib Mesylate is the standard of care in adults with chronic myeloid leukemia (CML) in chronic phase (CP). Only a few studies have been performed to assess its efficacy in children. Adult experience provides basis of recommendations for its use in children. This review was carried out to evaluate its efficacy and tolerance in Paediatric CML in a developing country with limited resources.

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ITD/NPM1 mutations were detected in only 2 out of 164 cases and 1 patient disclosed FLT3-ITD: 14.7%, FLT3-TKD: 5.9%, NPM1: 23.5% and CEBPA: 11.8%. Both FLT3, NPM1: 6.1% and CEBPA: 2.4%, and within the group of AML with normal karyotype, the incidences of the studied mutations were: FLT3-ITD: 10.4%, FLT3-TKD: 6.7%, NPM1: 75 (22)% and NPM1 mut/FLT3-ITDneg: 86 (13)%. The pEFS (SE) of patients with normal karyotype were: total population: 47 (9.9)%, ALK-AML: 60.9% and 59.2%, respectively. Transplant-related mortality (n = 4) was the predominating cause of deaths over leukemic progression (n = 2). Eight out of 14 alive patients have at least one comorbid condition such as severe growth impairment (n = 3), hypothyroidism (n = 3), severe chronic GVHD requiring sustained immunosuppressants (n = 3), and neurologic sequelae (n = 1).

Conclusion: Despite the treatment progress in pediatric cancer, only about 50% of children with AML can be cured. More effective risk stratification with MRD assessment and determination the predictive value of MRD level in pediatric AML still remain important clinical issues. WT1 gene, which is overexpressed in most patients with AML was chosen as a potentially useful molecular marker for MRD monitoring.

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Methods: A group of 124 newly diagnosed pediatric AML patients treated since 2006 according to AML – BFM 2004 INTERIM protocol in 14 centers of Polish Pediatric Leukemia/Lymphoma Study Group was assessed. Detection of MRD was conducted by molecular examination of WT1 gene expression by Real-Time Quantitative PCR according to the protocol established by Europe Against Cancer Program.

Results: Overexpression of WT1 gene in bone marrow samples at primary diagnosis was present in 97 (78.3%) patients. Analysis of MRD level in subsequent time points according to the treatment protocol revealed systematic decrease of WT1 gene expression. The prognostic significance of WT1 expression at diagnosis was analyzed. Neither the risk of relapse nor overall survival rate were correlated with WT1 expression, however significantly higher level of WT1 expression at diagnosis was observed in patients with worse response to induction chemotherapy (more than 5% of blasts on day 15 in bone marrow).

Conclusion: WT1 gene expression assessment does not seem to provide independent prognostic information to enhance risk stratification in pediatric AML. However, many reports indicate that level of WT1 expression after treatment completion might be useful as a MRD marker and for early relapse prediction as well. The question if WT1 expression analysis could be a useful tool for MRD monitoring in AML still remains open. Further research is warranted, as recognition of time-dependency and MRD levels and also rapidity of clearance of WT1 copy number may support prediction of AML recurrence.

PB005
LONG-TERM OUTCOME OF PEDIATRIC AML/ETO POSITIVE ACUTE MYELOID LEUKEMIA FOLLOWING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN FIRST COMPLETE REMISSION

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Purpose: Although AML/ETO(+) AML is considered a favorable prognostic factor, a strategy using allogeneic hematopoietic stem cell transplantation (allo-HSCT) in first complete remission (CR1) has been frequently applied. This study was aimed to investigate if this strategy would be a reasonable option for pediatric AML/ETO(+) AML.

Methods: We reviewed the medical records of 91 children newly diagnosed as de novo AML at our center from Jan 2001 to Aug 2009, during which period allo-HSCT was considered for AML in CR1 except acute promyelocytic leukemia and Down syndrome.

Results: AML/ETO was the leading cytogenetic abnormality representing 25.2% (n = 23) of patients. All patients achieved CR following one induction course (n = 22) or two (n = 1). Twenty patients underwent allo-HSCT in CR1, and their 5-y OS and EFS were 60.9% and 59.2%, respectively. Transplant-related mortality (n = 4) was the predominating cause of deaths over leukemic progression (n = 2). Eight out of 14 alive patients have at least one comorbid condition such as severe growth impairment (n = 3), hypothyroidism (n = 3), severe chronic GVHD requiring sustained immunosuppressants (n = 3), and neurologic sequelae (n = 1).

Conclusion: Despite an acceptable survival rate, a significant proportion of TRM and long-term comorbidity may jeopardize the use of allo-HSCT for AML/ETO(+) AML in CR1.

PB004
FLT3, NPM1 AND CEBPA MUTATIONS IN CHILDHOOD ACUTE MYELOID LEUKAEMIA IN ARGENTINA

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Purpose: Mutations of FLT3, NPM1 and CEBPA are frequently found in adult-AML. These mutations have significant prognostic value in patients with AML and normal karyotype. There are no conclusive reports about the incidence of these mutations in childhood-AML.

Methods: DNA samples from 164 patients with diagnosis of AML were retrospectively analysed. The mean age was 7 (0–18) years old. Detection of NPM1 and CEBPA mutations was performed by Gene-scanning; FLT3-ITD and FLT3-TKD were studied by RT-PCR and RFLP respectively.

Results: The incidences of the studied mutations were: FLT3-ITD: 10.4%, FLT3-TKD: 7.9%, NPM1: 6.1% and CEBPA: 2.4%, and within the group of AML with normal karyotype, were: FLT3-ITD: 14.7%, FLT3-TKD: 5.9%, NPM1: 23.5% and CEBPA: 11.8%. Both FLT3-ITD/NPM1 mutations were detected in only 2 out of 164 cases and 1 patient disclosed FLT3-TKD/CEBPA mutations. NPM1 and CEBPA mutations were significantly associated with normal karyotype (p < 0.0001) and FLT3-ITD with PML-RARA (p < 0.0001). The FAB subgroups were: FAB M1: 23 (61%), M2: 12 (31%), M3: 6 (16%), M4: 5 (13%), M5: 2 (3%); p < 0.0001). The age of patients with NPM1mut and FLT3-ITDmut was significantly higher (p = 0.0027 and p = 0.0001 respectively). The pEFS (SE) were: total population: 47 (9.9)%, ALK-AML: 60.9% and 59.2%, respectively. Transplant-related mortality (n = 4) was the predominating cause of deaths over leukemic progression (n = 2). Eight out of 14 alive patients have at least one comorbid condition such as severe growth impairment (n = 3), hypothyroidism (n = 3), severe chronic GVHD requiring sustained immunosuppressants (n = 3), and neurologic sequelae (n = 1).

Conclusion: Despite the treatment progress in pediatric cancer, only about 50% of children with AML can be cured. More effective risk stratification with MRD assessment and determination the predictive value of MRD level in pediatric AML still remain important clinical issues. WT1 gene, which is overexpressed in most patients with AML was chosen as a potentially useful molecular marker for MRD monitoring.
**Purpose**: Translocations involving ML1/L1q2 by are frequently associated with infant-acute leukaemia and therapy-related leukaemias. These abnormalities generate chimeric proteins that participate in the leukemogenic process. More than 64 ML1 translocation partners have been described, but only recurrent rearrangements are routinely studied by RT-PCR. Long Distance Inverse-PCR (LDI-PCR) allows the detection of rare ML1-partners, including partner genes which have not been previously reported. Besides, genomic fusion sequences can be used to design allele-specific oligonucleotide primers (ASO-Primers) for the monitoring of Minimal Residual Disease (MRD) particularly useful in patients with immature phenotypes without Ig/TCR rearrangements.

**Methods**: We analyzed 21 samples of acute leukaemia patients (19 infants) with diagnosis of ALL (n = 16) and AML (n = 5) in order to characterize ML1 rearrangements by LDI-PCR. ML1 abnormalities had been detected in 19 patients by cytogenetics (n = 17), RT-PCR (n = 12) or both techniques (n = 10). ASO-primers for MRD quantification were designed according to standard criteria.

**Results**: ML1 gene translocations were detected in 18/21 samples by LDI-PCR. The fusion partners detected were: AF4 (n = 6), AF8 (n = 4), ENL (n = 3), AF9 (n = 2), AF6 (n = 1), AF17 (n = 1) and BTB18 (n = 1). Six of these rearrangements were demonstrated only by LDI-PCR whereas conventional karyotype was normal (n = 2) or was suggestive of involvement of genes different from those detected (n = 4). 3 ML1-AF10, 1 ML1-AF6, 1 ML1-ENL and 1 novel ML1-BTBD18. One case disclosed t(11;22)(q23;q13) but LDI-PCR demonstrated ML1-ENL fusion gene. A second case with t(10;22)(11p13;11.2p13) disclosed ML1-AF10 fusion gene by LDI-PCR. In 8 cases, ASO-primers for MRD quantification could be designed and successfully used.

**Conclusion**: LDI-PCR was useful for detecting ML1 gene rearrangements in 6 cases in which the fusion partner was unknown, although the alteration was already suspected mainly due to the age of the patients. In addition, LDI-PCR allowed the description of a novel ML1 fusion partner and the design of ASO-primers for MRD monitoring.

**PB008**

**SYNERGISTIC AND ANTAGONISTIC AML CELL TYPE-SPECIFIC RESPONSES TO 5-aza-2-deoxycytidine and 1-h-d-arabinofuranosylcytosine**

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**Purpose**: The search for synergistic drug combinations is critical to the treatment of drug resistant cancers, such as acute myelogenous leukaemia (AML), which has 50% to 60% overall survival in children and lower in adults. Conventional treatments include the 5 phase-specific polymerase II inhibitor 1-h-d-Arabinofuranosylcytosine (ARA-C), but DNA methylation inhibitors such as 5-Aza-2’-deoxycytidine (DAC) also have activity in AML, through DNA genomic demethylation and altered gene expression. Although genome-wide changes in RNA expression associated with DAC and ARA-C are not fully understood, characterizing these responses is a critical step to increasing the efficacy of combinatorial therapies that include DAC and ARA-C.

**Methods**: RNA expression levels were assessed using the Human exon 1.0ST (Affymetrix) array 72 h after single-dose treatments with 1.0 μM DAC or ARA-C in UT7/epo, MolM13, and N4B cells. The half maximal effective concentration (EC50) of DAC and ARA-C was determined in each cell line, and the drug combination index (CI) was calculated using the Chou-Talalay method.

**Results**: While increased 5R2 expression is observed following ARA-C exposure and is associated with ARA-C resistance in UT7/epo cells, pre-treatment with DAC restores cellular sensitivity and correlates with increased RNA expression of the nucleoside transporter, SLCO2A1/HERT1. In contrast, DAC/ARA-C combinations are antagonistic in MolM13 cells, where each drug independently increases RNA expression of c-KIT and associated proliferation pathways.

**Conclusion**: Pre-treatment with DAC can sensitize ARA-C resistant AML cells, but can increase resistance in ARA-C sensitive AML cells. Possible molecular mechanisms for these results are suggested by the transcriptional response to DAC. These results show that responses to drug combinations are driven by the molecular responses of individual cell types. The results also provide an alternative approach for predicting what combination, dosing and scheduling of drug delivery should be used to better individualize therapy.

The first and second authors contribute equally in this work.

**PB009**

**CLADIRBINE(2-CDA) AND CYTARABINE(ARA-C) IS AN EFFECTIVE SALVAGE REGIMEN IN REFRACTORY/RELAPSED ACUTE MYELOID LEUKAEMIA IN CHILDREN**

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**Purpose**: Approximately 30–40% of children with AML experience a relapse in spite of intensive first line chemotherapy + HSCT. Salvage strategies have to take into that most patients would have received anthracyclines upfront and are likely to undergo HSCT after relapse. The outcomes of various salvage regimens are variable and a good strategy in relapsed AML is lacking. We report our experience of using a combination of 2-CDA/Ara-C as therapy aimed in relapsed/refractory AML.

**Methods**: This is a retrospective analysis of all patients with relapsed/refractory AML who underwent treatment with a salvage regimen of 2-CDA/Ara-C at our centre from 2006 to 2011. The regimen consisted of continuous infusion of cytarabine (500 mg/m2) over five days and Cladribine (9 mg/m2) from day 2 to 6. Patients in remission were considered for HSCT where feasible or went onto receive further cycles of chemotherapy.

**Results**: Nineteen children with relapsed/refractory AML were treated with the salvage regimen of 2-CDA/Ara-C. The commonest morphological subtype (FAB) was AML-M2 (56%) and the commonest cytogenetic abnormality was t(8;21) (31 patients). Two children had secondary AML and 2/19 patients had primary refractory disease. All relapsed patients had received primary treatment on an anthracycline/cytarabine based regimen. The median duration of remission (CR1) was 16 months (range 0.5 to 70 months). After salvage chemotherapy with 2-CDA/Ara-C, 12 patients achieved morphological remission, with a response rate of 80%. Four patients died during induction, before response could be assessed.

**Conclusion**: The combination of 2-CDA/Ara-C is an effective salvage regimen for inducing remission in relapsed/refractory AML in children. Remissions are short-lived and need to be consolidated with HSCT as soon as possible.

**PB010**

**A SINGLE CENTRE RETROSPECTIVE STUDY OF CYTOGENETIC PROFILE, MANAGEMENT AND OUTCOME OF ACUTE MYELOID LEUKAEMIA IN CHILDREN**

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**Purpose**: AML 15 was the first major trial to compare anthracycline based consolidation (MAC/MidAC) to a Cytosine Arabinoside (araC) based consolidation. Following closure of the trial, standard therapy of cytosome-arabinoside consolidation therapy is currently recommended. In 2010, 14 patients were diagnosed and treated for Acute Myeloid Leukaemia in the Royal Marsden hospital and >70% have subsequently relapsed. This prompted a review of the cytogenetic, treatment and outcome profiles for all patients diagnosed with Acute Myeloid Leukaemia.

**Methods**: A retrospective study was conducted at the Royal Marsden Hospital on children (aged less than 18), diagnosed to have Acute Myeloid Leukaemia. The combination of 2-CDA/Ara-C was studied. The outcomes of various salvage regimens are variable and a good strategy in relapsed AML is lacking. We report our experience of using a combination of 2-CDA/Ara-C as therapy aimed in relapsed/refractory AML.

**Results**: 7 patients had primary induction failure following standard treatment with ADE (Cytosine Ar agonisde, Daunorubicin and Etoposide). 48 patients were appropriate for comparison between the two consolidation treatment groups. 22 patients received treatment with cytosome-arabinoside (araC) based consolidation and 26 patients received treatment with anthracycline based therapy (MAC/MidDAC). 9 patients (41%) in the araC group relapsed and 3 of these patients subsequently died. In only 1 patient this was secondary to resistant disease. Of the 9 patients who relapsed 6 had adverse cytogenetics. Whole of the group of patients treated with MAC/MidDAC, 14 relapsed (54%) and of these, 9 patients subsequently died. 6 of the 13 relapsed patients had cytogenetic abnormalities known to be associated with adverse outcome, and one patient had favourable cytogenetics. No patient within the MAC/MidDAC group had treatment changed due to cardiotoxicity. Chi-squared analysis of both groups identified no significant difference in the rate of deaths with 0.05 < p < 0.1.

**Conclusion**: Rate of relapse and death occurs more frequently in the group of patients treated with anthracycline based consolidation therapy, although this has not reached the standard level of significance.


**PB011**

**FUNGAL INFECTIONS IN CHILDREN UNDERGOING CHEMOTHERAPY FOR ACUTE MYELOID LEUKAEMIA**

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Purpose: Invasive aspergillosis is an important cause of morbidity and mortality in neutropenic children with hematological malignancies. The purpose of our study was to study the frequency and outcome of invasive fungal infections in children undergoing treatment for Acute Myeloid Leukemia (AML).

Methods: Data were retrospectively collected by the clinical records of all 50 patients with AML treated to our unit from 1991 until 2011. All patients were treated with BFM protocols. We recorded the frequency of invasive fungal infections, which required treatment with appropriate agents.

Results: From all 182 infectious episodes occurring in 47 patients in 185 chemotherapy cycles, 13 cases of invasive fungal infections were reported in 13 children, of which 3 (23.08%) were proven, 5 (38.46%) probable and 5 (38.46%) possible. Two episodes of Candidaemia (1 albicans and 1 kensei, the latter resulting in death) occurred, both during neutropenia following 2nd course of chemotherapy (HAM). One child, following the 3rd course (AE) presented with visceral Alternaria. Invasive pulmonary aspergillosis occurred in 7 cases, 3 after AIE, 1 after HAM and 3 following HDAC/VP. Sinopulmonary aspergillosis occurred in 2 children following AI and sinus aspergillosis in 1 child, after induction. All 7 cases, 3 after AIE, 1 after HAM, and 3 following HDAC/VP. Sinopulmonary aspergillosis presented with visceral Alternaria. Invasive pulmonary aspergillosis occurred in children following 2nd course of chemotherapy (HAM). One child, following the 3rd course (AI) presented with visceral Alternaria. Invasive pulmonary aspergillosis occurred in 7 cases, 3 after AIE, 1 after HAM and 3 following HDAC/VP. Sinopulmonary aspergillosis occurred in 2 children following AI and sinus aspergillosis in 1 child, after induction. All patients were treated with Liposomal Amphotericin, in combination with Caspofungin or Voriconazole in the case of Aspergillosis. The overall mortality of invasive fungal infections in our Department was 23.08%, as 313 episodes resulted in death.

Conclusion: The rate of fungal infections in children undergoing chemotherapy for AML is quite high, obviously due to the prolonged neutropenia and the immunosuppressive effect of chemotherapy.

The good survival rates underline the efficacy and safety of modern agents for invasive fungal infections complicating childhood AML.

PB012
HYPEREOSINOPHILIC SYNDROME IN CHILDREN
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Purpose: Recently, according to the Hypereosinophilic Diseases Working Group of the International Eosinophilia Society, six variants of hypereosinophilic syndrome have been proposed, i.e. (1) myeloproliferative, (2) lymphoproliferative, (3) idiopathic/undefined, (4) overlap (5) associated and (6) familial variant. Hypereosinophilic syndrome is a rare disorder in children and can occur at any age during childhood. Corticosteroids are the treatment of choice, whereas other treatment options are hydroxyurea, IFNa, imatinib, vinristine, melphalan. We present a fulfilment fatal case of hypereosinophilic syndrome in a teenager with an initial presentation of an idiopathic thrombocytopenia (ITP) and present a narrative review of literature.

Methods: Literature was reviewed for published pediatric case reports of de novo hypereosinophilic syndrome using PubMed database, from 1999 until June 2011. The search term “hyper eosinophilic syndrome”, limited to children ages 0–18 years was used. Inclusion criteria for analysis were that only children with primary, de novo hyper eosinophilic syndrome were reported that fulfilled diagnostic criteria as previously described. Cases secondary to ALL were excluded.

Results: This resulted in 16 case reports, of which 21 case reports fulfilled the inclusion criteria for analysis, reporting 33 children

Conclusion: We confirm that it can present as ITP and that the disease can show a fulminant rapidly progressing course in children. Given the rarity of hyper eosinophilic syndrome, despite increasing knowledge on the genetic aspects, it is challenging to recognize the specific variant of the disease. The development of eosinophil specific and targeted therapy seems to have a potential clinical benefit both in FIP111-PDGFRα positive and negative patients. We strongly recommend future registration of children suffering from any variant of hyper eosinophilic syndrome, and treatment according to an international protocol, in order to gain knowledge on the true incidence and the course of the disease and we propose a pediatric approach on the treatment guideline as advised for adults.

PB013
DIAGNOSTIC IMAGING AND MANAGEMENT OF MEDIASTINAL MASS-ASSOCIATED AIRWAY AND VASCULAR COMPRESSION IN PAEDIATRIC T-CELL MALIGNANCY
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Purpose: To review the extent of mediastinal structure compression on diagnostic imaging and echocardiography, safety of anaesthesia for diagnostic procedures and perioperative outcomes, in addition to steroid pre-treatment prior to diagnostic procedures in paediatric malignant mediastinal diseases, in view of evidence-based practice guidelines.

Methods: A 5 year, single-institution, retrospective review of children with a mediastinal mass from T cell leukaemia and lymphoma, diagnosed between May 2005 and May 2010 at Starship Hospital. Diagnostic imaging results, including chest X-rays, CT scans and Echocardiography were reviewed. Data collected included presence of a mediastinal mass, pleural or pericardial effusions, airway obstruction (AEO) or great vessel compression, SVC syndrome (SVCS), in addition to steroid pre-treatment, timing and mode of diagnosis, post-operative disposition and anaesthetic outcome.

Results: 10/16 patients with T-lineage acute lymphoblastic leukaemia and 7/7 patients T cell lymphoma were identified to have a mediastinal mass on imaging; among T-NHL, patients 5/ 7 had SVC compression, 5/7 significant AEO, 4/7 admitted to paediatric ICU, 0/7 deaths. There were 3/16 T-ALL patient admissions to PICU, 1 death with cardiac arrest (clinical SVCS), 4 pericardial, 5 pleural effusions, 4/16 significant AEO. Oral corticosteroids administered in 4/23 (17%) patients for respiratory embarrassment (‘asthma’) did not compromise tissue integrity but delayed diagnosis.

Conclusion: The study of perioperative outcomes in paediatric patients with a compressive mediastinal mass is crucial to streamline management pathways for these patients, where CT imaging and minimally invasive diagnostic techniques are preferred. While safe inter-hospital transfer may be mediated by steroid use to reduce the size of a mass threatening airway or cardiovascular integrity, close liaison with Oncology and multidisciplinary team input is necessary to minimise risks of life-threatening events and facilitate urgent tissue diagnosis to maintain tissue integrity and minimise morbidity. Urgent lymph node biopsy under local anaesthetic will ideally fast-track histological diagnosis and facilitate early effective treatment.

LYMPHOMAS & HISTIOCYTOSES
PC001
EXCELLENT OUTCOME IN PEDIATRIC HODGKIN DISEASE WITH TREATMENT PRIMARILY BASED ON CHEMOTHERAPY WITH ABVD/COPDAC
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Purpose: To study the clinicopathological features and survival in pediatric Hodgkin’s Disease (HD) with treatment primarily based on chemotherapy with alternating courses of ABVD (adriamycin, bleomycin, vincristine and dacarbazine)/COPDAC (cyclophosphamide, vincristine, prednisolone and dacarbazine).

Methods: At our center we have been treating all newly diagnosed Hodgkin Disease with alternating cycles of ABVD (adriamycin, bleomycin, vincristine and dacarbazine) and COPDAC (cyclophosphamide, vincristine, prednisolone and dacarbazine). Based on the response on CT scan after two courses, 2–6 additional courses were given. Radiotherapy was given only to children with gross residual disease after 6 courses. Charts were reviewed of previously untreated HD patients from August 2000 till July, 2009.

Results: We had 99 previously untreated HD patients, Male to female ration was (4:1). The age range was 3–20 years (median 8). 18 (18%) patients were under 5 years of age, 45 (45%) were 5–10 years and 37 (37%) were > 10 years. 13 patients were in low, 49 were in intermediate and 37 were in high risk group. 65 (65%) patients presented with B symptoms; 5 (5%) patients had bone marrow involvement at presentation. Mixed cellularity (MC) was found in 66 (66%) of patients, followed by nodular sclerosis (NS) in 26 (26%) of patients. 10 children received 4, 16 received 8 while majority 73 received 6 courses of chemotherapy. 12 patient received involved field radiotherapy. One patient had disease progression on treatment and switched to second line therapy: 3 patients died (2 due to infection, 1 due to disease). 5 (5%) patients relapsed 2–18 months after treatment. With a median follow up of 6.5 years the overall and event free survival is 97 and 92% respectively.

Conclusion: Chemotherapy alone with alternating cycles of ABVD/COPDAC has excellent outcome in pediatric Hodgkin Disease, limiting the use of radiation therapy.

PC002
THE RESULTS OF MODIFIED VERSION OF GPOH-HD-95 IN CHILDREN WITH HODGKIN DISEASE: EGE PEDIATRIC ONCOLOGY GROUP EXPERIENCE
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Purpose: From 1999 to 2010, 123 children with Hodgkin Lymphoma were treated with a modified version of GPOH-HD-95 protocol in which low dose irradiation was used and the results were analyzed retrospectively.

Methods: Patients were grouped into 3 categories as TG1-1 (IA/IIA), TG-2 (IIA,IIIB,IIIA) and TG-3 (IIIEB,IIIEB,IIIB,IVB) Etoposide was used in boys instead of procarbazine (OEPA). Two cycles of OPPA were given to TG1, 2 cycles of OPPA and 2 cycles of COPP were given to TG2, and 2 cycles of OPPA and 4 cycles of COPP were given to TG3. Staging and response evaluation was done in joint meetings and irradiation was performed in the
same center. Chemotherapy was the same as HD95 study, however indications of irradiation and treatment fields were modified. Complete responders and those with more than 75% reduction in tumor size were irradiated to 20 Gy, those with less than 75% reduction were treated to 25–30 Gy and those with more than 50 cc tumor at the end of chemotherapy were treated to 35 Gy.

**Results:** Median age was 10, 89 of them were male and 34 of them were female. Histology was mixed in 55 patients, nodular sclerosing in 59 patients. There were 56 patients in group TG-1, 38 in TG-2 and 29 in TG-3. Median follow-up was 68 months. Recurrence was developed in 13 patients (infield relapse in 2, other side of the diaphragm in 4, same side of diaphragm in 3, bone marrow in 3 and distant organ relapse in 1). Three patients died due to progression of disease. The overall survival is 95% and BFS is 87% in 5-years. During the follow-up 22 patients reveal thyroid disorders, and thyroid cancer was experienced in two patients.

**Conclusion:** Modified version of GPOH-HD95 protocol proved to achieve long-term sustained cure.

PC003

**A LONG-TERM FOLLOW-UP REPORT ON THE MODIFIED PEDIATRIC PROTOCOL DAL-HD-90 FOR ADOLESCENTS AND YOUNG ADULTS WITH HODGKIN LYMPHOMA**

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**Purpose:** To determine a long-term results for adolescents and young adults with Hodgkin lymphoma (HL) treated by a pediatric protocol in our center.

**Methods:** During 03/1995–12/2009 in this study 99 (m=38, f=61) patients with median age 19.2 years (range 15–29) with de novo HL was enrolled. All patients were treated according to the modified pediatric protocol DAL-HD-90. Patients are allocated to three treatment groups (TGs). The original protocol was modified in the following positions: (1) procarbazine was replaced by dacarbazine; (2) young adults received vinblastine instead vincristine; (3) all TG3 patients received 2 cycles of ODPA independently from gender; (4) involved field radiotherapy doses were increased from 20–25 to 30 Gy. The cutoff for data analysis was 12/2011.

**Results:** Forty-nine adolescents (median – 16.5, range 15–18 years) and 50 young adults (median – 19.6, range 19–29 years) were available for the analysis. Median follow-up was 9.5 years. One patient lost to follow-up. Seven patients died. Second malignancies occurred in 2 girls (ovarian and thyroid carcinomas). 10-year EFS and OS were 91 ± 4% and 91 ± 4% (TG1, n = 11), 88 ± 6% and 94 ± 4% (TG2, n = 34), 73 ± 7% and 92 ± 4% (TG3, n = 54), respectively. 10-year EFS in TG (1 + 2) was 89 ± 5% versus 73 ± 7% in TG3 (P = 0.095). As a result of poor early response after two cycles of ODPA (stabilization or disease progression) the initial protocol was changed on the adult schedule BEACOPP. The overall survival is 95% and DFS is 87% in 5-years. During the follow-up 22 patients reveal thyroid disorders, and thyroid cancer was experienced in two patients.

**Conclusion:** Modified version of GPOH-HD95 protocol proved to achieve long-term sustained cure.

PC004

**PHENOTYPIC CHARACTERIZATION BY FLOW CYTOMETRY (FC) OF PAEDIATRIC NON-HODGKIN LYMPHOMA (NHL): EXPERIENCE OF A REFERRAL INSTITUTION IN ARGENTINA**

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**Purpose:** To describe the results of phenotypic characterization by FC of pediatric NHL seen in our institution.

**Methods:** A retrospective analysis was made on 192 referred samples (76%) of NHL cases. Bone marrow samples (n: 27), CSF/other fluids (n: 30) and biopsies (n: 85) were analyzed by FC.

**Results:** B-lineage (n: 97), T-lineage (n: 40), T/NK (n: 1), and non-B/non-T-lineages (n: 4) were assigned to NHL cases based on FC. In 75 (78%) of B-lineage lymphomas, pathologic mature-B cells were identified by kappa/lambda restriction (K: 36%+ 39% with CD19+) in 73% and Td(n-) in 92%. FC and HP results could be compared in 52 samples and 100% of phenotype concordance was found. Burkitt-NHL (n: 26) was the most frequent subtype. Of 22 precursor B-lineage lymphomas, 16 FCI were compared with HP, finding 14 coincidences and 2 discordances: a Kappa + and T-lineage lymphoblastic lymphomas (LLBLAS). Another five cases were classified as Burkitt. FC exclusively allowed the diagnosis of B-lineage Lymphoproliferalymphomas (n: 5). FC identified a typical thymic phenotype (CD45+ cd69+, cd11aL(t+) in 38 T-lineage-lymphomas, 26 classified as T-lineage LLBLAS. Two were ALC and CD30+ by FC. One case of Mycosis fungoids with mature T- phenotype showed restricted TCRαβ. Out of 192 referred samples (76%) of NHL cases. Bone marrow samples (n: 27), CSF/other fluids (n: 30) and biopsies (n: 85) were analyzed by FC.

**Conclusion:** FC is a rapid tool for assignment of NHL lineage and also for defining diagnosis of lymphoproliferalymphomas cases. Rare findings like DC marker expression or Burkitt-NHL with B-precursor phenotype could be identified by FC.

PC005

**CURRENT OUTCOMES OF HODGKIN'S DISEASE (HD) AMONG CHILDREN IN INDIA: A SYSTEMATIC ANALYSIS**

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**Purpose:** Published literature from India on HD in children is scant. This comprehensive review of published and grey literature was conducted to understand the current management and outcome of childhood HD.

**Methods:** A search of MEDLINE and EMBASE was carried out. The search was limited to studies published from 2000 onwards. Abstracts presented at SIOP annual congresses (2000–2011) were also hand-searched.

**Results:** Of the 103 studies identified, 16 single-centre studies (4 papers and 12 abstracts) from 14 centres met the inclusion criteria. There were a total of 958 children with HD (11–148 children/study). The median age at presentation was 7–9 years in majority of the studies and the median male to female ratio was 4:1. Majority (median 64%, range 33–92%) had stage II/III HD at presentation. Mixed cellularity was the most common histology (median 50%, range 27–86%). Positive Emission Tomography (PET) was not used in any treatment center. Concerned treatment of chemotherapy ± radiotherapy but there was considerable variation among centers. Several chemotherapy regimens were used, most commonly ABVD, COPP or ABVD/COPP; often without risk stratification. Radiotherapy use varied from no use to use in selected patients (e.g. bulky disease or non-responders), to use in all patients. There was evidence from a single RCT of the benefit of involved field RT to patients with B symptoms and bulky disease (1). Median OS was 92% (range 43–100%) and EFS 84% (Range 63–100%). Reported range of relapse, mortality and abandonment rates were 4.5–33, 0.7–20.8 and 3.7–21% respectively. Data on long term side effects and locally relevant prognostic factors was very limited.

**Conclusion:** Survival outcomes of HD in children in India are encouraging. We recommend co-ordinated multicentre approach in treating and analysing the experiences to address several questions including risk stratification and late effects to improve the outcome further.

**References:**

PC006

**PEDIATRIC MATURE B CELL NON-HODGKIN LYMPHOMA. THE CHILDREN CANCER HOSPITAL – EGYPT EXPERIENCE**

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**Purpose:** To investigate treatment outcome, Overall Survival (OS) and Event Free Survival (EFS) for newly diagnosed mature B Non Hodgkin Lymphoma patients treated at the Children’s Cancer Hospital Egypt.

**Methods:** Retrospective review of charts of newly diagnosed pediatric Non Hodgkin Lymphoma patients diagnosed in the period between July 2007 and the end of December 2010. All patients were followed up till the end of December 2011.

**Results:** This study included 240 patients (182 males and 57 females) representing about 7% of the 312 patients treated at the study the period. Median age was 6 years. Abdominal mass was the most common clinical presentation seen in 163 patients (64%). Bone marrow involvement (ALL) L3 was seen in 24 patients (10%), while CNS involvement occurred in 23 patients (9.5%). Burkitt lymphoma was the most common subtype 216/240 (90%) followed
by Diffuse large B cell (6.6%). Stage III was the most commonly seen in 89 patients (37%), followed by stage II (35%). The most common treatment group seen was group B in 162 patients (69%). Among group C patients, CNS was negative in 28 patients (12%). LMB06 was given to 231/240 (96.2%) of the patients. Toxic deaths were 42 out of 235 patients (17.5%). The 3 years OS for the whole group was 80.2%, while the EFS was 76.4% (mean follow up duration = 17.6 months, median = 16, Range 2–44m). OS for group A was 100%, group B 83%, group C 77.4%, while for group C CNS positive was 44.9%.

Conclusion: FAB LMB 96 protocol is well tolerated, giving results close to the international literature for both group A and B patients, while it seems toxic for group C CNS positive patients mandating better tailoring of our institutional supportive care guidelines.

**PC007**

**CIRCULATING EPSTEIN–BARR VIRUS-DNA AS A BIOMARKER OF TREATMENT RESPONSE IN PEDIATRIC HODGKIN LYMPHOMA**

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Purpose: Over 90% of Indian childhood Hodgkin lymphoma (HL) cases display Epstein–Barr virus (EBV)-positive tumor cells. We assessed the value of circulating EBV-DNA as a biomarker of treatment response in EBV-associated pediatric HL.

Methods: Newly diagnosed cases of HL were prospectively included between 2007 and 2011. Fifty age-sex-matched controls were selected. Plasma EBV real-time quantitative-PCR (RQ-PCR) was assessed in controls and in pre-treatment HL cases with LightCycler2.0, Roche. EBV-LMP1 immunohistochemistry was done on HL lymph-node biopsies. Patients were treated with ABVD regimen. Treatment response was assessed after 2 (stage I–II) or 4 cycles (stage III–IV). Post-chemotherapy RQ-PCR was reassessed after the first and last ABVD cycles and on follow-up.

Results: Twenty-three children with HL were enrolled, median age 10 years (range 3–21), stage I–II, III–IV, III–IV, 10:4. EBV-LMP1 was detected in 14 (63.6%) out of 22 analysed (13/16 MC, 1/4 NS, 0/2 LP) and RQ-PCR positive in 13 (56.5%) out of 23, with 81.8% accuracy (Kappa coefficient = 0.63). RQ-PCR sensitivity and specificity were 78.6 and 87.5% respectively. EBV-association was lower than previous reports from India. All controls were RQ-PCR negative (p < 0.0001). Out of 13 RQ-PCR positive cases, one died of advanced disease before starting chemotherapy; all other 12 showed EBV clearance after the first cycle and had after 2 or 4 cycles partial response (PR)-4, very good PR-5 or complete remission (CR)-3. Ten were in CR and RQ-PCR negative at the end of therapy, 2 haven’t completed treatment yet. The only refractory disease was seen in a girl with EBV-negative LP-HL. A boy with unknown EBV status at diagnosis, RQ-PCR negative on follow-up, became RQ-PCR positive at relapse 7 months later.

Conclusion: Circulating EBV-DNA becomes undetectable early after initiating HL therapy and may increase in case of relapse. It can possibly be used as a biomarker of treatment response in EBV-associated HL.

**PC008**

**MLL REARRANGEMENT IN NON-INFILTRATED BONE MARROW IN AN INFANT WITH ISOLATED PRECURSOR B-LYMPHOBlastic LYMPHOMA**

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Purpose: Precursor B-lymphoblastic lymphoma cells are indistinguishable by morphology and immunophenotype from lymphoblasts in acute leukemia which in infancy is often associated with MLL rearrangements and a poor prognosis. The role of MLL gene deregulation in rare cases of isolated lymphoblastic lymphoma in infants is obscure. We report the case of a 10 month old child who presented with a cutaneous nodule on the left foot. Histological diagnosis was precursor B-lymphoblastic lymphoma, with expression of CD10, PAX5, CD79a and nuclear TdT and the presence of a clonal IgH rearrangement. Despite the cytogenomically absent bone marrow lymphoblasts, the young age of the patient motivated us to investigate the presence of an MLL rearrangement.

Methods: Cytogenetic and molecular genetic analyses were performed. The data processing was based on the examined lymph node region or organs. In peripheral lymph node regions both methods evaluate occasionally reactive lymph nodes as lymphoma infiltrates. MRI DWIBS is comparable to PET-CT. Both values depend on the examined lymph node region or organs. In peripheral lymph node regions both methods evaluate occasionally reactive lymph nodes as lymphoma infiltrates. MRI DWIBS is less sensitive to brown fat tissue and bowel wall inflammation. It works without radiation, so it could provide a close follow up even for children.

**PC009**

**EVALUATION OF PET/CT AND CECT FOR STAGING, INTERIM AND POST-TREATMENT RESPONSE ASSESSMENT IN PEDIATRIC HODGKIN LYMPHOMA: A PROSPECTIVE STUDY**

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Purpose: Data whether PET/CT is better than conventional CT in pediatric Hodgkin lymphoma (HL) is lacking. Presently we prospectively evaluated PET/CT and conventional CT for staging, interim and post-treatment response assessment in pediatric HL.

Methods: Consecutive HL patients <18 years were enrolled between January 2008 and December 2010 at our cancer centre. Patients received 4–6 cycles of ABVD chemotherapy with/without involved-field radiotherapy. Patients underwent whole body PET/CT and contrast-enhanced CT (CECT) of neck, chest, abdomen and pelvis for staging, after 2 chemotherapy cycles for interim and after completion of either 4 or 6 cycles for post-treatment assessment.

Results: 57 patients were enrolled with male:female ratio of 42:15 and median age 10 years. Fifty-five of 57 patients are alive at median follow-up of 35.93 months. 2/57 patients had disease progression, 2 died, one due to disease progression and other due to bleomycin toxicity. PET/CT in comparison to CECT upstaged 23/57 patients and down-staged 4/57 patients (P = 0.004). Change in staging based on PET/CT would have required more intense treatment in 6/57 patients and less intense treatment in 1/57 patients. There was significant discordance between interim PET/CT and CECT assessment (P = 0.0192). No discordance was seen between post-treatment PET/CT and CECT assessment (P = 0.424).

Conclusion: PET/CT in comparison to CECT significantly upstages patient and leads to change in treatment. PET/CT was more specific than CECT for interim and post-treatment assessment; however, PET/CT had lesser sensitivity, PPV and NPV compared to CECT for interim and post treatment assessment.

**PC010**

**EVALUATION OF MRI DWIBS AND FDG PET-CT IN FOLLOW UP OF PEDIATRIC LYMPHOMAS**

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Purpose: In treatment follow up of childhood lymphomas FDG PET-CT is widely used as the most suitable method to assess the tumor viability. MRI DWIBS diffusion-weighted whole body imaging with background body-signal suppression is a new method without radiation. Based on the literature it could also reliably determine the viability, but its sensitivity and specificity is yet unknown. The aim of this study is the comparison of the two methods, and determination of the role of DWIBS in childhood lymphomas.

Methods: In our study we investigated 16 children with Hodgkin (HD) and 12 with non-Hodgkin (NHL) lymphomas. 55 pairs of comparative PET-CT and MRI DWIBS examinations were performed. The average age of the patients at the diagnosis was 12.86 years. Average time between MRI and PET-CT was 4.10–19.1 days. The imaging results were compared with clinical data and/or biopsy results. The data processing was based on medical records and on the reports of imaging procedures. In case of uncertain results MRI and PET-CT images reevaluated.

Conclusion: Sensitivity and specificity of MRI DWIBS is comparable to PET-CT. Both values depend on the examined lymph node region or organs. In peripheral lymph node regions both methods evaluate occasionally reactive lymph nodes as lymphoma infiltrates. MRI DWIBS is less sensitive to brown fat tissue and bowel wall inflammation. It works without radiation, so it could provide a close follow up even for children.
Conclusion: Based on our results MRI DWIBS could play an important role in follow up of lymphoma patients. The real prognostic value of this method must be evaluated in the future.

PC011

PTLD IN CHILDREN: A SINGLE CENTRE EXPERIENCE

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Purpose: To obtain detailed information concerning post-transplant lymphoproliferative disorder (PTLD) in paediatric patients.

Methods: Patients < 18 years with PTLD after organ or stem cell transplantation (HSCT) between 1989 to 2010 were identified. Patient, transplantation and disease characteristics and outcome were collected.

Results: We identified 22 patients (17 males, 5 females) 2 HSCT (9%), 2 heart (18%), 6 liver (27%), 2 lung (9%) and 8 kidney (36%) transplantations. Mean age at transplantation was 8.87 years and mean age at PTLD was 14.62 years. Mean time between transplantation and PTLD was 5.75 years. According to the Ann Arbor classification 16 patients had advanced stage: stage IV (n = 6), stage III (n = 3), stage II (n = 1) and stage I (n = 6). Among NBS patients 10 patients had early lesions, 1 patient polymorphic lesions. Eleven patients suffered from a monomorphic DLBCL and 7 from a Hodgkin/non DLBCL type. In 5 patients EBV in situ was absent and 7 patients were CD 20 negative. In all patients reduction of immunosuppression (Ris) was the first therapeutic intervention: Ris alone (n = 1), Ris with other, except rituximab or chemotherapy (n = 2), Ris and rituximab (n = 10), Ris and chemotherapy (n = 3), or Ris and chemotherapy and rituximab (n = 6). Complete remission was achieved in 14 children, partial remission in 3 and progressive disease in 5. Eighteen children are alive, 3 died because of PTLD and one died of another cause.

Conclusion: PTLD in children is more common in solid organ transplantation than in HSCT. The majority of the children had advanced stage disease. Further analysis of different risk factors is necessary to encounter this severe late effects of transplant patients.

PC012

DIFFERENCES IN CLINICAL COURSE BETWEEN NON-HODGKIN LYMPHOMA (NHL) IN IMMUNOCOMPETENT AND IMMUNOCOMPROMIZED PATIENTS WITH NIJMEGEN BREAKAGE SYNDROME (NBS)

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Purpose: To compare clinical features, diagnostic, treatment process and outcome between NHL in immunocompromized NBS and immunocompetent patients treated in the Department of Oncology Department CMHII between 1997 and 2008 years.

Methods: 124 patients: 19 with NBS and 105 immunocompetent (reference group, RG); were analyzed for: age, sex, time from first symptoms to NHL diagnosis, localization, type of lymphoma, stage and course of treatment, its complications and outcome. Comparison among the 2 groups was performed.

Results: Median age was 10.2 yrs in both groups, in NBS group girls afflicted were more often (60 vs 40% in RG) and time laps to diagnosis was longer (median 13 vs 5 weeks, p = 0.0127). Dominant localization was mediastinum in NBS (30% vs 8%, p = 0.0268) and in RG (54 vs 20%, p = 0.04181). In NBS patients two types of lymphomas dominated: TLB (42%) and DLBCL (37%) vs 19 and 12% in RG. The course of TLB did not differ among patients with NBS and RG, the course of DLBCL was different. NBS patients were younger (median age 11.5 vs 14.2 yrs in RG), and had a more advanced disease (stage III and IV in 57% and 14% of NBS patients, vs. 50% and 0% in RG). Time to miliosupression was shorter and complications after chemotherapy were remarkably more frequent in NBS patients (p = 0.0059 and p = 0.0373). Among NBS patients 5-year OS was 75%, while in RG 82% (p = 0.00036). Median survival time was 3.8 years in the NBS group and 10.3 years in RG.

Conclusion: The clinical features, course and results of NHLs treatment were significantly different in NBS patients than in immunocompetent children.

PC013

OSTEONECROSIS IN ADOLESCENTS TREATED FOR HODGKIN LYMPHOMA, A TERTIARY UNIT EXPERIENCE

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Purpose: Osteonecrosis (ON) of bone may result in serious long-term morbidity. We reviewed the incidence, natural history and risk factors for development of ON in adolescents treated for Hodgkin Lymphoma (HL).

Methods: A retrospective radiological review was performed in adolescents aged 12–19 years with classical (chL) or nodular lymphocyte predominant HL (NLPHL) who were treated in accordance with the EuroNet HL trials between April 2005–Nov 2011. MRI or CT scans were performed at following time points: diagnosis, early response assessment (ERA) at 2 months, end of treatment and at 3 and 12 months after treatment.

Results: Of 101 patients reviewed, 86 had chL while 15 had NLPHL. 23/101 patients (22 chL and 1 NLPHL) developed radiological features of ON. In 13/23, ON was first detected at the ERA scan, while it was first detected in 6 at the end of treatment and in 4 on routine surveillance scans post treatment. The iliac bones were the most common site of ON (n = 14) followed by proximal femur (n = 9) and proximal humerus (n = 8). Only 5/23 had significant symptoms or functional impairment while 18/23 are asymptomatic to date. ON either resolved or was resolved in 6/23 at the 12 month post treatment. The cumulative rate of preosseus ranged between 1.8 g/m²(low risk) to 4.2 g/m²(high risk). ON was more common in females (27.7 vs 17%). No other risk factor was significant.

Conclusion: ON was detected in 23% of patients however the majority of these were asymptomatic. Imaging detected ON in a significant proportion of adolescents with HL. Further studies are needed to understand the natural history of ON and whether early medical intervention may prevent significant joint damage.

References

PC014

GENETIC ABERRATIONS IN PEDIATRIC FOLLICULAR LYMPHOMA

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Purpose: Pediatric follicular lymphoma (FL) is a rare disease that differs from its adult counterpart both genetically and clinically. Excluding pediatric FL with IRF4-translocation, the genetic events associated with pediatric FL have not yet been defined.

Methods: We applied array-comparative genomic hybridization and molecular inversion probe assay adapted to formalin-fixed paraffin-embedded tissues from 18 patients aged ≤18 years diagnosed with FL. All lacked t(14;18).

Results: Only six pediatric cases displayed chromosomal imbalances, with gain/ amplification of 6pter-p24.3 (including IRF4) and deletion/copy-neutral loss of heterozygosity in 1p16 (including TCF15) being the most frequent alterations.

Conclusion: Combination of molecular and genetic features differentiated two subsets of pediatric FL, one with genomic aberrations associated with higher FL grade and/or DLBCL component and more widespread disease, and another one lacking genetic alterations and associated with more limited stage disease.

PC015

DIAGNOSTIC PROSPECTS AND ISOFORM-DEPENDENT FUNCTIONS OF BURKITT LYMPHOMA SPECIFIC PROTEIN ZNF385B

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Purpose: Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL) are common types of childhood mature B-cell non-Hodgkin lymphoma (NHL). Both are postulated to be derived from Germinal Center (GC) B-cells but they are independent disease entities of NHL. It is not uncommon to have difficulty in differentiating BL from DLBCL. ZNF385B is a zinc
finger protein that we previously identified as a molecule specifically expressed in BL using gene expression analyses. The biological significance of this protein has not been clarified at all. Therefore, we intend to elucidate diagnostic prospects and isoform-dependent functions of ZNF385B in B cells.

**Methods:** The expression of ZNF385B in clinical specimens of BL and DLBCL and normal tissue was analyzed using immunohistochemistry and real-time PCR. We established a protein inducible system in a tetracycline-dependent manner for both ZNF385B IF-1 and its deletion mutant IF-1/DEL corresponds to IF-2/3 in BJB cells.

**Results:** ZNF385B was expressed in BL and normal lymphoid tissue but not in DLBCL. Interestingly, although BL cell lines expressed the longest transcript variant isoform (IF-1) predominantly, normal lymphoid tissue expressed shorter transcript variant IF-2/3 mainly. Ectopic expression of ZNF385B IF-1 induced up-regulation of PERP (p53 apoptosis effector related to PMP-22) and activation of caspase-3 and -8, resulting in apoptosis induction, whereas IF-1/DEL did not. Furthermore, IF-1/DEL inhibited apoptosis induced by CD20 and B-cell receptor stimulation and yeast cells expressing the direct binding of ZNF385B with p53. Since PERP is known to be a p53 transcriptional target, these results suggest the involvement of ZNF385B in B-cell apoptosis by modulating p53 transactivation.

**Conclusion:** Prospects for ZNF385B in diagnosis were shown. ZNF385B had both pro-apoptotic and anti-apoptotic activities depending on the type of isoform and possibly is involved in the regulation of death and survival that specifically occurs in GC B cells.

**PC016**

**LANGERHANS CELL HISTIOCYTOSIS (LCH): THE EXPERIENCE OF THE ISTITUTO NAZIONALE DEI TUMORI OF MILAN, ITALY**

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**Purpose:** LCH is a non-malignant disease characterized by proliferation and accumulation of clonal dendritic cells bearing an immunophenotype very close to that of the normal epidermal Langerhans cells of the skin and the mucous membranes. This study presents the retrospective long-term treatment results of a single-institutional series.

**Methods:** From 1975 to 2007, 129 patients (M 80, F 49) < 18 years (age 5 months – 17 years, median 63 months) affected by LCH were admitted at our unit. The treatment was defined according to disease extent and involvement of “risk” organs, based on the Ranney-D’Angio staging. Surgery was the only treatment for localized disease. Chemotherapy was reserved for extended unifocal LCH or special sites (intracranial and spinal lesions) and for multifocal and disseminated disease: Vincristine and Cyclophosphamide plus Prednisone for 6/12 months was the first line regimen, Adriamycin plus Vinblastine and 6-Mercaptopurine plus Methotrexate were the second-line regimens.

**Results:** With a median follow-up of 125 months (6–404 months), 10-year EFS and OS were 66.5% and 98.4%, respectively. At the univariate analysis, disease staging strongly influenced EFS. When patients were retrospectively re-classified according to the International Third LCH Study staging system, 10-year EFS, that was 18% and 30% in multi-system high-risk and low-risk patients, and 67% and 80% in single-system multiple and single site patients, respectively (p < 0.0001). Conversely, OS was not influenced by tumor stage (p > 0.90% for multi-system and single-system patients), suggesting the possibility to achieve further continuous remission with second-line therapy. Age < 24 months was not prognostic.

**Conclusion:** Our series confirmed that multi-systemic presentation with high-risk organ involvement had a clinical behavior and a different intrinsic aggressiveness than other forms, being a significant adverse prognostic variable for EFS.Systemic therapy are effective in countering balanced disease aggressiveness as concern OS.

**PC017**

**HEMOPHAGOCYTIC L YMPHOHISTIOCYTOSIS (HLH) IN INFANTS: A SINGLE CENTRE EXPERIENCE**

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**Purpose:** Hemophagocytic lymphohistiocytosis (HLH) is a rare and fatal prototype of the hemophagocytic syndrome. HLH occurs as a consequence of uncontrolled, dysregulated cellular immune reactivity caused by a number of different underlying diseases.

**Methods:** We report nine infants with suspected HLH, confirmed using revised HLH 2004 guidelines, admitted at a single center from January 2010 to December 2011 and evaluated further. Confirmed cases were managed with dexamethasone, cyclosporine and etoposide (VP 16) based on HLH 2004 guidelines. Acute manifestations were managed symptomatically. DNA samples from the patients and their parents were sent to Sweden for further genetic analysis with parental consent. Progress was assessed using clinical examination along with laboratory parameters (complete blood counts, serum triglyceride, ferritin and triglyceride levels).

**Results:** There were 9 infants (7 Male and 2 female). Mean age of presentation was 7.1 months (range 1–11). Family history of sibling dying with similar illness was present in one. Three had history of consanguinity. Mean ferritin levels were 7485 ng/ml. Three had deranged liver function. None had CNS involvement. Mutation analysis were possible in eight. One had Griscelli syndrome type 2. (Rab27). One had FHLH type 2 (mutation in perforin gene), two had FHLH type 3 (Munc gene), three had non-FHLH 2/3, one report is awaited. Four patients had associated cytomegalovirus infection as triggering factor. All were treated as per HLH 2004 protocol. One is under treatment, 6 patient died after initial response to treatment. One underwent matched sibling donor allogenic stem cell transplant, and disease free after 10 months of follow up. One underwent unrelated cord transplant who died after 4 months due to Foscarnet induced renal failure.

**Conclusion:** Early suspicion is necessary to diagnose familial HLH in infants. Mutation analysis is must for offering stem cell transplant early.

**PC018**

**CHILDHOOD HISTIOCYTOSIS IN SOUTH AFRICAN PAEDIATRIC ONCOLOGY UNITS**

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**Purpose:** Langerhans cell histiocytosis (LCH; Histiocytosis X) is a rare disease, with variable presentation, which can develop in persons of any age. To date very little has been published regarding children with LCH in Sub-Saharan Africa.

**Methods:** Data were extracted from the South African Cancer Study Group (SACCSG) Tumour Registry of biopsy-proven LCH (1983–2008). The data were analyzed for sex, age at diagnosis, race and system affected. Currently final outcome is investigated and will be presented.

**Results:** Only 0.7% of the patients or 111 children, registered in the SACCSG Tumour registry, had a diagnosis of LCH. More than half the patients were younger than 2 years of age (61%), with a range of 0 to 160 months and median age of 2 years. There was a slight male dominance with a male to female ratio of 1:1.2:1. Race representation was as follows: 38% mixed race (Coloured); 37% black; 34% white and 1% Indian. The majority had unifocal disease (42%), followed by multifocal disease (20%) and multisystem disease (21%), while it was not documented in 17%. Bone was the most common system affected (28%); followed by systemic disease (21%); lymph node involvement (20%); skin (17%) and unknown primary site (17%). Chemotherapy consisted of standard treatment protocols including Vinblastine, Steroids and Etoposide.

**Conclusion:** This is the first documented analysis of LCH in children in Sub-Saharan Africa and outcome will be discussed. Survival is dependent on the extent of disease with disseminated disease associated with a poor outcome.

**PC019**

**TREATMENT OF RELAPSED/REFRACTORY LANGERHANS CELL HISTIOCYTOSIS: A SINGLE CENTRE EXPERIENCE FROM DEVELOPING WORLD**

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**Purpose:** The course of Langerhans cell histiocytosis (LCH) is unpredictable, varying from spontaneous regression and resolution to rapid progression and death or repeated recurrence and recrudescence with the risk of permanent consequences. Children with multisystem LCH and risk organ involvement (i.e., hematopoietic system, liver, spleen, lungs) who fail to respond to conventional chemotherapy or relapse have an extremely poor prognosis. We describe here our experience of treatment of relapsed or refractory LCH.

**Methods:** It was a retrospective analysis of seven children who had refractory or relapsed disease. One patient died prior to treatment. One underwent matched sibling donor allogenic stem cell transplant, and disease free after 10 months of follow up. One underwent unrelated cord transplant who died after 4 months due to Foscarnet induced renal failure.

**Results:** Three patients were previously treated on LCH II protocol, three on LCH III and one received CHOP regime previously. All patients had risk organ involvement initially. Five patients had refractory disease and two had relapse following initial chemotherapy. Cldarbrin was administered at a dose of 9 mg/m2/day over two hours IV daily for three days and repeated every 3 weeks. Two patients also received Ara-C at a dose of 500 mg/m2/day for 2 days.

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5 days and repeated every three weeks for 3 courses. After a median of 5 courses of cladribine (range 2–8) with or without Ara-C, one achieved complete response, five patients achieved partial response. In maintenance therapy, 12 courses of vincristine, prednisolone were given every two weeks for 6 months along with daily 6-MP and weekly methotrexate for 14 years. One patient underwent liver transplantation following sclerosing cholangitis with cirrhosis of liver. Two patients experienced grade 3 hematological toxicity and one had E. coli sepsis. At a median follow-up of 39 months (range 5–68 months), six are alive and one patient died of refractory disease after 2 courses of cladribine.

Conclusion: It is feasible to treat refractory and relapsed LCH in the developing world.

**PC020**

**INFECTION TREATMENTS AT DIAGNOSIS IN 54 SPANISH CHILDREN WITH LYMPHOHISTIOCYTIC TUMOR HEMOFAGOCYTIC (HLH)**

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**Purpose:** Infectious agents are triggers in primary immunodeficiencies. They are often detected in both genetic and acquired HLH. Clinical presentation is identical, so specific HLH diagnostic tests must be performed in order to identify primary cases which need transplantation (HSCT) for cure. The aim is to analyze the infectious agents detected at diagnosis in HLH children.

**Methods:** Revision of infectious agents detected in Spanish HLH cases for 7 years (2004–2011). Analysis of clinical, laboratory, microbiological and cytological data at diagnosis in 54 paediatric patients.


**Conclusion:** Due to the lack of specificity of clinical presentation and biomarkers in HLH, results cannot be compared with other studies. Infectious trigger is detected in nearly half of the patients. Infections were identified in 29/54 patients, so HLH specific genetic and immunological studies should be performed in specialized laboratories.

**PD001**

**SHOULD ADOLESCENTS WITH Ewing Sarcoma BE TREATED IN PAEDIATRIC OR NON-PAEDIATRIC ONCOLOGY INSTITUTIONS? AN ANALYSIS OF GPOH Ewing Trial (CESS-EICESS/EURO-E.W.L.N.G.) DATA**

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**Purpose:** 25% of Ewing sarcoma (ES) patients are 15–20 years of age; their outcome is worse than in children. The impact of the type (paediatric versus non-paediatic) and experience (patients per year) of the treating institution on outcome is unclear.

**Methods:** 725 patients aged 15–20 years, homogeneously treated on consecutive GPOH ES trials (CESS-81, CESS-86, EICESS-92, EURO-EWING99), were analysed regarding event-free survival (EFS) in relation to type and experience of institution (“small”: < 1 patient/year), 498 patients (68.7%) presented with localized disease (R1), 93 patients (12.8%) had pulmonary metastases (R2pulm), 134 patients (18.5%) had extra-pulmonary metastases (R3).

**Results:** Median follow-up was 3.85 years (range 0.20–28.63).

**Conclusion:** In the early trials (EURO-EWING81-86, 92), patients aged 15–20 years fared better when treated in paediatric (3y-EFS 0.54), SE = 0.03) than in other institutions (3y-EFS 0.43, SE = 0.05, p = 0.10; n = 384). In the EURO-EWING99 trial, no effect of the type of institution (3y-EFS 0.57 vs. 0.61; p = 0.536; n = 341) was found. In the early trials, outcome was worse in small institutions, but this effect disappeared in the recent EURO-EWING99 trial. Small institutions demonstrated improvements in patient outcome in EURO-EWING99 compared to previous trials (3y-EFS 0.63 versus 0.46; p = 0.003), whereas larger institutions did not (3y-EFS 0.56 versus 0.52; p = 0.607). In multivariate analyses, the interactions observed in the univariate analyses between period of treatment and experience of institution (treatment x institution) remained significant even when corrected for known confounders (p = 0.05).

**PD002**

**LONG TERM OUTCOME OF CONVENTIONAL HIGH GRADE OSTEOSARCOMA IN CHINESE CHILDREN AND ADOLESCENTS**

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**Purpose:** Objective of this report was to assess the long-term outcome in Chinese children and adolescents with conventional high grade osteosarcoma.

**Methods:** Patients with osteosarcoma treated in our centre between Jan 1994 and Dec 2008 were included. They received neo-adjuvant chemotherapy with cisplatin, Adriamycin and methotrexate, tumour resection at week 10, and post-operative chemotherapy, total of 27 weeks for good responders with >90% tumour necrosis, or of 40 weeks with methotrexate replaced by ifosfamide and etoposide for poor responders.

**Results:** Sixty-four patients (38 males, 26 females; median age 12.6, range 3–20, years) were treated. Fourteen (22%) patients had metastases (pulmonary, n = 12; bone and pulmonary, n = 2) at presentation. Tumour resection could be performed in 61 (94%) patients. Twenty (31%) patients developed relapses 0.48–12.74 (median 2.0) years from diagnosis. Sites of relapses included lungs (n = 14), distant bone (n = 4), intracardiac (n = 1) and local (n = 1). Twelve relapsed patients had further definitive surgery and chemotherapy, 8 of them were alive without disease 0.3–15 (median 7.0) years after relapses. All patients with relapses not amenable to surgery died. At the median follow-up of 7 years,
19 patients died with disease progression or after relapses and 1 from early post-operative complication. The 5-year OS and EFS for patients with localized diseases were 83.9% and 69.5%, while that for patients with metastatic diseases were both 28.6%. Late complications included therapy-related acute myeloid leukemia (n = 1), renal function impairment (n = 6) and high tone hearing loss (n = 4) were observed. Two patients developed second malignancies (glioblastoma multiforme, papillary carcinoma of thyroid). Two patients gave birth to babies 5 and 10 years after initial diagnosis.

**Conclusion:** Our treatment protocol yields favourable results that are comparable with international groups. Prolonged survival and cure is possible for surgically amendable relapses. However, new strategy need to be explored for patients with metastatic diseases.

**PD003**

**SUCCESSFUL TREATMENT FOR OSTEOSARCOMA PATIENTS UNDER 25 YEARS OF AGE**

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**Purpose:** To evaluate the efficacy of intensified preoperative chemotherapy for osteosarcoma patients under age 25.

**Methods:** Between 1984 and 2008, 39 osteosarcoma patients younger than 25 years of age (IBB, 31; II.B, 8) were treated at the Kyoto Prefectural University of Medicine. Between 1984 and 2005, 24 were treated with the KP-OS84 protocol including a preoperative phase with cisplatin and doxorubicin. Since 1996, 15 cases were treated with a new chemotherapy regimen (KP-OS96) containing a preoperative phase with cisplatin, doxorubicin, methotrexate, and ifosfamide.

**Results:** The rates of IIIB patients were 20.8% and 20% respectively, in the KP-OS84 and KP-OS96 protocols. The rate of a good histological response (tumor necrosis < 90%) was 25% in the KP-OS84 and 47% in the KP-OS96 patients (P = 0.01). The 5-year event-free survival rate of patients treated under the KP-OS96 protocol was better than that in the KP-OS84 protocol (86.7% and 45.8%, respectively, P = 0.02). The 5-year overall survival rates were 93.3% in the KP-OS96 and 54.2% in the KP-OS84 patients (P = 0.02). Limb salvage surgery was possible in 20 patients (83.3%) and 15 patients (100%) in the KP-OS84 and KP-OS96 protocol patients, respectively. Therapy-related complications occurred in 4 patients (26.7%) in the KP-OS96 protocol.

**Conclusion:** The use of intensified preoperative chemotherapy added to high dose methotrexate and ifosfamide is effective for young osteosarcoma patients. This makes it possible to reduce the postoperative chemotherapy for histologically good responders in the next step of treatment.

**PD004**

**CLINICAL RESULTS AND PROGNOSTIC FACTORS OF PRIMARY OSTEOSARCOMA OF EXTREMITIES WITH PULMONARY METASTASIS: CCHE EXPERIENCE**

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**Purpose:** To identify the potential prognostic factors in patients presenting with osteosarcoma of extremities with clinically detectable pulmonary metastases at initial presentation, to study their survival, and to evaluate the results of the treatment protocol.

**Methods:** 113 patients with newly diagnosed high-grade osteosarcomas of bone were registered in our hospital between July 2007 and December 2010. Thirty three patients (29.2%) had proven pulmonary metastases at diagnosis and were enrolled onto an analysis of demographic-, different prognostic variables, response, and survival. The treatment strategy included primary chemotherapy, resection of primary tumor and when possible, of all metastatic disease.

**Results:** With a median follow-up of 20 months (12–54 months), fifteen patients were alive, seven of whom were in continuously complete remission. The 2-year event-free survival (EFS) and overall survival (OS) were 36.1% and 54.6%, respectively. These results are significantly poorer than those achieved in 57 patients with non-metastatic disease at presentation, treated at our hospital with the same chemotherapy protocol (2-year EFS and OS of 70.5% and 89%, respectively). Prognostic factors that were associated significantly with a shorter survival were the presence of pulmonary nodules (RHR = 0.001), bilateral lung metastases (P = 0.015), high serum level of alkaline phosphatase (P = 0.026) and incomplete surgical resection of all tumor sites (P = 0.001). After multivariate Cox regression analysis, incomplete surgical resection (RHR = 7.75), > 5 pulmonary nodules (RHR = 6.89) and high serum level of alkaline phosphatase (RHR = 3.94) remained significantly associated with inferior outcomes.

**Conclusion:** The results of our study confirm the poor prognosis of patients with osteosarcoma of the extremity with pulmonary metastases at presentation despite the use of aggressive treatment. The number of metastases at diagnosis, serum level of alkaline phosphatase and completeness of surgical resection of all clinically detected tumor sites are independent prognostic factors. To improve the prognosis for this group of patients new therapeutic approaches are needed.

**PD005**

**IMPACT OF PULMONARY NODULES IDENTIFIED BY CT SCAN ON TREATMENT AND OUTCOME OF CHILDREN WITH SOLID TUMORS**

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**Purpose:** The etiology and significance of pulmonary nodules seen on computed tomography (CT) at the time of diagnosis of a solid tumor during childhood can be unclear. Guidelines that define which nodules should be biopsied have not been established. We describe the experience at Children’s Memorial Hospital that did not include biopsy of pulmonary nodules identified at the time of diagnosis in children with sarcomas or renal tumors.

**Methods:** Retrospective chart review was performed on 51 pediatric patients with pulmonary nodules at the time of diagnosis with sarcomas or kidney tumors from 2000 to 2008. Chest CT scan findings were examined in conjunction with treatment and outcome.

**Results:** No patient underwent biopsy or resection of nodules at the time of diagnosis. Of those classified as localized disease (n = 22), 5 (23%) had bilateral nodules, 3 (14%) had nodules > 5 mm and 9 (41%) had 2 or more nodules. In 3 patients, the size of nodules grew on follow-up CT imaging. Two patients died with progressive disease: one (9%) in the lungs alone, and 3 (14%) in the lungs and primary site. Of those classified as metastatic disease (n = 29), 21 (72%) were treated with pulmonary radiation, pulmonary metastatectomy, or increased intensity of chemotherapy. 5 (17%) patients progressed on pulmonary directed therapy and expired. 80% of patients with metastatic disease had bilateral nodules. 97% had nodules > 5 mm in size and 90% had multiple nodules. With a median follow-up of 30.5 months. 14 (48%) patients with metastatic disease died of disease with 7 (24%) experiencing pulmonary progression. Nodule size > 5 mm was the only feature correlated with classification as metastatic disease.

**Conclusion:** Classification of patients for treatment purposes based on imaging findings alone provides outcomes comparable to those expected.

**PD006**

**PHARMACOKINETICS (PK) AND PHARMACODYNAMICS (PD) OF LIPOSOMAL METHOTREXATE (L-MTP-PE): ADULT VOLUNTEERS WITH MILD AND MODERATE RENAL IMPAIRMENT (RI)**

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**Purpose:** L-MTP-PE (MEPACT®) is approved in Europe and Mexico for treatment of high-grade resectable non-metastatic osteosarcoma in combination with postoperative multi-agent chemotherapy in children, adolescents and young adults. This study evaluated the PK and PD of L-MTP-PE in adult subjects with mild and moderate RI versus subjects with normal renal function (C20001; EndruCT 2009-017204-89).

**Methods:** Adults with mild RI (creatinine clearance [CLCr] 50–80 mL/min) or moderate RI (CLCr 30–50 mL/min), and age-, weight- and sex-matched healthy adults with normal renal function were included. A single dose of 250 mg of L-MTP-PE via 1-h intravenous infusion was administered. Blood specimens were collected over 72 h for plasma PK (total and non-liposome associated [free] MTP-PE) and serum PD (interleukin-6 [IL-6], tumor necrosis factor-alpha [TNF-a], C-reactive protein).

**Results:** 35 subjects (median age 62 years) were included: 9 with mild RI, 8 with moderate RI and 18 with normal renal function. Geometric mean (%CV) total MTP-PE AUC(0-t) , mild RI, moderate RI, and normal renal function were 89.5 (51.8), 85.1 (29.0) and 95.1 (22.7) nM x h, respectively. MTP-PE clearance was not correlated with Cockcroft-Gault CLCr, estimated glomerular filtration rate (Modification of Diet in Renal Disease method), or serum creatinine (all r < 0.01). Free MTP-PE AUC(0-t) was also similar across renal function groups. Median (range) areas under the baseline-adjusted concentration-time curves of IL-6 were 335 (280), 368 (270), and 508 (240) ng/mL in mild RI, moderate RI and normal renal function, respectively.

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renal function, respectively, and for TNE=-3, 5820 (663–11,200), 14,600 (2480–28,200) and 6320 (2530–14,100) h x g/mL, respectively.

Conclusion: Neither mild nor moderate RI had an effect on the PK or PD of L-MTP-PE; therefore, dose modifications of L-MTP-PE are not required.

PD007

PHARMACOKINETICS OF METHOTREXATE IN PEDIATRIC OSTEOSARCOMA

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Purpose: As the cure rates for osteosarcoma increase, it has become essential to find the optimal balance between the efficiency and the toxicity of the treatment. Previous studies have reported that delayed methotrexate elimination was associated with higher frequency of methotrexate toxicity. Higher methotrexate serum levels were associated with better survival. Our objective was to analyze the relationship between methotrexate pharmacokinetics, toxicity and survival in pediatric osteosarcoma.

Methods: Pharmacokinetic data of 105 patients with osteosarcoma treated with 98 HD-MTX courses were evaluated. Pharmacokinetic parameters (clearance, half-life and AUC) were calculated based on methotrexate serum levels measured at 6, 24, 36, 48 hours after the initiation of the infusion. Methotrexate dose intensity was calculated. Clinical data were collected by retrospective chart review. Hepato-, nphro- and myelotoxicity parameters were categorized according to Common Toxicity Criteria v3.0 (CTCAE). Event-free and overall survival were estimated according to the Kaplan–Meier method.

Results: Incidence of serious hepato-toxicity had significant correlation with higher AUC (p < 0.0001), peak concentration (p < 0.001), 24 hour (p = 0.001) and 48 hour (p = 0.008) serum levels and lower clearance (p = 0.0002). There was no association between the incidence of toxicity and age, gender, presence of metastases and histologic response. Higher 48 hour methotrexate levels were associated with better event-free and overall survival. Higher dose intensity correlated with better event-free survival. There was no association between toxicity and treatment outcome.

Conclusion: Correlation exists between MTX exposure and the incidence of toxicity. Higher serum concentrations at 48 hours were associated with a better 5-year OS and DFS. These results suggest that higher MTX exposure may lead to serious side effects, but it also improves treatment outcome.

PD008

PHARMACOKINETIC, PHARMACOGENETIC AND PHARMACODYNAMIC STUDY OF HIGH DOSE METHOTREXATE IN PEDIATRIC OSTEOSARCOMA PATIENTS AT A SINGLE INSTITUTION IN ARGENTINA

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Purpose: In Argentina, 20 new osteosarcoma cases are reported every year. Chemotherapy treatment includes cisplatin/doxorubicin and high-dose methotrexate (HDMTX). MTX plasma monitoring is used to reduce the incidence of severe toxicity. We aimed to characterize HDMTX pharmacokinetics/pharmacogenetics (PK/PG) and to evaluate possible associations with safety and efficacy in osteosarcoma patients.

Methods: Between June 2009 to February 2012, 11 patients with osteosarcoma (5 lung metastasis) were enrolled in the present study and received 12 courses of HDMTX (12 g/m²/C2) and C0.

Results: A total of 59 HD-MTX cycles were analyzed. The median age and dose (range) was 15.1 years (4.1–16) and 17.2 g (8.4–22.2), respectively. The median (range) C4 and AUC was 1100 (714–1375) µM and 6529 (5999–11470) µM h, respectively. The estimated population pharmacokinetic parameters included (mean; SE): Vd (14.4 L/m²; 0.7), Ke (0.248 h⁻¹; 0.002). The genotype frequencies were C677T, 70%CC, 20%CT and 10%TT; DHFR, 99%, TN.

Conclusion: This is the first PK/PG/PD study in pediatric osteosarcoma patients performed in Argentina. We emphasize the importance of PK/PG/PD characterization to optimize chemotherapy.

PD009

EFFICACY AND SAFETY OF GLUCARPIDASE FOR ROUTINE USE AFTER HIGH DOSE METHOTREXATE IN PATIENTS WITH OSTEOSARCOMA

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Purpose: High-dose methotrexate (HD-MTX) is an essential component of osteosarcoma treatment. Despite supportive measures MTX-related toxicity results in delays in subsequent chemotherapy administration and potentially reduced treatment efficacy. It is essential to explore alternative rescue regimens such as routine use of glucarpidase.

Methods: GLU 1, a phase II randomised cross-over clinical trial, was set up to examine the efficacy and safety of routine use of glucarpidase after HD-MTX. Patients were randomised to receive two HD-MTX courses with Fancon Anemia (FA) rescue (cycle FA) followed by two HD-MTX courses with FA and glucarpidase (cycle gluFA), or cycle gluFA first followed by cycle FA. The primary objective of the trial was to examine whether glucarpidase rescue after HD-MTX reduces delay to subsequent cycles of chemotherapy due to MTX toxicity. The data of 16 patients enrolled up to the interim analysis of the trial were analysed.

Results: MTX toxicity resulted in delays in 47% of glu/FA cycles and 75% of FA cycles. There was no difference in MTX peak plasma concentrations between the two rescue regimens. More importantly the use of glucarpidase was not associated with a statistically significant reduction of MTX AUC. Severe mucositis clinical (CTCAE v3.0, grade ≥3) complicated 23% and 7% of FA and glu/FA cycles, respectively. Mucositis-functional (CTCAE v3.0, grade ≥3) complicated 8% FA treatment cycles and none of glu/FA cycles. The incidence and severity of MTX-related nephrotoxicity was similar in both rescue regimens. No glucarpidase toxicity was observed.

Conclusion: Glucarpidase offers a promising opportunity for rescue from MTX toxicity. The GLU 1 clinical trial is ongoing.

PD010

LYMPHOPENIA AS A PROGNOSTIC FACTOR FOR OUTCOME IN OSTEOSARCOMA

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Purpose: Lymphopenia is frequent in advanced cancers and predicts chemotoxicity. However, its effect on prognosis and ability to comply with prescribed treatment is uncertain.

Methods: We retrospectively investigated the prognostic value of lymphopenia for histological-necrosis (HN) and compliance to neoadjuvant-chemotherapy (NACT) in a prospectively collected series of osteosarcoma patients during the year 2010. Compliance was defined as receipt of planned cycles of chemotherapy in the planned doses, within the planned duration or up to 25% additional time. Good responders (GR) included those with tumors showing >90% HN. Lymphopenia was defined as lymphocyte count < 1000 mm³.

Univariate analysis of prognostic factors for HN and compliance was performed using the Mann Whitney test.

Result: Of 124 patients, 115 were analyzed for post NACT histological response; 73 (65%) were compliant and 42 (35%) were noncompliant to NACT. In the compliant group 64% were GR while in noncompliant group 43% were GR. Baseline serum albumin, alkaline phosphatase, lactate dehydrogenase, ECOG-performance status, hemoglobin, metastasis, baseline total lactate count, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), day 11–15 or day 16–20 ANC and ALC after the first cycle of NACT were correlated with HN and compliance. On univariate analysis none of these variables were significantly associated with histological necrosis including baseline lymphopenia of < 1,000 mm³.

However on further exploratory analysis baseline ALC > 1,900 mm³ significantly correlated with good HN (p = 0.046) but not with number of chemotherapy cycles. On univariate analysis, the other variables were not significantly correlated with HN; hence multivariate analysis was not done. ALC recovery to >610 mm³ between day 11–15 and >990 mm³ between day 16–20 were significantly correlated with NACT-compliance (p = 0.016 and 0.012 respectively).

Conclusion: Present analysis suggests that baseline lymphopenia of < 1,900 mm³ may be associated with poor histological response to NACT and early lymphocyte recovery could predict better chemotherapy compliance. This could be due to immunological and cytokine related factors and need to be explored in further studies.

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ASSESSMENT OF KINETICS OF PERIPHERAL BLOOD T REGULATORY CELLS

PD011

THE VALUE OF DIFFUSION-WEIGHTED IMAGING IN EWING’S SARCOMA AND OSSEOUS SARCOMA IN CHILDREN AND YOUNG ADULTS: A RELIABLE PARAMETER FOR THERAPY ASSESSMENT? PRELIMINARY RESULTS:

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Purpose: To evaluate the use of diffusion-weighted imaging (DWI) in bone sarcomas as a parameter for chemotherapeutic response, in correlation to histopathological results.

Methods: Seven patients with osteosarcoma (OS) and 4 patients with Ewing’s sarcoma (ES) were examined prospectively. DWI and magnetic resonance (MR) images were performed before, during and after chemotherapy. Overlays of DW-images on anatomical T2-weighted images were used to delineate the entire bone tumour on all slices and histograms of the apparent diffusion coefficient (ADC) and b1000 values were acquired. In OS-patients, histopathological examination of resection specimen was performed to determine percentage of tumour necrosis. In ES-group, correlation of the imaging analysis with clinical follow-up was made.

Results: In OS-group, 6 patients showed a good response (> 90% tumour necrosis), 1 patient had a partial response of 60–70% of tumour necrosis. In ES-group, only 1 patient had a tumour relapse. In all patients a decrease of volume was found between the two time points. The partial responder in OS group failed to show a 41% decrease from baseline to the post-chemo time points, and remained relatively stable afterwards. However, OS patients showed a much slower SI decrease between consecutive time points. On ADC, similar findings could be demonstrated in the ES group. However, the ADC values of the OS group did not alter strongly between the different time points. The partial responder in OS group failed to show a decrease in b1000 SI, suggestive of low treatment response.

Conclusion: Overall, bone sarcoma therapy response assessment was feasible using combined b1000 and ADC assessments, although differences in evolution could be seen in both tumour types. B1000 assessment was useful for both types, whereas ADC calculation showed additional value in the ES group.

PD012

ASSESSMENT OF KINETICS OF PERIPHERAL BLOOD T REGULATORY REGULATORY CELLS (TREGS) IN PNET/EWING SARCOMA: A PROSPECTIVE STUDY

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Purpose: Bone marrow Tregs have been evaluated in PNET patients; data on peripheral blood circulating Tregs is lacking. The objective of our study was to determine baseline and inter-Treg frequency in PNET patients and correlate with patient characteristics and outcome.

Methods: Five ml blood was evaluated in de novo PNET patients at diagnosis and post neoadjuvant chemotherapy along with quality of rehabilitation, which is problematic in small children.

Results: Thirty-eight patients with median age 17 years: male/female ratio 5.5:1 had significantly higher baseline Tregs than healthy controls [9.17% ± 3.08 vs 3.16 ± 1.49%; p < 0.0001]. Eight patients (21%) had fever at baseline presentation; disease was extra-skeletal in one and metastatic in 11 (28.9%) patients. The median Treg frequency was 8.84% (Range: 2.49–16.31). When the Tregs were categorized as high and low based on the median cut-off value, patients with fever had a significantly higher Tregs than those without fever [11.3% ± 3.5% vs 8.66% ± 2.7%; p = 0.02]. Ten patients relapsed and eight died. The EFS was 67% and OS 72% of the entire cohort at a median follow up of 16 months. There was significant reduction in the circulating Tregs after neoadjuvant chemotherapy [9.07% ± 3.2 vs 3.2% ± 1.7; p < 0.001]. No significant association of peripheral blood Treg cells frequency was noted with other factors like age, sex, metastatic disease, relapse or death.

PD013

OSTEOSARCOMA – WHAT CHOICE DOES THE PATIENT HAVE IN A RESOURCE LIMITED SETTING?

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Purpose: To compare the outcome of two chemotherapy protocols; Cisplatin + Doxorubicin (CD) vs Cisplatin, Doxorubicin and methotrexate (PAM).

Methods: From 2004 till 2011, 81 children (42 males 39 females, ages 3 years to 17 years) with osteosarcoma attended our unit. The choice of chemotherapy for these children was based on their financial status as all patients have to pay for their treatment. Those with limited finances received CD and the others received PAM chemotherapy. 61 are eligible for further analysis; 30 opted for CDDP/Dox and 31 received PAM chemotherapy. Data were collected from their clinical records.

Results: 24/30 children in CD and 30/31 in PAM group underwent surgery; 15 and 10 in each group had amputation and 9 and 20 in each group had limb salvage surgery. Information on tumour necrosis was available in 18 and 26 in each group with >90% necrosis documented in 8 and 14 in the two groups. 21/30 in the CD group completed treatment, with a mean follow up of 18 months (1–59 months), 3 relapsed and died, 5 lost to follow up and 13 are alive and well. In the PAM group of the 25/31 completed treatment, 6 died of relapse, 1 of unknown cause, 18, including one with pulmonary metastasis, are alive and well on a mean follow up of 28 months (1–76 months).

Conclusion: Abandonment rate in the CD group was 26% compared to 6% in the PAM group. 2/3 had amputation of limb in the CD group compared to 1/3 in the PAM group. The overall survival in the CD group is 43% compared to 58% in the PAM group at the time of this analysis. In a resource limited setting chemotherapy using CD followed by amputation is an acceptable choice of treatment.

PD014

RECONSTRUCTION WITH GROWING ENDOPROSTHESIS AFTER RESECTION PRIMARY MALIGNANT BONE TUMORS IN CHILDREN IN YOUTH – CLINICAL EXPERIENCE

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Purpose: The therapy consists of combined procedure including chemotherapy, surgery and/or radiotherapy and is the standard treatment of primary malignant bone tumors in children and youth.

Methods: In the period 2000–2010 in our Clinic 117 patients have been operated, 68 boys and 50 girls, in age from 4 to 16 years, average 12 years. In histopathologic diagnosis were osteosarcoma in 89 pts., Ewing sarcoma in 25 pts., chondrosarcoma in 3 pts. and haemangioendotheliosarcoma in 1. In 112 pts. growing endoprostheses have been transplanted after primary tumor’s resection and in 6 pts. in the second stage. Were used 3 different endoprosthesis and 2 methods of lengthening endoprosthesis; – extension required surgical intervention – 37 Starmore endoprostheses; – electromagnetic endoprostheses elongated by non invasive method through exposition for external electromagnetic field – 4 Wright, 67 Implantcast.

Results: Complications after reelongation by invasive surgical method in 15/47pts. (31.9%), after elongation by non invasive method in 2/4 pts. (50%) and 18/67 pts. Implantcast (26.8%) but only 10/67 pts. problems with endoprostheses lengthening (14.9%).

Conclusion: The use growing endoprostheses enables limb lengthening following child’s growth, complications accompany both, none-invasive and invasive methods, the final results depends on quality of rehabilitation, which is problematic in small children.

PD015

DELAY IN PRESENTATION AND TREATMENT OF PATIENTS WITH CONFIRMED OSTEOSARCOMA TO A SINGLE SOUTH AFRICA INSTITUTION

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Purpose: There are many challenges that face treatment of children with osteosarcoma. Delay in diagnosis often results high mortality rates. The study is to evaluate the delay in presentation, referral, diagnosis and treatment of patients with confirmed osteosarcoma. With the view to establish strategies to improve access to care.

Methods: A retrospective analysis of all patients admitted in the Paediatric Oncology Ward in a tertiary level, referral hospital in Pretoria, South Africa from 1st of January 2001 unit 31st of December 2011. Information obtained included, primary site, histological subtype, Pediatric Blood Cancer DOI 10.1002/pbc
stage of the disease at presentation, time from first symptoms to definitive treatment, treatment offered and outcome.

Results: Thirty-eight patients were included in the study. The median age was 137 months (range 72–184). There were 22 male patients. Fifty percent of the patients (n = 19) had evidence of metastatic disease at presentation. The most common site of metastases was the lung. The time from first symptom to receiving definitive medical care was 6 months. Most patients were seen by at least one medical professional before referral to an oncology centre. Chondroblastic osteosarcoma represented 47% of the cases. More than 50% of the patients that qualified for amputation initially refused amputation as a result of cultural beliefs. Limb sparing surgery was only offered to one child. The survival was only 15% (n = 6). The main cause of death was progression of disease n = 30. The treatment related mortality was 5%.

Conclusion: Delay in referral to definitive specialised multidisciplinary oncology care remains a challenge. A better understanding of the cultural beliefs and active education programs in the community and health facilities have been improved. The aim is to simplifying the referral pathway. Patients with a delay in diagnosis will benefit as being regarded as having metastatic disease and high risk treatment strategies will be adopted for future patients.

PD016

HYPOXIA-INDUCED CYTOTOXIC DRUG RESISTANCE IN OSTEOSARCOMA IS INDEPENDENT OF HIF-1 ALPHA

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Purpose: Survival in metastatic osteosarcoma is poor, and new therapeutic approaches are urgently needed. Hypoxia in solid tumours is common and associated with poor outcome. Childhood cancer cell lines are resistant to chemotherapy under hypoxia and this is dependent on the transcription factor hypoxia inducible factor (HIF-1). We evaluated the effect of hypoxia on the response to clinically relevant cytotoxic agents in osteosarcoma cell lines.

Methods: The response of osteosarcoma cell lines 791T, HOS and U2OS to cisplatin, doxorubicin and etoposide was assessed under normoxia and hypoxia (1% O2) using the sulpherhodamine-B assay. Drug-induced apoptosis was assessed by morphological changes, annexin V/7-AAD positivity and cleavage of caspase-3 and PARP. HIF-1 activity was induced in normoxia using cobalt chloride and measured in hypoxia using shRNAi to HIF-1α, transient transfection of a dominant-negative HIF vector and the small molecule NCI-334754. Phosphatidylinositol 3-kinase (PI3K) was inhibited using PI-103.

Results: Hypoxia induced significant resistance to all 3 drugs in all 3 cell lines. Hypoxia significantly reduced drug induced-apoptosis. Doxorubicin entry and efflux, formation of a/c/Rag2/B10 animals. Next, animals were randomized as controls (no treatment), treated with cisplatin (2 mg/kg x 3 days/wk x 4 wk, i.p.), treated with Delta-24-RGD (3.8 x 107 pfu/wk x 3 wk, i.v.) or cisplatin + Delta-24-RGD. Animals were followed with X-ray and FDG-PET (day 45), sacrificed and the tumoral lesions were analyzed by H&E staining, necrosis evaluation and IHC. Our preliminary data indicate that the virus was able to replicate in vivo resulting in a robust oncolytic activity in the tumoral lesions, which are significantly reduced and necrosed compared to those from untreated or cisplatin alone.

Conclusion: Treatment with the adenovirus Delta-24-RGD resulted in a potent antimuscular effect through autophagic cell death in vivo and in vitro in our osteosarcoma model. Our preliminary data suggest that exploiting autophagic cell death could provide new approaches to antiasarcoma therapies.

PD017

THE ONCOLYTIC ADENOVIRUS DELTA-24-RGD INDUCES A POTENT ANTITUMOR EFFECT IN VITRO AND IN VIVO IN PEDIATRIC OSTEOSARCOMA

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Purpose: This study was designed to ascertain whether the combination of the oncolytic adenovirus Delta24-RGD with cisplatin would result in an enhanced antiasarcoma effect due to autophagic cell death in an in-house murine orthotopic osteosarcoma model.

Methods: Studies performed: infectivity, cytopathic effect and replication capacity, cell cycle analysis, autophagic death electron microscopy and biochemical). Orthotopic osteosarcoma model was induced with injection of 250,000 531MII cells in y3/Rag2/2B10 animals. Results: All the cell lines (developed from 4 metastatic osteosarcoma tumors) were susceptible to Delta-24-RGD infection ranging from 60 to 100% of infected cells at 25 MOI. Moreover, the virus showed cytopathic effect and replication capacity. The cisplatin antitumoral activity was synergistically enhanced by combination with Delta-24-RGD, lowering the IC50 in > 2 logs. Treatment with cisplatin resulted in G2-M cell cycle arrest that was overcome by the combination with Delta-24-RGD leading to autophagic cell death. On the other hand, we have developed an orthotropic osteosarcoma model by injection of 531MII cells in the tibial tuberosity, resulting in the development of tumors in 90% of y3/Rag2/2B10 animals. Next, animals were randomized as controls (no treatment), treated with cisplatin (2 mg/kg x 3 days/wk x 4 wk, i.p.), treated with Delta-24-RGD (3.8 x 107 pfu/wk x 3 wk, i.v.) or cisplatin + Delta-24-RGD. Animals were followed with X-ray and FDG-PET (day 45), sacrificed and the tumoral lesions were analyzed by H&E staining, necrosis evaluation and IHC. Our preliminary data indicate that the virus was able to replicate in vivo resulting in a robust oncolytic activity in the tumoral lesions, which are significantly reduced and necrosed compared to those from untreated or cisplatin alone.

Conclusion: Treatment with the adenovirus Delta-24-RGD resulted in a potent antimuscular effect through autophagic cell death in vivo and in vitro in our osteosarcoma model. Our preliminary data suggest that exploiting autophagic cell death could provide new approaches to antiasarcoma therapies.

PD018

ACTIVATED NK CELLS EFFICIENTLY ELIMINATE Ewing SARCOMA CELLS IN A SPHERE MODEL OF MICROMETASTATIC TUMOR GROWTH

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Purpose: Systemic relapses of Ewing sarcoma are caused by (sub)microscopic residual cells capable to reinstitute tumor growth. Targeting of residual cells by cellular immunotherapy may sustain remission and improve outcome. Specifically, activated NK cells have promising activity against Ewing sarcoma cells in vitro. To further explore the value of immune targeting, preclinical models are needed that mimics the anchorage-independent, multicellular growth of micrometastases.

Methods: We generated Ewing sarcoma spheres under serum-free conditions from various cell lines (VH-64, TC-32, TC-71, A4573) and primary tumor cell cultures (MSPS1-4, MSPS4-4, DC-ES-6) established from Ewing sarcoma biopsies.

Results: Flow cytometry analysis revealed heterogeneous expression of surface markers among individual Ewing sarcomas and between spheres and monolayers. While the supposed stem cell marker CD133, the Ewing sarcoma marker CD99 and ligands for NK cell activating receptors (NKG2D, DNAM-1) were expressed at comparable densities, levels of the neural crest marker CD34 and of MHC class I proteins were significantly higher in spheres. Side populations determined by Hoechst dye exclusion and postulated to be enriched for tumor initiating cells could be identified in three of four VH-64 sphere cultures. However, tumor cells resuspended from spheres did not form tumors in immunodeficient NODscid mice at higher efficiencies than monolayer cultures, arguing against higher tumorigenicity of sphere cultured cells. VH-64 spheres were more resistant to doxorubicine than monolayers, and chemoresistance was only partially overcome by resuspension to single cells. Long-term coconabation of Ewing sarcoma spheres with in vitro activated allogeneic NK cells resulted in efficient disintegration of spheres. This was successfully reproduced in the autologous setting.

Conclusion: Thus, Ewing sarcoma cells cultured under variable in vitro conditions differ with regard to phenotype and susceptibility to both chemo- and immunotherapy. Activated allogeneic and autologous NK cells efficiently target Ewing sarcoma cells including multicellular spheres, supporting the development of NK-cell based treatment strategies in Ewing sarcoma.

PD019

SERUM IGF-1 LEVELS IN PATIENTS WITH HIGH-GRADE CENTRAL OSTEOSARCOMA ARE NOT CORRELATED TO PROGNOSIS

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Purpose: The peak incidence of osteosarcoma occurs during the pubertal growth spurt (with highest levels of serum IGF-1; and IGF-I may play a role in osteosarcoma pathogenesis and disease course.

Methods: We prospectively investigated whether IGF-I serum levels correlated with patient-, tumor-related factors, and outcome in patients with high-grade central osteosarcoma.
Intended treatment included surgery and multidrug neoadjuvant and adjuvant chemotherapy with high-dose methotrexate, doxorubicin, cisplatin, and ifosfamide.

Results: 78 patients were evaluable with a median age of 14 years (range: 5–58 years); 42 male and 36 female; 10 with primary metastases. 73 patients achieved a first complete remission, of whom 26 patients developed recurrences. The median follow up was 6.1 years (range: 0.9–12.4 years). When dichotomized at median IGF-I serum level (299 ng/ml), no correlations between IGF-I serum levels and tumor site or tumor volume, histological subtype, primary metastatic status, response to chemotherapy or development of recurrence were found. The known age dependency of IGF-I levels was confirmed. When dichotomized at age-specific IGF-I serum levels (prepubertal 131, pubertal 329, postpubertal 266 ng/ml), no correlations to patient or tumor related factors were found. In addition, there was no significant correlation between IGF-I serum levels and either event-free or overall survival probabilities when analyzing the total cohort of 78 patients.

Conclusion: This prospective study did not detect correlations between serum IGF-I levels obtained prior to definitive surgery and either patient-(except for age) or tumor-related variables or prognosis.

References
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PD020
MMP9 GENE EXPRESSION IN THE PERIPHERAL BLOOD:
A POTENTIAL MARKER FOR MONITORING THE METASTATIC DISEASE IN OSTEOSARCOMA

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Purpose: Matrix metalloproteinase 9 (MMP9) plays an important role in preparing the lung metastatic site to tumour cells colonization. MMP9-expressing tumour associated macrophages are responsible for signaling the pulmonary site of metastasis through the induction of MMP9 expression in lung endothelial cells, leading to tissue remodeling and neovascularization. This study was the first to access MMP9 gene expression in the peripheral blood of osteosarcoma patients pre-/post-chemotherapy and also in the nonmalignant lung tissue adjacent to osteosarcoma metastasis.

Methods: We followed 30 osteosarcoma patients from 2007 to 2011 that were treated with the Brazilian OSTEO 2006 Protocol. We analyzed MMP9 expression using quantitative Real Time PCR in 72 samples of peripheral blood from the followed patients: 30 pre-chemotherapy, 15 post-chemotherapy and 27 after the end of treatment. We also evaluated MMP9 expression in 24 osteosarcoma biopsies free of treatment and in 29 osteosarcoma lung metastases with their respective nonmalignant adjacent lungs.

Results: MMP9 expression was significantly higher in the blood of patients prechemotherapy and decreased post-chemotherapy and after six months the end of treatment (P < 0.0001). We evaluated the overall survival of osteosarcoma patients based on their MMP9 expression in the blood at the time of biopsy and we found a worse survival for those that had MMP9 levels at least four times higher (P = 0.0349). High MMP9 expression was also detected in the osteosarcoma biopsies prior to chemotherapy (P = 0.0087) and in the nonmalignant adjacent lungs (P = 0.0011), but not in the respective paired metastases (P = 0.5340).

Conclusion: Our findings suggest that the high MMP9 expression we detected in the blood of our patients probably corresponds to tumour associated macrophages that trigger MMP9 up-regulation in the adjacent lung tissue. MMP9 expression in the blood could be used in the future as a marker for osteosarcoma dissemination, given the crucial role of MMP9 in directing lung-specific metastases.

PD021
CYTOLYTIC NK CELL INTERACTIONS WITH EWING SARCOMA CELLS IN THE PRESENCE OF ZOLEDRONIC ACID

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Purpose: Adoptive Natural Killer (NK) cell transfer in Ewing sarcoma is a promising strategy to eliminate residual tumor cells after conventional treatment and thereby prevent relapse. Combinatorial approaches including both cellular targeting and novel drugs have only recently started to be explored. Based on first evidence that the aminobisphosphonate zoledronic acid (ZA) combined with chemotherapy is effective in refractory Ewing sarcoma, the drug has been integrated into the current EWING 2008 trial. Aminobisphosphonates have immunomodulating effects that may contribute to or interfere with their antitumor activity. Here we investigated whether ZA directly affects cytolytic responses of NK cells to Ewing sarcoma cells.

Methods: NK cell lines were generated from five healthy donors and two Ewing sarcoma patients by a single round of in vitro stimulation of blood mononuclear cells with K-562.mbr15CD317L stimulator cells and subsequent 10-day expansion.

Results: Activated NK cells efficiently interacted with both K-562 leukemia targets and Ewing sarcoma cells. The sensitivity of four different Ewing sarcoma cell lines (VH-64, WE-68, TC-71, Cado) to allogeneic NK cells was highly variable, but consistent among donors. Cytolytic degranulation responses by CD107a expression were comparable in the absence and presence of increasing concentrations of ZA throughout various stimulator-to-responder ratios. NK cells directly isolated from peripheral blood of three donors had substantially lower degranulation responses to both K-562 and Ewing sarcoma targets, and, again, responses were unaffected by ZA.

Conclusion: We conclude that ZA does not substantially impede cytolytic NK cell responses to Ewing sarcoma. Ongoing experiments address differentiation and activating receptor expression of NK cells expanded in the presence of ZA. Moreover, NK cell phenotype and function are investigated ex vivo in patients undergoing ZA treatment compared to matched controls. Our current approach and further studies aimed to determine the interactions of novel drugs, targeted therapies and immunotherapy may lead to more effective combination strategies.

PD022
CHARACTERIZATION OF GENES CRITICAL FOR CHONDRO-OSEOUS DIFFERENTIATION, METASTASIS AND OSTEOTROPISM IN EWING TUMORS

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Purpose: Ewing Tumors (ET) are highly malignant, mainly localized in bone tissue and are molecularly defined by events translocations and metastatic spread in ET is frequent and hematogenous.

Methods: Microarray analysis revealed BRIC/OSHO domain containing proteins important for chondrogenic differentiation and canonical Wnt antagonist Dickkopf, Xenopus, Homolog of (DKK) 2 critical for terminal bone development, to be over-expressed in ET.

Results: None of them seemed directly induced via EWS-FLI1 transcription factor activity RNA interference of DKK2 expression in ET suppressed in vitro proliferation and decreased the ability for colony formation as well as invasive growth of ET cells, while BRIC/HOS proteins seemed essential for the maintenance of a precursor state of chondrogenic differentiation. Similarly, local tumor growth and metastasis of ET after DKK2 knock down was significantly decreased in Rag2-/- ; gammaC-/- mice. In an orthotopic tumor model model DKK2 knock down in ET cells resulted in a strongly decreased capacity for invasive growth into bone tissue while RNA interference of BRIC/HOS proteins surprisingly increased their invasiveness when compared to controls. Microarray analysis after DKK2 knock down and subsequent validation with real-time RT-PCR revealed DKK2-mediated induction of CD44, ICAM1, Matrix Metalloproteinase (MMP) 1, and endochondral bone development important Parathyroid hormone-like Hormone (PTHRP) in ET. Furthermore, subsequent functional assays demonstrated that invasiveness of ET cells was Matrix Metalloproteinase (MMP) 1 mediated, while knock down of one BRIC/HOS protein resulted in an increased MMP9 expression, indicating the critical involvement of matrix metalloproteases for the invasive ET growth behavior.

Conclusion: DKK2 and BRIC/HOS domain containing proteins orchestrate and promote bone invasiveness and metastatic spread of this tumor, and provide significant conceptual progress in understanding both the pathogenesis of invasive bone growth of ET in particular and osteotropism in general.

PD023
FIBROBLAST GROWTH FACTOR RECEPTOR SIGNALING CONTROLS CANCER CELL SURVIVAL

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Purpose: Overactivation of fibroblast growth factor (FGF) signaling can lead to uncontrolled cell growth, angiogenesis and tumor cell metastasis and is involved in the progression of many cancers. We have previously developed a neutralizing antibody against FGF receptor 1 (FGFR1). In this study, we used this antibody (811) to study how FGFR signaling regulates osteosarcoma cell growth.

Methods: We first screened the expression of FGFR1 by Western blotting in a range of human osteosarcoma cell lines and primary human osteosarcoma cells. To assess the role of FGFR in cancer cell growth, we examined the effect of FGFR inhibitors (small-molecule

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relapsed disease was detected in almost all patients by MIBG scan, UCats and catecholamines (UCats), 2 by bone scan, 1 by Ultrasound (US) and 1 by CXR. Two patients years (range 0.18–6.66 years). 32/50 relapses were detected by scheduled surveillance observed following resection (low-risk). Median time from diagnosis to relapse was 1.20 (median age 3.54 years, range 0.04–8.30 years). 42/50 (84%) were initially treated on high-intensity of post-therapy surveillance may also be guided by initial disease risk stratification. We reviewed all cases of relapsed NBL at Sick Kids between January 2000 and radiation. NBL will ultimately relapse, for which there are generally no curative therapies. Surveillance cancer. Approximately 50% NBL are localised at diagnosis and 25–35% of all patients with neuroblastomas (NBL) are the most common type of extra-cranial solid tumors presenting in childhood and more young children die from NBL than from any other type of cancer. Approximately 50% NBL are localized at diagnosis and 25–35% of all patients with NBL will ultimately relapse, for which there are generally no curative therapies. Surveillance involves multiple CT and MIbG scans, resulting in relatively high cumulative doses of radiation. Methods: We reviewed all cases of relapsed NBL at Sick Kids between January 2000 and December 2011 to determine how relapses were detected and determined whether routine surveillance investigations can diagnose relapses without using regular CT/MRI imaging. Results: 38/183 children with NBL were treated during the study period. 50/183 (27%) relapsed (median age 3.54 years, range 0.04–83 years). 42/50 (84%) were initially treated on high-risk protocols (COG, POG, CCG), 3 were treated on intermediate-risk protocols and 5 were observed following resection (low-risk). Median time from diagnosis to relapse was 1.20 years (range 0.18–6.66 years). 32/50 relapses were detected by scheduled surveillance investigations and 18/50 due to new onset symptoms. 37/50 had new lesions visible by MIbG at relapse. Of the remaining 13, 5 recurrences were detected by elevated urinary catecholamines (UCats), 2 by bone scan, 1 by ultrasound (US) and 1 by CXR. Two patients relapsed at initial sites of disease and did not have a concurrent MIbG and two patients had relapse diagnosed by CT due to symptomatic. Conclusion: Relapsed disease was detected in almost all patients by MIbG scan, UCats and CXR/US alone, supporting the reduced use of CT imaging in post therapy surveillance. The intensity of post-therapy surveillance may also be guided by initial disease risk stratification. A small sub-group of patients may require 3-D imaging as part of post-therapy monitoring. of 8 weeks after treatment. Two patients with progressive disease on 123I-mIbG evaluation, also had progressive disease on 18F-FDG-PET/CT. Of two patients with inevaluable response on 123I-mIbG imaging, one had a complete response and one a partial response on 18F-FDG-PET/CT. Six reassessment 123I-mIbG scans showed stable disease. Of these, two had complete response by both semi-quantitative scoring and PERCIST using 18F-FDG-PET. Four showed stable disease by semi-quantitative scoring but partial metabolic response in 2 and stable metabolic disease in 2 on PERCIST using 18F-FDG-PET Seven reassessment 123I-mIbG scans showed partial response. Semi-quantitative 18F-FDG-PET showed 2 complete and 4 partial responses and 1 minor response. PERCIST using 18F-FDG-PET showed 2 complete and 4 partial metabolic responses and 1 stable metabolic disease. Conclusion: 18F-FDG-PET/CT gives supplementary information to 123I-mIbG scintigraphy in patients with stable disease and partial responses. The clinical significance of this is uncertain and requires further evaluation.

**NEUROBLASTOMA AND RENAL TUMOURS**

**PH001**

THE ROLE OF IMAGING IN DETECTING RELAPSE IN PATIENTS WITH NEUROBLASTOMA. CAN POST-THERAPY SURVEILLANCE PROGRAMS BE SIMPLIFIED TO DECREASE RADIATION EXPOSURE?

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**Purpose:** Neuroblastomas (NBL) are the most common type of extra-cranial solid tumors presenting in childhood and more young children die from NBL than from any other type of cancer. We postulated that plasma metanephrines should be measured in healthy children as a possible screening tool for NBL.

**Materials:** 191 healthy children (age 0–17 years, 122 boys) constituted the reference population. The following upper reference limits of total and free plasma NNN and MT were established in nmol/l (95% CI): tNNN 9.95 (9.63–35.43), IMT 6.97 (5.67–19.43), NNN 0.79 (0.72–1.01), IMT 0.07 (0.04–0.09). The following cut-off values with sensitivity/ specificity/FPP/NPV for ten neuroblastoma patients were determined: tNNN 19.64–100%/ 99.48%/90.01%/100%; IMT 9.43–100%/98.55%/83.33%/100%; NNN 3.16–100%/98.48%.

**Methods:** Blood samples (1 ml) were drawn prospectively from healthy children aged 0–18 years needing venous puncture for other reasons and put in lithium heparinized tube, immediately stocked at –70 °C and sent to laboratory for analysis. Total and free plasma normetanephrine and methoxytyramine (MT) was measured by HPLC with electrochemical detection. Patients with suspected neuroblastoma underwent the usual diagnostic procedures.

**Results:** 191 healthy children (age 0–17 years, 122 boys) constituted the reference population. The following upper reference limits of total and free plasma NNN and MT were established in nmol/l (95% CI): tNNN 9.95 (9.63–35.43), IMT 6.97 (5.67–19.43), NNN 0.79 (0.72–1.01), IMT 0.07 (0.04–0.09). The following cut-off values with sensitivity/ specificity/FPP/NPV for ten neuroblastoma patients were determined: tNNN 19.64–100%/ 99.48%/90.01%/100%; IMT 9.43–100%/98.55%/83.33%/100%; NNN 3.16–100%/98.48%.

**Conclusion:** Plasma total and free metanephrines are the gold standard for diagnosis of phaeochromocytoma in adults and children with higher sensitivity and specificity than urinary catecholamines and their metabolites. We postulated that plasma metanephrines should be more sensitive markers also in neuroblastoma because directly produced by the tumor. The aim of our study was to establish complete reference values for plasma total and free metanephrines in healthy children and to provide preliminary results on its diagnostic value in patients diagnosed with neuroblastoma.

**PH002**

COMPARISON OF PAIRED 123I-META IODOBENZYL GUANIDINE SCINTIGRAPHY AND 18F–FLOUREDODEXYGLUCOSE POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHY SCANS BEFORE AND AFTER 131I-META IODOBENZYL GUANIDINE THERAPY FOR NEUROBLASTOMA

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**Purpose:** This study evaluates the use of 18F fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) imaging in addition to 131I-meta iodo benzylguanidine (mIBG) scintigraphy for response assessment in patients with metastatic neuroblastoma. It aims to establish whether 18F-FDG-PET/CT gives additional information to 123I-mIBG scintigraphy for staging of neuroblastoma. For risk stratification which dictates treatment strategy. The 18F FDG PET/CT scan has emerged as a novel diagnostic tool for staging of neuroblastoma with promising results. The present study was undertaken to see the feasibility of this modality in comparison to the conventionally used mIBG scintigraphy for staging of neuroblastoma.

**Methods:** 22 diagnosed cases of neuroblastoma were subjected to 18F FDG PET/CT and 1131-MIBG scan as a part of pre treatment evaluation. Both the scans were done within a time span of 3 days. The images were compared for concordance of uptake in the primary lesion, loco regional and distant metastases.

**Results:** All the lesions noted on 131I-MIBG scans were also seen on 18F FDG PET/CT scans. FDG scan revealed additional lesions in 55% (12/22) patients. Additional loco regional nodal lesions were noted in 3 patients, distant nodal lesions in 0 patients, marrow lesions in 2 patients. Percalicular deposits, peritoneal deposits and inferior temporal fossa deposits were other lesions seen on FDG scan but not seen on MIBG scan.

**Conclusion:** 18F FDG PET/CT scan has a higher sensitivity and upstages 55% cases. Upstaging neuroblastoma may shift patients to higher risk category. The poorer sensitivity of 1131 MIBG may be due to the “TUMOR SINK EFFECT” and lower spatial resolution. Higher sensitivity, better spatial resolution, ease of availability and simultaneous morphological CT correlation make 18F FDG PET/CT scan a first stop shop for staging of Neuroblastoma; especially in those parts of the world where 131MIBG is not available.
Neuroblastoma is a heterogeneous tumor of global prevalence with considerable variation in clinical, genetic, and prognostic characteristics. The clinical and genetic profile of neuroblastoma in a country with different ethnicity and living conditions than usually investigated. Results may contribute to understanding of neuroblastoma.

References
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PH005
APPLICATION OF REAL-TIME PCR AND FLOW CYTOMETRY TECHNIQUES FOR BONE MARROW INVOLVEMENT ASSESSMENT IN NEUROBLASTOMA PATIENTS

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Purpose: Bone marrow (BM) involvement detection in neuroblastoma is a useful tool for patients’ stratification, prognosis defining and risk-adapted treatment. Real-time quantitative PCR (RQ-PCR) of tumor-specific gene transcripts and multicolor flow cytometry (FC) are commonly applied for this purpose.

Methods: RQ-PCR of gene expression detection and tumor cells percentage calculation were performed in 326 BM samples from 52 neuroblastoma patients. 108 samples were obtained at the time of primary diagnoses, 168 during treatment and 51 at the time of relapse.

Results: Analytical sensitivity of RQ-PCR PHOX2B detection achieved IE-06 while specificity of FC ranged from IE-03 to IE-05. In 193(59.2%) samples BM involvement was not detected by both methods, 38 (11.7%) samples were negative by FC but positive for PHOX2B expression, 31 (9.5%) samples were false positive by FC but negative for PHOX2B and 64 (19.6%) samples were positive by both techniques. Thus overall qualitative concordance between RQ-PCR and FC achieved 78.8%. Concordance between two methods was 75.0% in samples taken at the time of diagnosis, 80.8% during treatment and 80.4% at the time of relapse (p = 0.490). In groups of localized (stages I–III) and disseminated (stage IV) neuroblastoma concordance values were 80.7% and 79.9%, respectively (p = 0.981).

Concordance did not depend on FC sensitivity (higher or lower than 1E-04): 81.1% and 76.6%, correspondingly (p = 0.292).

Conclusion: Thus qualitative concordance between PCR-based PHOX2B expression detection and FC for BM involvement detection in neuroblastoma patients achieved 78.8% and did not depend on time of BM sampling, stage of the disease or FC sensitivity.

PH006
ETHNIC DIFFERENCES IN NEUROBLASTOMA GENETICS INDICATED BY HIGH FREQUENCY OF ALK MUTATIONS IN VIETNAMESE TUMORS: IDENTIFICATION OF EIGHT NOVEL TYROSINE KINASE DOMAIN MISSENSE MUTATIONS

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Purpose: Neuroblastoma is a heterogeneous tumor of global prevalence with considerable variation in impact on rich and poor societies. Ethnic differences in incidence and biology have rarely been investigated. We studied tumors from Vietnam and compared them with neuroblastoma from Sweden and elsewhere.

Methods: Neuroblastomas from Vietnam were collected and sections of FFPE blocks were used for DNA extraction. DNA samples were analyzed by 250k SNP array (Affymetrix/CGH arrays) and mutation screening of the tyrosine kinase domain (TKD) of the ALK gene and focused on clinical and biological parameters (age at diagnosis, stage, group of risk, MYCN status and the onset of relapses or deaths) in the NB patients. The data of screening detected cases suggested that these ALK activating tumors usually develop in infants with a high capacity for recurrence and some of them might appear as unfavorable tumors at older age.


PH007
ALK ACTIVATING INFANT NEUROBLASTOMA CASES INCLUDING MASS-SCREENING DETECTED CASES

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Purpose: ALK (anaplastic lymphoma kinase) has recently been identified as a gene conferring a predisposition for neuroblastoma (NBL). We have analyzed tyrosine kinase domain mutations and amplification/expression of the ALK gene and focused on clinical features of infant neuroblastoma cases with ALK aberrations.

Methods: The frequency of ALK mutations, copy number gain, and expression were analyzed in NBL tumors derived from 212 infant cases, including 161 cases detected by mass-screening and 149 cases diagnosed at more than 12 months of age. These cases were analyzed using clinicopathological features including the International Neuroblastoma Staging System (INSS) and outcomes of the patients.

Results: Eleven cases (5.2%) had missense mutations at positions F1174, F1245, D1249, and R1275 and one case had ALK amplification. Among them, eight cases (5.0%) were detected by mass-screening and one multiple neuroblastoma with germ-line mutation. Of these eleven infants, three cases showed relapse and one case died of disease. Among screening-detected cases, ALK activating cases showed significant worse prognosis (P = 0.002). In the older cases, five cases (3.4%) showed ALK missense mutation and two cases had ALK amplification. Among them five had MYC-amplification and five died of disease. The expression levels of ALK mRNA were up-regulated in the cases with ALK mutation or amplification. In cases with these ALK activating NBLs, survival rates of the cases detected by screening were significantly better than those of the clinical detected cases (P = 0.025).

Conclusion: The results of the present study support the hypothesis that ALK activating tumors represent a specific subset of NBLs. The data of screening detected cases suggested that these ALK activating tumors usually develop in infants with a high capacity for recurrence and some of them might appear as unfavorable tumors at older age.


PH008
METHYLATION STATUS IN NEUROBLASTOMA AND ITS PROGNOSTIC VALUE

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Purpose: The study of epigenetic mechanisms involved in NB progression could contribute to a better understanding of this heterogeneous tumor. The aim of the present study was to identify epigenetic biomarkers with prognostic value in NB.

Methods: Illumina’s Infinium HumanMethylation2 assay was performed in DNA samples extracted from 48 fresh frozen tumors from NB patients at diagnosis. Chi square and Fisher test methods in combination with multivariate analysis were used as well as Functional Enrichment and Gene Set Enrichment analyses.

Results: We studied the association between the methylation status and clinical and biological parameters (age at diagnosis, stage, group of risk, MYCN status and the onset of relapses or deaths) in the NB patients. The more relevant results were found when comparing the established subgroups with regard to the hypermethylation status than when using the hypomethylation ones. Risk parameter showed the highest number of significant probes in a comparison of the methylation status among the 3 different risk groups. The high risk group with relapses or deaths was the one that produced the most relevant results. In addition, the percentage of hypermethylation in our series was higher in the NB patients who had died (p = 0.036). We found 80 genes whose hypermethylation status is significantly associated with the patient’s outcome, being of special interest those involved in maturation pathways.
and maintenance of the overall structure of the nervous system (NNAT), control of the cell cycle (CCND1, JAK2, TP73), cell growth and differentiation (DUSP2, PAX8), tumorigenesis and tumor progression (MAGEA2, RKNX 3, CTX2, TDOC1, TSHN3), apoptosis (JAK2, PECAM1, RB1) and DNA repair mechanisms such as MGMT.

Conclusion: We identified a group of hypermethylated genes with prognostic value in NB, some of them not previously reported as such. Studying the epigenetic alterations in the entire genome would help reveal the epigenomic approach of NB.

PH009

TARGET EPIGENETIC REGULATION AT A SPECIFIC GENOMIC REGION TO INDUCE STEM CELL LIKE PHENOTYPE IN NEUROBLASTOMA CELLS

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Purpose: Pyrrole-Imidazole (PI) polycyclic molecule was originally designed from structures of natural DNA binding molecule, such as Distamycin and Dicoumarbicine and has been recognized as a synthetic molecule which binds the minor groove of Watson–Crick base pair of double-stranded DNA in a sequence-dependent manner. We hypothesized conjugates between this synthetic DNA binding molecule and Histone Deacetylase inhibitor (HDACi) of Suberoylanilide hydroxamic acid (SAHA) should regulate histone acetylation in a specific region of the genome in neuroblastoma.

Methods: We have taken two strategies to confirm this hypothesis. One is the candidate gene approach and another is chemical library approach. A synthesized library of sequence-specific PI polycydes conjugated with the potent HDAC inhibitor, termed SAHA-PIP has been screened on the expression of Yamanaka factors in mouse embryonal fibroblast (MEF) and the hit SAHA-PIPs for mouse neuroblastoma stemness or quiescence using the TH-MYC transgenic mouse model.

Results: Chromatin immunoprecipitation analysis revealed SAHA-PIP induces acetylation of Histone H4 and H3 in the promoter region of Oct-4 and Nanog. SAHA-PIP showed significant induction against c-Myc, Oct-3/4, Sox-2, and Klf-4, respectively in MEF. We also confirmed only SAHA did not show such histone acetylation and transcription induction, which implicated the role of PI polycydes conjugates in the induction of histone acetylation in specific genomic regions. Furthermore, a significant change in MEF morphology was demonstrated with alkaline phosphatase staining by our hit SAHA-PIPs. We are testing this hit SAHA-PIPs for mouse neuroblastoma model.

Conclusion: Those data suggest that a capability of PIP-SAHAA regulate histone modification in a genomic sequence specific manner and promote agents for reprogramming efficiency in order to generate IPS like cell phenotype, hopefully in neuroblastoma.

References


PH010

HDAC11 CONTROLS MITOTIC CELL CYCLE PROGRESSION OF NEUROBLASTOMA CELLS

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Purpose: Expression of HDAC11, the most recently identified histone deacetylase, is restricted to the cell nuclei in poorly differentiated neuroblastomas. We have previously shown that HDAC11 depletion induces a prognostically favorable neuroblastoma transcriptome, partly by reverting BMP4 epigenetic silencing, thereby, triggering this developmental pathway. Here we aimed to decipher the functional relevance of further distinct alterations in gene expression caused by HDAC11 depletion.

Methods: Whole-genome expression was evaluated in time-course in p53-wildtype and mutant MYCN-amplified neuroblastoma cells following HDAC11 depletion. Differential expression of candidate genes in primary neuroblastomas was assessed in three independent datasets from 468, 102 and 88 tumors. Cell cycle and death assays were conducted after target gene depletion in neuroblastoma cell lines.

Results: HDAC11 depletion caused the genome-wide differential expression of 259 and 167 genes in p53-mutant BE(2)-C and p53-wildtype IMR-32 cells, respectively. The biological function of genes consistently regulated over time across each cell system were assessed by analyzing gene ontology term over-representation. Genes necessary for mitotic cell cycle progression and cell division were most prominently enriched. All ten of these genes were strongly repressed by HDAC11 depletion, followed by a G2/M arrest and apoptosis in functional assays. High candidate gene expression levels in primary neuroblastomas strongly correlated with unfavorable overall patient survival in all 3 datasets, demonstrating their clinical relevance. Depletion of 6 candidate genes, singly, reduced metabolic activity up to 90% and increased caspase-3/7-like activity up to 10-fold, mimicking the phenotype caused by HDAC11 depletion. HDAC11 depletion did not affect viability of nonneurotogenic cells.

Conclusion: Here we investigate a group of cell cycle-promoting genes repressed by HDAC11 depletion, being both, predictors of patient outcome and essential for neuroblastoma cell viability. Our data further support HDAC11 inhibition as a novel targeted therapeutic approach for the treatment of high-risk neuroblastomas, regardless of p53 status.

PH011

EPIGENETIC DRUG COMBINATION INDUCES GENOME-WIDE DEMETHYLATION AND ALTERED GENE EXPRESSION IN NEURO-ECTODERMAL CELL LINES

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Purpose: Epigenetic alterations, especially in the apoptotic pathways are a fundamental aspect of pediatric neuro-ectodermal tumors. This suggests that neuroblastoma and PNET/ Ewing tumors may be sensitive for epigenetic drugs. Here, we studied the molecular and functional effects of low dosage epigenetic drugs in neuro-ectodermal tumor cell lines.

Methods: In 17 neuroblastoma (NBL) and 5 peripheral primitive neuro-ectodermal tumor (PNET) cell lines, short term combination treatment of 3-aza-2-deoxycytidine (DAC) and Trichostatin A (TSA) at 30 and 25 nMol, respectively were array profiled for expression (HU133plus2.0 arrays; Affymetrix, USA) and DNA methylation (244K CpG island microarrays; Agilent).

Results: First, DAC/TSA treatment was optimized at 30-25 nMol dosages, based on demethylating effects of known methylated genes. Treatment with the combination resulted in reduced proliferation of cell lines, without direct cytotoxic effects, no measurable cell cycle arrest or changes in apoptosis. We observed wide-spread demethylating and gene expression effects. Methylation changed in 29.5% of neuroblastoma genes and were enriched in homeobox genes, compared to 39.3% of PNET genes, enriched in ‘membrane ruffle’ genes. The correlation between expression and demethylation was strong. Among 1798 genes significantly upregulated after treatment in NBL, 749 (41.7%) were significantly demethylated, enriched in phosphoproteins and apoptotic genes (such as KRT19, a known methylated gene in NBL). In PNETs the overlap was in 53.3% of re-expressed genes. Ingenuity analysis of affected genes showed that almost every cellular pathway (193/200) demonstrated altered expression after treatment, with upregulation of known epigenetically regulated genes (X-chromosomal, tissue-specific, and some imprinted genes and known tumor suppressor genes).

Conclusion: Genome-wide methylation and gene expression changes are induced by DAC and TSA treatment at nanomolar dosages in neuro-ectodermal cell lines.

PH012

EPITHELIAL TO MESENCHYMAL TRANSITION AND TUMOR PROGRESSION IN NEUROBLASTOMA

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Purpose: Neuroblastoma (NB) is a highly metastatic tumor in children. The epithelial to mesenchymal transition (EMT) is an important mechanism for both the initiation of tumor invasion and subsequent metastasis. The purpose of this study was to investigate the role of EMT in the progression of NB.

Methods: Using EMT assays on samples from 11 tumors, we identified 14 genes that were either differentially expressed between tumors of different stages or highly upregulated in NB. Quantitative RT-PCR of these genes was conducted in 96 NB tumors and their expression levels were compared between stages and between tumors with the presence and absence of MYCN amplification. The association of survival rate with differential gene expression was investigated. The correlation between gene expression and in vitro invasive ability was examined using six NB cell lines.

Results: Expression of KRT19 was significantly decreased in stage 3 or 4 NB as well as stage 45 NB compared with stage 1 or 2 NB. Expression levels of KRT19 and ERBB3 were significantly low, and expression levels of TWST1 and TF3 were high in MYCN-amplified NB. The patients with low expression of KRT19 or ERBB3 showed significantly worse overall survival. The correlation between high invasive ability and low expression of KRT19 and ERBB3 was confirmed in vitro using NB cell lines.

Conclusion: Downregulation of KRT19 was highly associated with tumor progression in NB and metastasis in localized primary NB. Low expression of ERBB3 was also associated with progression of NB.
PH013
FUNCTIONALLY ACTIVE MYELOID DERIVED SUPPRESSOR CELLS (MDSCS) ARE FOUND WITHIN THE BLOOD OF PATIENTS WITH NEUROBLASTOMA
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Purpose: The ability of tumours to evade detection and destruction by a patient’s immune system is a subject of increasing interest. Myeloid Derived Suppressor Cells (MDSCs), a subset of immune cells, play a role in the development of an immunosuppressive tumour microenvironment. The exact immunophenotype of human MDSCs is controversial although a consensus view is that the suppressive phenotype is associated with expression of the markers CD33, CD11b and CD66b, and absence of HLA-DR staining. A number of studies in adult cancer have reported an inverse correlation between circulating numbers of MDSC and both prognosis and clinical stage. To date only a limited number of studies have evaluated the role of MDSCs in neuroblastoma. This study aims to determine whether elevated levels of circulating MDSCs, with suppressive function, are present in the blood of neuroblastoma patients.

Methods: Blood samples from patients with neuroblastoma were taken at diagnosis or immediately prior to surgery (paired with excised tumour). Blood samples from age-matched children were analysed as controls. Samples were stained with the following multi-fluorochrome panel of antibodies: CD33, CD11b, CD66b, CD14, CD15, HLA-DR. The stained cells were detected using the BD LSRII flow cytometer and analysed using FacsDiv software. Suppressive function was assayed using thymidine incorporation and CFSE dilution.

Results: Our initial results suggest a population of CD33 + CD11b + CD66b + HLA-DR- cells is present in the blood of both patients with neuroblastoma and age-matched controls. A striking difference in the suppressive function of cells with this immunophenotype was seen: CD33+CD11b+CD66b+HLA-DR- cells from neuroblastoma patients suppressed T cell proliferation in vitro, while those from healthy controls had no effect.

Conclusion: Our results support the hypothesis that MDSCs are present in patients with neuroblastoma. Correlation with tumour stage or treatment outcome is subject to further study. The identification of MDSCs in patients may provide an important therapeutic target.

PH015
NEUROBLASTOMA STAGE 4S IS A MULTIFOCAL STEM CELL DISEASE OF DEFECTED NEURAL CREST PRECURSOR CELLS
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The etiology of neuroblastoma stage 4S (NB4S) is unknown. It is considered a metastasized neuroblastoma of infancy, although the pattern of tumor spread contrasts sharply with stage 4 neuroblastoma (c4N). Especially localization of tumor nodules in all liver segments, skin, a restricted involvement in bone marrow and often bilateral adrenal localization is unexplained and very different from c4N. Furthermore, the favorable outcome of NB4S and high rate of spontaneous tumor regression in NB4S is incompatible with a classic metastasizing tumor etiology. Study of the migration pattern of neural crest cells directs to a model in which NB4S is a multifocal disease of migrating neural crest cells.

Methods: Comparison of the state-of-the-art migration pattern of the neural crest in relation to clinical symptomaticity in NB4S

Results: Neuroblastomas tumors arise from early neural crest progenitor cells. Neural crest stem cells (NCSC) migrate from the dorsal NC to their target organs, including adrenal glands (chromaffin cells), the sympathetic ganglia (side chain, enteric ganglia) and melanocytes in the skin. Recently it was shown that NCSC also enter the bloodstream and travel through the liver and invade the bone marrow and form a small population of hematopoietic stem cells (Nagoshi et al., < query > Cell Stem Cell 2008). In E14.5 mouse embryo’s NCSCs were shown in all segments of the fetal liver and at E18.5 NCSCs appear in the bone marrow. These data reveal that NCSCs migrate through, and populate sites in the embryo that coincide exactly with tumor locations in NB4S: adrenal glands, liver, skin and a small population in the bone marrow.

Conclusion: A model will be presented in which NB4S tumors originate from defective pre-migratory NCSCs (van Noesel, Lancet Oncol 2012). During migration, these defective NCSCs are seeded in different NC organs and form nodules of undifferentiated NCSC. In this model, tumor regression seems a delayed activation of normal, developmentally regulated apoptotic pathways.

PH016
NLRR3 IS NEGATIVELY REGULATED BY MYCN AND ITS DOWN-REGULATION IS ASSOCIATED WITH THE PATIENTS’ POOR OUTCOME IN NEUROBLASTOMA
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Purpose: Human NLRR family genes were originally identified from the cDNA libraries of primary neuroblastomas (NBs) as genes whose expression is differentially expressed in favorable vs unfavorable NBs. The NLRR family genes encode orphan receptors. Our preliminary data showed that expression of NLRR3 is high in unfavorable NBs whereas that of NLRR3 is high in favorable NBs. However, their precise molecular mechanisms remain elusive.

Methods: Transcriptional profiling, immunoprecipitation and chromatim Immunoprecipitation assays were performed to investigate the transcriptional regulation of NLRR3. Quantitative real-time PCR was applied to examine the expression of NLRR3 or McI3 or MTCN miRNA.

Results: Expression of NLRR3 mRNA was significantly high in favorable NBs as compared to unfavorable ones, whereas that of NLRR1 was high in unfavorable NBs. The immunohistochemical study showed that NLRR3 is strongly positive in favorable NB cells, though it mainly localized in the cell nucleus. The multivariate analysis showed that expression of NLRR3 was an independent prognostic factor of NB. NLRR3 was up-regulated during retinoic acid-induced differentiation of NB cells accompanying with down-regulation of endogenous MYCN. In addition, expression of NLRR3 was down-regulated by overexpression of MYCN and was up-regulated by knockdown of MYCN at both mRNA and protein levels. Furthermore, like NLRR3, MTCN1, which is a co-repressor of MYCN, is highly expressed in favorable NBs (p < 0.0004), suggesting that NLRR3 expression may be regulated by MYCN and MTCN1. Indeed, MYCN repressed transcription of NLRR3 in cooperation with MTCN1. The chromatim Immunoprecipitation analysis also demonstrated that MYCN, MTCN1 and MTCN3 are recruited to the promoter regions of NLRR3 gene and act as a transcriptional repressor complex for NLRR3 expression.

Conclusion: Our results show that NLRR3 regulates neuronal differentiation and survival and that its expression is negatively regulated by MYCN in association with MTCN1 in aggressive NBs.
Correlate with stage or histology but significantly with MYCN amplification (p < 0.0001). The array analysis identified four genes overexpressed in invasive compared to non-invasive NB. These code for components of the transforming growth factor-beta (TGFβ1, TGFβ3, and TGFβR3) and bone morphogenetic protein (BMP2) signal transduction pathway known to control tumor migration, invasion and metastases.

Conclusion: One quarter of advanced NB grow invasively into vessel walls and/or solid organs which is associated with MYCN amplification and impaired prognosis. Invasive NB seem to be characterized by an upregulation of genes involved in TGFβ/BMP signaling. This could be used for detection strategies to identify NB that are at risk for incomplete surgical resection.

Purpose: Neuroblastoma (NB) is the most common extra-cranial solid tumor of childhood. Despite improvements in outcome for those with low-risk NB, the outcome for children with high-risk NB is still poor, underscoring the need for novel therapeutic strategies. FTY720, an immunomodulating drug approved for multiple sclerosis, has been investigated in cancers with promising preclinical activities. Its effect in NB has not been explored. Herein we propose for the first time in neuroblastoma, a technically simple PCR-based single score predictor model. The model robustly classified patients in the total cohort, accepted risk stratification systems, the model robustly classified patients in the total cohort, and in different clinically relevant risk subgroups.

Methods: Real-time PCR gene expression data from 96 neuroblastoma mouse model were monitored for tumor-associated inflammation at various stages of disease using flow cytometry, immunohistochemistry and qRT-PCR. Homozygous pups with two transgene copies received daily low-dose aspirin using oral gavage (10 mg/kg, n = 8) or no treatment (n = 15), from the age of 4.5 weeks to 6 weeks of age.

Results: Ex vivo analysis of tumors revealed a transition from an adaptive immune response predominated by CD8+ T-cells in neoplastic lesions from 5 week old homzygous mice, towards enrichment in immature cells of the innate immune system, including myeloid-derived suppressor cells, dendritic cells (DCs), and tumor-associated macrophages (TAMs) during tumor progression. A M1 to M2 transition of TAMs was demonstrated, paralleled by a deterioration of DC status. Ten days of anti-inflammatory treatment with low-dose aspirin to homzygous mice significantly reduced tumor burden (p < 0.001) and the presence of tumor-associated cells of the innate immune system (p < 0.01).


Purpose: Neuroblastoma is an embryonal tumor with contrasting clinical courses. Despite elaborate stratification strategies, precise clinical risk assessment still remains a challenge. The purpose of this study was to develop a PCR-based predictor model to improve clinical risk assessment of neuroblastoma patients.

Methods: The model was developed using real-time PCR gene expression data from 96 samples, and tested on separate expression data sets obtained from real-time PCR and microarray studies comprising 362 patients.

Results: Based on our prior study of differentially expressed genes in favorable and unfavorable neuroblastoma subgroups, we identified three genes, CHD5, PAFAH1B1 and NME1, strongly associated with patient outcome. The expression pattern of these genes was used to develop a PCR-based single score predictor model. The model discriminated patients into two groups with significantly different clinical outcome (Spt 1-year overall survival [OS]: 0.93 ± 0.03 vs 0.53 ± 0.06, 5-year event free survival [EFS]: 0.85 ± 0.04 vs 0.61 ± 0.02, both P < 0.001, Set 2 OS: 0.97 ± 0.02 vs 0.61 ± 0.1, P = 0.005, EFS 0.91 ± 0.08 vs 0.56 ± 0.1, P < 0.001 and Set 3 OS: 0.99 ± 0.01 vs 0.56 ± 0.06, EFS 0.96 ± 0.02 vs 0.43 ± 0.05, both P < 0.001). Multivariate analysis showed that the model was an independent marker for survival (P < 0.001, for all). In comparison with accepted risk stratification systems, the model robustly classified patients in the total cohort, and in different clinically relevant risk subgroups. Conclusion: We propose for the first time in neuroblastoma, a technically simple PCR-based predictor model that could help refine current risk stratification systems.
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Purpose: High risk neuroblastoma (NB) has a poor prognosis. We retrospectively analysed treatment outcome by different maintenance therapeutic methods in Chinese high risk NB in CR/GPR after multimodal therapy.

Methods: From Jan 2004 to June 2010, we treated high risk NB by using chemotherapy and surgery and/or radiotherapy. The patients who had achieved CR/GPR after multimodal therapy were divided into three groups based on the patient’s family economic status: Group A received autologous stem cell transplantation (ASCT) then oral 13-cis-retinoic acid (13cRA) for one year; Group B received one year of 13cRA plus six months of Interferon-α1b, Interferon-α2b (IFN-α1/2-L2); Group C received only observation. We analyzed and compared the survival rate of these three groups of patients.

Results: Total 58 untreated high-risk stage IV neuroblastoma patients with median age of 4 years (range 2–18 years) were enrolled. Forty-four patients were 60.0 ± 8.8% for all 44 patients in CR/GPR, respectively; the 3-year OS was 60.0 ± 15.5% for group A, 63.4 ± 13.5% for group B, and 24.9 ± 12.2% for group C. The 5-year OS was 30.0 ± 14.5% for group A, 42.3 ± 19.5% for group B and 24.9 ± 12.2% for group C. There were no severe side effects for 13cRA plus IFN-α1/2-L2.

Conclusion: Our study showed that the 13cRA combined with IFN-α1/2-L2 as maintenance therapy was tolerable; and the survival rate was not inferior to the patients who received ASCT plus 13cRA in Chinese high-risk stage 4 neuroblastoma patients in CR/GPR.

PH022
PHASE II STUDY OF THE COMBINATION OF BEVACIZUMAB PLUS IRINOTECAN AND TEMOZOLOMIDE FOR RELAPSED OR REFRACTORY NEUROBLASTOMA: PRELIMINARY RESULTS

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Purpose: The rationale for studying the combination of bevacizumab plus irinotecan and temozolomide (BIT) is based on: (a) Vascular endothelial growth factor (VEGF) expression is associated with aggressive phenotype in neuroblastoma. (b) Anti-VEGF antibody bevacizumab enhances irinotecan-mediated suppression of neuroblastoma xenografts. (c) Irinotecan + temozolomide is a standard salvage chemotherapy for NB. (d) Bevacizumab is associated with aggressive phenotype in neuroblastoma. (e) Anti-VEGF antibody bevacizumab enhances irinotecan-mediated suppression of neuroblastoma xenografts. (f) Irinotecan + temozolomide is a standard salvage chemotherapy for NB. (g) Bevacizumab enhances irinotecan-mediated suppression of neuroblastoma xenografts.

Methods: Preliminary results from this first study of BIT in neuroblastoma do not indicate a major improvement in response rates for relapsed or refractory neuroblastoma compared to historical data for irinotecan + temozolomide (JCO 24:5271, 2006). The study is ongoing.

PH024
LATE OUTCOMES IN SURVIVORS OF HIGH-RISK NEUROBLASTOMA

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Purpose: To determine the prevalence of adverse late outcomes in survivors of aggressive chemotherapy, surgery and radiation treatment for high risk neuroblastoma (HR NBL).

Methods: Retrospective analysis of serially treated patients with high risk neuroblastoma undergoing high-dose therapy with stem cell rescue (HDTSCR) at a single institution. All patients completed treatment with aggressive chemotherapy, radiation, surgery and consolidation HDTSCR during a 13-year period; most patients received a regimen that included tandem HDT-SCR and total body irradiation (TBI). All eligible patients were alive without relapse at one year after completion of neuroblastoma therapy. Clinical records were systematically reviewed.

Results: Fifty-one eligible patients, with a median time from completion of therapy of 6.1 years (range 1.0–15.2 years), were identified. A high prevalence of late sequelae was noted, including ovarian failure (observed in 9 of 12 girls whose current age is >13 yo) and hearing loss in 58 of 51 patients, as well as dental disease, echocardiographic abnormalities, scoliosis and educational special needs. Height was significantly impacted both in TBI-treated and non-TBI treated patients; seven patients received recombinant growth hormone therapy. 59% of patients required treatment for hypothyroidism, and hypothyroidism continued to occur with longer follow-up. In these 51 patients who had at least one year of follow-up without relapse after completion of neuroblastoma therapy, there were 9 later relapses. Three patients developed secondary cancers. There were seven deaths occurring one year or more after HDT/SCR, all of them from progression of NBL.

Conclusion: There is a high prevalence of clinically significant late effects in survivors of high risk neuroblastoma. Newer therapies, which have eliminated total body irradiation as a component of therapy, may decrease the risks of some late effects, but follow-up studies are indicated in this high-risk group.

PH025
DISTINCT METASTATIC PATTERNS IN NEUROBLASTOMA ARE CORRELATED WITH MYCN AMPLIFICATION

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Purpose: MycN amplification is associated with aggressive phenotype in neuroblastoma. It is correlated with higher metastatic rate and higher risk of death for patients with advanced neuroblastoma.

Methods: A phase II study was conducted to analyze distinct metastatic patterns in neuroblastoma patients and to correlate these patterns with MycN amplification.

Results: The metastatic rate in neuroblastoma patients with MycN amplification was higher than in those without amplification. The most common metastatic sites were liver, lung and bone.

Conclusion: Distinct metastatic patterns in neuroblastoma are correlated with MycN amplification.
Conclusion: In both the European and the COG cohort two patterns of metastasis can be discriminated in stage 4 neuroblastomas: a 'focal-limited' pattern in MYCN amplified cases and a 'diffuse-extensive' pattern in MYCN non-amplified patients.

PH026
EVALUATION OF SURGICAL RISK FACTORS INCLUDING IMAGE DEFINED RISK FACTORS FOR LOCALIZED NEUROBLASTOMA
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Purpose: Surgery is usually the main therapeutic tool for localized neuroblastoma. Therefore, treatment complications may be minimized by avoiding surgical complications. Image defined risk factors (IDRF) have been proposed for neuroblastoma. This study retrospectively evaluated the surgical risk factors including IDRF for localized neuroblastoma in order to minimize surgical risks.

Methods: Localized neuroblastomas diagnosed between 1991 and 2009 were entered in this study. Sixty-four patients who underwent surgery including biopsy were selected. Patients with or without surgical complications were divided into group A or group B, respectively. The study evaluated: age at diagnosis, detection by mass screening, primary tumor site, metastases, and lymph node involvement. IDRF, INSS, initial treatment, biology, histology (INPC). The Chi-square test and a logistic test were used the statistical analysis.

Results: There were 18 and 46 patients in group A and B, respectively. Major surgical complications included kidney problems (resection, atrophy, and infarction) in 6 cases, injury of major vessels in 3 cases, residual tumor regrowth in 3 cases. In univariate analysis, the surgical risks were significantly associated with non-stage 1 (group A: 16/18, group B: 25/46), delayed primary surgery (7/18, 6/46), older patients (mean age of month: group A: 17.7, group B: 9.7), diploid/tetraploid (7/18, 5/46). Positive IDRF (8/18, 12/46) was not a significant factor but have a tendency to associate with surgical complication. In multivariate analysis, the surgical risks were significantly associated only with non-stage 1 (Odds ratio: 10.13) and diploid/tetraploid (Odds ratio: 10.20). There were no deaths in group A, while 2 patients in group B died (one with disease, one without disease).

Conclusion: Surgical complications were observed in 28% of localized neuroblastoma patients. Most frequently observed complications were associated with the kidneys. In univariate analysis, non-stage 1, delayed primary operation, older patients, diploid/tetraploid were significantly associated with surgical complications, while in multivariate analysis, only non-stage 1 and diploid/tetraploid remained significant.

PH027
NEUROBLASTOMA IN OLDER CHILDREN, ADOLESCENTS AND YOUNG ADULTS: A REPORT FROM THE INTERNATIONAL NEUROBLASTOMA RISK GROUP PROJECT
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Purpose: Neuroblastoma in older children and adolescents has been reported to have an indolent phenotype and poor outcome, but little is known about the clinical and biological characteristics that distinguish this rare subgroup. We sought to determine if an optimal age cut-off exists that defines indolent disease and if currently accepted prognostic factors and treatment approaches for young patients are applicable to older children.

Methods: Using data from the International Neuroblastoma Risk Group, among patients >18 months old (n = 4,027), monthly age cut-offs were tested to determine the effect of age on survival. The prognostic effect of baseline characteristics and autologous hematopoietic cell transplant (AHCT) for advanced disease was assessed within two age cohorts: ≥5 to <10 years (n = 730) and ≥10 years (n = 200).

Results: Older age was prognostic of poor survival, with outcome gradually worsening with increasing age at diagnosis, without statistical evidence for an optimal age cut-off ≥18 months. Among patients ≥5 years, factors significantly prognostic of lower event-free survival (EFS) and overall survival (OS) in multivariable analyses were INSS stage 4, MYCN amplification and unfavorable Shimada histology classification. Among stage 4 patients, AHCT provided a significant EFS and OS benefit. Following relapse, patients in both older cohorts had prolonged OS compared to those ≥18 months <5 years (p < 0.0001).

Conclusion: Despite indolent disease and infrequent MYCN amplification, older children and adolescents with advanced disease have poor survival, without evidence for a specific age cut-off. Future data suggest that AHCT may provide a survival benefit in older patients with advanced disease. Novel and consistent therapeutic approaches are required to more effectively treat these patients.

PH028
MOLECULAR RADIOThERAPY WITH MATIN: JODINE-131 META-IODOBENZYLGLUANIDINE AND TOPotecan IN NEUROBLASTOMA. A SIOPEN STUDY
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Purpose: To evaluate the toxicity and long term outcomes following molecular radiotherapy with MATIN, a schedule of Jodine-131 meta-iodobenzylguanidine (131I-mIBG) and topotecan in neuroblastoma in a European multi-centre setting. It incorporates higher than conventional administered activities of 131I-mIBG, given with topotecan as a radiosensitiser, and autologous haemopoietic support.

Methods: Patients with refractory high-risk neuroblastoma, or disease which had relapsed following myeloablative therapy (MAT), were eligible if stem cells were available. MATIN delivers two administrations of 131I-mIBG prescribed to give a whole body radiation dose of 4 Gy, with concomitant topotecan. Autologous stem cells were returned around two weeks after the second mIBG administration.

Results: Patients: MATIN has been used 5 European centres in 69 patients with neuroblastoma. 44 male, 25 female, median age 6 years. 46 patients had refractory or progressive disease without prior MAT, 23 had relapsed after MAT Toxicity. In 2 patients, full treatment was not given because of adverse events. There was 1 treatment-related death. 5 patients failed to regain normal platelet counts. Further therapy: In 61% of refractory patients, further potentially curative treatment including MAT was delivered. In six patients, repeat MATIN was given. Survival: For all patients, three year event free survival (EFS) was 0.16 (± 0.05) and overall survival (OS) was 0.26 ± 0.05. For patients without prior MAT, EFS and OS were 0.25 (± 0.07) and 0.37 (± 0.09). For relapsed patients, EFS was 0 and OS 0.07 (± 0.07). These differences are statistically significant (p < 0.002).

Conclusion: Patients with metastatic neuroblastoma who respond poorly to induction chemotherapy have a poor prognosis; those who relapse following MAT have a worse outcome. The MATIN schedule is safe. In poor responders, MATIN enabled further, potentially curative, treatment to be given resulting in encouraging survival rates. MATIN will be further evaluated in a SIOPEN randomised trial.
PH029

FACTORS ASSOCIATED WITH RECURRENTNESS AND LENGTH OF SURVIVAL FOLLOWING RELAPSE IN PATIENTS WITH NEUROBLASTOMA: A PILOT STUDY

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Purpose: Despite advances in therapy for neuroblastoma, survival from high risk disease is poor. This UK based study aimed to investigate epidemiological, clinical and biological factors associated with recurrence and length of survival following relapse in neuroblastoma to compare with a recent international study (Nakagawa et al. 2011:29:3286–3290).

Methods: All cases of relapsed neuroblastoma diagnosed from 1990 to 2010 were identified from two specialist tumour registries. Kaplan–Meier survival analyses were used to calculate the median overall survival time from diagnosis and post relapse overall survival. Log rank tests and Cox regression analyses were used to investigate survival.

Results: 82 cases of relapsed neuroblastoma were identified for analyses. The median age at diagnosis was 2.9 years (range 0.1–19), 72 cases had stage 4 disease at diagnosis and 8 had stage 3 (2 unknown). MYCN status was known for 61 cases, 22 were MYCN amplified, 39 were non-MYCN amplified, and 18 status was not known for 30 cases, 18 had ip deleted tumours. 12 were normal. Median overall survival (OS), from time of diagnosis, was 23 months and median post relapse survival (PRS) 4 months. MYCN amplified disease was associated with worse OS 15 months (95% CI 10.0–28.5) vs 28 months (95% CI 24.5–39.4) (P < 0.0006) for non-amplified cases and worse PRS, 2 months (95% CI 1.05–4.40) vs 9 months for non-amplified cases (95% CI 4.23–12.74) (P < 0.001). Cox univariate analysis showed PRS was worse for MYCN amplified cases (P < 0.0001), for 1p deleted cases (P = 0.01), for stage 4 disease (P < 0.0001) but not age at diagnosis (<18 months vs >18 months) or time to relapse from diagnosis (>6 months vs ≤6 months).

Conclusion: This preliminary analysis from the UK confirms that relapsed neuroblastoma cases have worse survival for MYCN amplified and stage 4 cases, but also 1p deleted cases. We are currently obtaining more cases from two other centres for a further analysis.

PH030

A RETROSPECTIVE ANALYSIS OF PROGNOSTIC FACTORS FOR SURVIVAL IN PATIENTS WITH HIGH-RISK NEUROBLASTOMA AFTER 1ST RECURRENCE: A REPORT FROM THE JAPAN NEUROBLASTOMA STUDY GROUP

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Purpose: We aimed to identify prognostic factors predicting long-term survival in patients with high-risk neuroblastoma after 1st recurrence.

Methods: A retrospective study was performed in patients classified to COG high-risk category with 1st recurrent neuroblastoma. Analysis was performed on clinical characteristics at initial diagnosis and recurrence and treatment. Patients were diagnosed during from 2002 to 2008 and treated in institutes participating in Japan Neuroblastoma Study Group.

Results: Fifty-two patients were reported from 32 institutes. Mean age at initial presentation was 42 months (SD: 18 months) and median duration from the onset to 1st recurrence was 19 months (7–65 months). The 4-year overall survival (OS) of the time of 1st recurrence was 12.1% ± 6.3%. The OS for patients without bone recurrence was significantly higher than those with it; the 4-year OS was 28.9% ± 13.4% versus 0% (P = 0.035). Bone marrow recurrence, the duration of 1st CR, NMYC status or the site of metastasis at presentation was not related to the time of survival after 1st recurrence. Allogeneic stem cell transplantation (SCT) was performed in 22 patients after 1st recurrence. A marginal benefit of SCT was observed. 4-year OS was 28.7% vs 12.9% and 0% for patients who underwent SCT and did not, respectively (P = 0.060). Recurrence sites in all patients in continuous 2nd CR longer than 12 months (18, 23, 64 and 69 months) were local tumor sites, lymph nodes or brain. Multivariate Cox regression identified the bone recurrence as a significant prognostic factor for shorter survival after the 1st recurrence.

Conclusion: Relatively longer survival after the 1st recurrence may be anticipated in high-risk patients with recurrences at sites other than bone.

PH031

A PROSPECTIVE STUDY OF EXPECTANT OBSERVATION AS PRIMARY THERAPY FOR NEUROBLASTOMA IN YOUNG INFANTS, A CHILDREN’S ONCOLOGY GROUP STUDY

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Purpose: Neuroblastoma is the most common malignant tumor in infants, and in young infants, 90% are located in the adrenal gland. Although surgical resection is standard therapy, multiple observations suggest that expectant observation could be a safe alternative. The purpose of this study was to demonstrate that expectant observation of young infants with adrenal masses would result in excellent overall and event-free survival (OS and EFS).

Methods: A prospective study of infants less than six months of age with small adrenal masses and no evidence of spread beyond the primary tumor was performed at all participating Children’s Oncology Group institutions. Parents could choose observation or immediate surgical resection. Serial abdominal sonograms and urinary VMA and HVA measurements were performed over a ninety-week interval. Infants experiencing a 50% increase in the volume of the mass or urine catecholamine values, or an increase in the HVA/VMA ratio > 2 were referred for surgical resection.

Results: 87 patients were enrolled, 83 elected observation and 4 chose immediate surgery. 16 observation patients ultimately had surgery; 8 had INSS stage 1 neuroblastoma, 2 had higher stage neuroblastoma (2B and 4S), 2 had low grade adrenocortical neoplasm, 2 had adrenal hemorrhage and 2 had extralobar pulmonary sequestration. Nine of the neuroblastoma patients had signs of tumor growth or progressive disease and one patient underwent resection at the request of the parents. The two patients with adrenocortical tumors were resected for > 50% increase in tumor volume. The 3 year EFS for a neuroblastoma event was 97.7 ± 2.3%. The overall survival was 100% with median follow-up of 2.9 years. 81% of patients on the observation arm were spared surgery.

Conclusion: Expectant observation of infants with small adrenal masses led to excellent EFS and OS while avoiding surgical intervention in a large majority of the patients.

PH032

MINIMALLY INVASIVE SURGERY IN NEUROGENIC TUMORS IN CHILDREN: INDICATIONS ARE DEPENDINg ON LOCATIONS AND IDDRFs

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Purpose: To determine the indications and limits of minimally invasive surgery (MIS) in neurogenic tumors according to tumor location and image-defined risk factors (IDDRFs).

Methods: From 2006 to 2012, 43169 (25%) patients underwent MIS for treatment of neurogenic tumors using thoracoscopic (n = 20), laparoscopic (n = 1) or robotic approaches (n = 22). Tumors locations were paravertebral (n = 20), psoas (n = 6), adrenal (n = 16) and pelvic (n = 1). Tumor was retrospectively classified as L1 in 26 patients (including 3M and 1Ms) and L2 in 17 (including 4M, 2Ms). Ten patients (6 M, 1 Ms, 3 L2) received preoperative chemotherapy according to the running protocols. In 3 patients, surgery was performed for a relapse. Mean tumor height was 36 mm for thoracic tumors [7–65] and 33 mm for abdominal [10–75]. Mean follow-up was 21 months [1–112].

Results: IO resection was achieved in 19 patients, R1 in 17 (4 thoracic and 3 abdominal) and R2 in 7 cases (3 ganglioneuroma or intermixed ganglioneuroblastoma, 2 durnbbells and 2 biopsies). Conversion occurred in 3 psoas thoracic L2 tumors and 1 abdominal L1 tumor (cotticosurrenaloma aspect). Postoperative complications were chylothorax in 2 L1 and 1 L2 paravertebral thoracic lesions, Horner sign in a psoas tumor and renal artery spasm leading to renal atrophy in one L2 renal pedicle located tumor. Adrenal and abdominal masses were resected in 1 patient. Conversion was performed in 1 patient with chylothorax and 1 with Horner sign.
paravertebral locations had no complications. Overall survival was 100% with only one bone recurrence in a M patient.

Conclusion: This study demonstrated that MIS allows safe and carcinologic resection of neurogenic tumors in children not only in adrenal and thoracic paravertebral lesions but also in other locations (except perivascular median lesions). In tumors non-sensitive to chemotherapy, the presence of some IBRFs does not exclude MIS approaches. In all cases, conversion should be considered if organ or vascular control and/or quality of resection are compromised.

PH033
LONG TERM COMPLICATIONS IN CHILDREN TREATED FOR ADVANCED NEUROBLASTOMA
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Purpose: Advanced neuroblastoma (stage 3 and 4) requires aggressive treatment, including surgery, chemotherapy and radiotherapy and autologous bone marrow transplantation. Although long term survival rates are disappointing, those children who survive are prone to develop long term complications. Our aim is to report the long term complications rate and quality in children treated for stage 3 and 4 neuroblastoma.

Methods: The charts of stage 3 and 4 children with neuroblastoma treated from January/1983 through October/2003 were reviewed and those surviving and with no evidence of disease for more than 5 years were selected. Late effects were classified as second malignancies, endocrinological, neuromotor, hepatic, sensorial, benign tumors, infectious diseases and psychiatric disease and others. Associations with treatment modalities were disclosed.

Results: Among 263 children with stage 3 and 4 neuroblastoma, 40 (15%) are long term survivors. 2040 (50%) present one or more complications, being 2 (10%) second malignant neoplasia, 4 (20%) endocrinological disturbances, 4 (20%) neuromotor, 5 (25%) hepatic, 4 (20%) sensorial, 3 (1.1%) benign tumors, and infertility, psychiatric disease and hepatitis C infection in 5 (1%) episode each. 10/20 (50%) of the children were less than 18 months at diagnosis, and 12/20 (60%) were stage 3 and 8/20 (40%) were stage 4. All children were submitted to chemotherapy and 7/20 (35%) to autologous bone marrow transplantation. In 10/20 (50%) patients radiotherapy was also included, and 4/10 (40%) presented functional lesions in the irradiated field. All endocrinologic sequelae were detected in the ABMT group. Second malignant neoplasia were not related to RTD (1 ALL and 1 thyroid carcinoma).

Conclusion: Children surviving aggressive therapy for neuroblastoma are at risk of late effects, particularly endocrinological and neurological complications, requiring close observation to prompt intervention when necessary, avoiding impairments in quality of life or even life threatening situations. Second malignant neoplasia require special concern.

PH034
RENAL TUMOURS IN ADOLESCENTS AND ADULTS: A RETROSPECTIVE ANALYSIS OF PATIENTS TREATED ACCORDING TO SIOP PROTOCOLS IN GERMANY
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Purpose: From 1993 to 2011, the Renal Tumour Study Centre in Germany registered 81 patients with renal tumours older than 15 years of age. They were uniformly treated according to SIOP paediatric Wilms tumour (WT) protocols or the adapted adult WT guidelines. Our intention was to identify risk factors for outcome in this patient cohort. Special emphasis was given to patients with metastatic disease. During the same time period 590 patients were diagnosed being younger than 15 years.

Methods: We retrospectively analysed WT patients, treated in 53 different German hospitals.

for data collection the same forms were used as in children.

Results: Patient’s age ranged from 15 to 62 years with a median age of 20 years. 58 patients were primarily operated, 23 received pre-operative chemotherapy. Median time to start correct treatment after diagnosis was 3 days (0–64 d). Out of 81 patients 61 patients were scheduled with WT and 20 with renal tumours of other histology. In the WT cohort 19 patients had metastases at diagnosis. This rate is higher than in patients below 15 years (31% vs. 17%; p < 0.005). Local stage distribution was: 36% stage I, 19% stage II, and 45% stage III. There was no difference in overall survival of non-metastatic adult WT compared to stage IV in children (5-year OS: 85% vs. 80%; p = 0.396). Stage IV adult WT patients did worse than younger (5-year OS: 48% vs. 80%; p < 0.001).

Conclusion: Our data show that non-metastatic WT in adolescents and adults do have a similar prognosis as those at younger age. This is not the case for stage IV patients. The reason for this is unclear. We strongly recommend that adolescents and adults with WT should be treated within prospective clinical trials including molecular genetic analysis of biomaterials in order to get a better insight into these rare tumours.

PH035
TREATMENT OF WILMS TUMOR (WT) WITHIN THE CENTRAL AMERICAN ASSOCIATION OF PEDIATRIC HEMATOLOGY/Oncology (AHOPCA): REPORT FROM GUATEMALA, HONDURAS, EL SALVADOR, AND NICARAGUA: IMPROVING RESULTS BY CHANGING STRATEGY NOT THERAPY
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Purpose: Since 2000 AHOPCA based their WT therapy on NWTS-4. Since inception of the protocol the WT group has been refining their strategy, to continuously improve the outcome of children that commonly present with large masses and in poor clinical condition.

Methods: When the protocol opened each physician applied the therapy as best he could without external consultation; all patient characteristics, outcome, and follow up data where prospectively entered in a Web-based database shared by all the countries (POND). In 2005 analysis of the data revealed the challenges faced by each and the group decided to implement some quality improvement strategies: data quality control, monthly web-based conferences to discuss difficult cases within the group and with international colleagues, and designation of local principal investigators to lead discussions and monitor adherence to protocol, within a formal AHOPCA WT Working Group. In 2010 improvement in outcome and careful data analysis lead to further refine strategies: systematic selection of patients that would benefit of primary chemotherapy, definition of radiation field according to clinical and surgical findings and emphasis on the surgeons to perform adequate staging; conferences were scheduled weekly to encourage discussion of (hopefully all) cases.

Results: Between 2000 and 2004, 138 newly diagnosed patients with WT were diagnosed and treated and between 2005 and 2011, 251 patients. The abandonment rate dropped from 20% (first era) to 14% (second era). For patients that did not abandon 3-year EFS was 63% (SE, 4.5%) in the first and 72% (SE, 3.5%) in the second era.

Conclusion: Improvement of outcome was achieved through protocol therapy, detailed attention to data collection and analysis and critical discussion of cases, rather than change in therapy. Areas to improve: involvement of radiation therapists and timely access to radiotherapy, central pathology review, systematic surgical staging, prevention of abandonment and early diagnosis.

PH036
TREATMENT OF NEPHROBLASTOMA IN AFRICA: WHICH ONE AND AT WHAT COST?
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Purpose: Nephroblastoma or Wilms tumour (WT) is one of the most common childhood cancers on the African continent and relatively easy to diagnose and treat. Despite the existence of two widely used protocols (SIOP and COG), there is a need for specific protocols for the management of WTs in Africa adapted to the context as well as its cost. The aim of the study was to assess the burden of WT in Africa, formulate an adapted protocol and to calculate the cost of its treatment, based on South African experience.

Methods: An analysis of the distribution of childhood malignancies in Africa and of the cost.

Results: WT is the 4th most common malignancy pediatric tumor in South Africa (SA) comprising 12.3% of all malignant tumors. It is the 2nd most common cancer in children in Ivory Coast (14.7%) and Eastern part of Uganda, and varies between the 2nd and 4th most common cancers on the African continent and relatively easy to diagnose and treat. Despite the.

Conclusion: The cost of treatment (chemotherapy only) is $400 for Stage 1 (2 drugs, 4–6 weeks), $750 for stage 2 and 3 (2 drugs, 27 weeks) and just under $1000 for 3 drugs.

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Conclusion: The mortality due to WT remains high in Africa due to advanced disease at presentation, lack of adapted protocols and supportive care. There is a need for closer collaboration between countries and centers in order to produce adapted guidelines for diagnosis and treatment of WT in Africa.

PH037
TREATMENT OF NEPHROBLASTOMA IN SENEGAL
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Purpose: Nephroblastoma is a frequent cancer in Africa. In Senegal with protocols initiated by the FAPOGO, we developed a program intending to treat children with cancer. For Wilms tumor, our main objective is to evaluate the feasibility of adapted SIOP-2001 regimen in an African setting.

Methods: Adaptation regards: low risks are treated according to the intermediate risk regimen. In stage I-IV CCR and I ACT additional doses are given and stages beyond I receive the VCR, ACT, ADRIA, reference regimen. Patients less than 18 years and more than 6 months, with a diagnosis of unilateral nephroblastoma based are included. Patients whose general conditions do not allow chemotherapy and patients having received significant treatment before admission to the unit are excluded. Unfavorable anaplastic or predominant blastemal nephroblastoma.

Results: From April 1, 2005 to March 31, 2008, 53 patients were included; 9 excluded initially (5 for poor general status at diagnosis died before surgery; 1 refused treatment and 1 was treated earlier for lymphoma, 2 patients with bilateral nephroblastoma). Six patients were secondarily excluded, all of them with predominant blastemal nephroblastoma. Thus, 35 cases were retained for this study. Thirty-three had localized nephroblastoma and 3 had a metastatic disease. Median age was 3 years and 9 months and the sex ratio was 0.62. All children had an abdominal mass. The clinical diagnosis and that of disease extent was based on an abdominal ultrasound and a chest X-ray. Overall survival was 74.3%. Two of the 3 children with metastatic disease died. Four patients were lost to follow up and 5 died.

Conclusion: These preliminary results must be considered as encouraging and demonstrate the feasibility of such studies in developing countries. However, we must improve the level of precision of the surgical and anatopathological summaries, and make radiotherapy available to the patients at stage III.

PH038
EPIDEMIOLOGIC AND CLINICAL CHARACTERISTICS OF WILMS TUMOR IN MEXICO: EXPERIENCE AT INSTITUTO NACIONAL DE PEDIATRÍA
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Purpose: Wilms Tumor is the most common malignant renal tumor in children and the classical paradigm of biological diversity. To inform the clinical and epidemiologic findings and the prognostic factors affecting the disease-free survival (DFS).

Methods: Retrospective, longitudinal and clinical study, performed from Jan/1980–Dec/1990, 119 patients younger than 18 years were included.

Results: Sixty-three (53%) were female and fifty-six (47%) were male. Median age at diagnosis of unilateral tumors (92.4%) was 36 months and 23 months for bilateral tumors (7.6%). The more frequent clinical presentation was an asymptomatic abdominal mass incidentally noted, abdominal pain and fever, other symptoms less frequent were weight loss, macroscopic hematuria, vomiting and hypertension. Thirty-three patients (27.7%) had some congenital malformation; genitourinary anomalies were the most frequent (45.4%). Only 6% had some genetic syndrome associated as aniridia and hemihypertrophy. Eighteen percent (15.3%) of patients had metastases at diagnosis, pulmonary and hepatic were the most frequent. 8.7% were E-I (85% 5y-DFS), 77.5% E-II (81.5% 5y-DFS), 15.9% E-III (62.5% 5y-DFS), 26% E-IV (66.6% 5y-DFS) and 11.5% E-V (60% 5y-SLE), anaplastic histology was the most important prognostic marker. The long-term late effects were secondary use to radiotherapy, mainly muscle-skeletal hipoplasia. No second malignancies were seen.

Conclusion: As in pediatric oncology centers in the world, at our hospital, on the last decades, has had a progressive improvement in duration of survival in children with Wilms tumor which has been the result of important advances in the treatment, new surgical techniques and chemotherapy-radiotherapy regimens designed to give less therapy to patients with early stage disease and more aggressive therapy to children with more advanced disease in an attempt to decrease morbidity, mortality and secondary late effects.

PH039
OUTCOMES OF WILMS TUMOUR IN INDIA: FINDINGS FROM A SYSTEMATIC ANALYSIS
Pediatr Blood Cancer DOI 10.1002/pbc

Conclusion: Understanding of the outcomes of children with Wilms tumour in India is limited by the lack of published and multi-centre studies and heterogeneity of available data. Nevertheless based on published and grey literature the survival of children with Wilms tumour in India is modest with an unacceptably high relapse and abandonment rate. Neo-adjuvant chemotherapy rather than the upfront surgery may have benefit in resource limited setup although this needs further research. A large multicentre study adhering to appropriate staging, surgery, treatment protocol and outcome monitoring is the way forward.

PH040
WOULD FURTHER REFINEMENT IN MANAGEMENT OF WILMS TUMOR HAVE AN IMPACT ON OUTCOME?
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Purpose: Outcome of patients with Wilms tumor has improved as a result of advances in chemotherapy, surgical management, radiotherapy. We previously reported 5 year survival of 86.7% for immediate nephrectomy compared to 52.2% for delayed nephrectomy (P = 0.025). The latter group experienced higher relapse rate (P = 0.003). To study the impact of implementing a local institutional protocol following the SIOP risk stratification based on stage and histological response.

Methods: We reviewed data between 2 eras (1986–2004) when UK and NWTS regimens were used and (2005–2012) when we switched to SIOP 2001 and implemented our local protocol. Data collected included: age, sex, stage, histology, histological response, pre-operative chemotherapy, regimen used, and outcome.

Results: Thirty-one (31) patients registered in 2nd era, M:F 1:2.3, mean age 3 yr (0.1–9.5), stage 1 (12), stage 2 (5), stage 3 (6), stage 4 (7), stage 5 (1), histological risk (LR 2, IR 23, and HR 6), FH (26), UH (5), IV and renal thrombus reported in 6 (19%), early nephrectomy 17 (55%), delayed nephrectomy 14 (45%). Pre-operative chemotherapy 2 drugs (6), 3 drugs (8), Regimens used; Reg.1 with 2 drugs (10), Reg. 2 (3), Reg. AVD (11), and High risk with 4 drugs (7). Local and pulmonary radiotherapy given to 1/3 (12%). Relapse was local in 4/51 (13%) and one patient had pulmonary relapse. Comparing patients between both the EFS improved from 72 to 84% and OS fr 78% to 87% in 2nd era. Incidence of relapse declined from 21% to 13%. OS for patients with delayed nephrectomy improved from 52% to 86%.

Conclusion: Risk stratification based on stage and histological response in addition to implementation of a local institutional protocol resulted in improved survival. This improvement included patients with delayed nephrectomy. This suggests that upgrading patients with poor histological response and patients with delayed nephrectomy positively impacted outcome.

References

PH041
PATIENTS WITH NEPHROBLASTOMA TREATED WITH SIOP 2001 PROTOCOL IN NATIONAL HOSPITAL OF PEDIATRICS, HANOI, VIETNAM
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Purpose: Published literature on Wilms tumour from India is scant. A comprehensive review of published and grey literature was conducted to delineate the current management and outcome of children with Wilms tumour in India. Methods: A literature search of Medline and Embase using appropriate key words was done. The search was limited to studies published from 2000 onwards. Abstracts presented at SIOP and ASCO Annual Congresses (2000–2011) were hand-searched.

Results: Initial search identified 331 studies of which 9 single-centre studies (2 papers and 7 abstracts) from 8 centres met the inclusion criteria for the review. There were a total of 466 patients (20–118 patients) and heterogeneity in clinical features and staging among the studies were noted. Similarly there was heterogeneity in treatment approaches with both upfront surgery (NWTS approach) and neo-adjuvant chemotherapy (SIOP UKCCSG approach) being used and the use of upfront surgery were prevalent in most of the centres. Intraoperative spill of tumour was more likely when upfront surgery was used although the reliability of this conclusion is limited by the data available. The disease free survival ranged from 44 to 77% at 5 year. Reported relapse ranged from 5 to 30% (5–15% in centres which used neo-adjuvant chemotherapy and 15–30% which used upfront surgery). Abandonment rates, where reported, ranged from 4 to 37%.

Conclusion: These preliminary results must be considered as encouraging and demonstrate the feasibility of such studies in developing countries. However, we must improve the level of precision of the surgical and anatopathological summaries, and make radiotherapy available to the patients at stage III.
1062 SIOP ABSTRACTS

Purpose: In NHP, we used NWTS 5 and later SIOP 2001 protocols for the treatment of patients with nephroblastoma. Our aim is to estimate the outcome of SIOP 2001 protocol and ability to apply it in our condition.

Methods: All patients who are eligible to SIOP 2001 inclusion criteria will be enrolled to the study. All patients with stage II, intermediate risk treated with AV2 regimen without doxorubicin and radiotherapy (no randomization).

Results: From July 2008 to November 2011, we had 56 patients eligible for enrollment on SIOP 2001 protocol. 5 patients had immediate operation (2 with tumor rupture; 3 had imaging diagnosis other than nephroblastoma) and their definitive diagnosis was nephroblastoma. 51 patients had preoperative chemotherapy: 2 abandoned of treatment, 4 died (7.8%), 45 patients had been operated. The diagnosis of nephroblastoma was confirmed in 37 patients. For the 37 patients, their pretreatment staging were: 34 stages III, 2 stage IVa and 1 stage V; the postoperative staging were: 14 stage I, 1 stage II and 7 stage III. In total we had 42 patients with nephroblastoma, diagnosis confirmed by pathological anatomy. Up to February 2012, 2 patients died. 2 relapsed and 1 abandoned of preoperative chemotherapy and radiotherapy. There are 87.8% of patients in EFS (follow up time ranging from 3 to 42 months, mean time 19 months).

Conclusion: In NHP protocol SIOP 2001 can be applied and had so far good outcome and long term follow up is required to estimate the result of treatment.

PH042

BILATERAL WILMS TUMOR (BWT): ONE CENTER EXPERIENCE

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Purpose: Wilms tumor (WT) is the most common primary malignant renal neoplasm in children with established risk based treatment and excellent outcome. Management of BWT is more challenging, focused on the eradication of tumor and preservation of renal function. We present our experience with such cases.

Methods: Retrospective analysis of 24 patients (out of 179 patients with WT; 23 synchronous, 1 metachronous – 2 yrs 8m from 1st diagnosis), 15 girls and 9 boys, aged 6 months-5.5 years (median 1yr 8m) treated between 1997 and 2011 was performed. All patients were treated with preoperative chemotherapy. Type of preoperative chemotherapy: 2 drug ACTD, VCR or 3 drug ACTD, VCR, DOXO and its duration depended on tumor response. Post surgical treatment was carried out according to disease stage and histology. Treatment, tumor histology and outcomes were analyzed.

Results: Pre-resection chemotherapy with ACTDT, VCR was administered to 1 patient, the remaining 23 patients required 3 drug chemotherapy (ACTDT, VCR, DOXO) to decrease tumor volume. The median duration of preoperative chemotherapy was 3 months. 36 kidneys in 23 patients were managed with delayed resection: 12 complete unilateral nephrectomies, 3 partial nephrectomies and 9 tumor enucleations in 17 patients were performed; 6 pts had unsresponsive to chemotherapy, progressive tumors and underwent bilateral nephrectomies. One patient was treated with chemotherapy alone. Tumor histology was as follows: standard risk 17 pts, intermediate risk 6 pts (2 diffuse anaplasia, 4 blastemal type). Twenty out of 24 patients are alive with a median follow up of 9 years, 3 of them after bilateral nephrectomies (1 with transplanted kidney, 2 awaiting for kidney transplantation). Four patients died, 3 of disseminated disease – all with unfavorable histology, 1 of dialysis complications.

Conclusion: Preoperative chemotherapy is crucial in the management of patients with BWT allowing to perform nephron sparing surgery. Type of chemotherapy and its duration must be adjusted to tumor response. Unresponsive tumors not amendable for resection require radical bilateral nephrectomies.

PH043

FAVORABLE HISTOLOGY WILMS TUMOR: A REVIEW OF 6 YEARS DATA FROM KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE (KFHSRC), RIYADH, SAUDI ARABIA

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Purpose: While reports from developed countries showed excellent survival of patients with favorable histology Wilms tumor, reports from developing countries are still scanty. This study from KFHSRC is to review our experience in this disease.

Methods: From 2005 to 2010, 59 cases of favorable histology Wilms tumor were seen at KFHSRC excluding bilateral disease. 50 (84.7%) were evaluable, 9 excluded for various reasons. Diagnosis established by excision biopsy in 28, open biopsy in 10, FNA 3, Tru Cut biopsy 3, by others in 6. As per National Wilms Tumor Study (NWTS) staging system, 12 (24%) were in stage 1, 6 (12%) stage 2, 20 (40%) stage 3, and 12 (24%) stage 4. Therapy consisted of surgery, radiation and chemotherapy as per NWTS protocol.

Results: Median age at diagnosis was 3.6 years (range: 0.43 -11.96), 33 (66%) were females. 50 were evaluable for response after 1st-line therapy; 48 (96%) in complete remission (CR). 2 (4%) progressive disease (PD). Among 48 in CR, 31.3% relapsed off therapy. Second line chemotherapy ± surgery, ± radiation therapy were given to all relapsed/PD cases, except one relapsed patient who had died. Out of 14 relapse and 2 PD cases, 12 (85.7%) and 1 (50%) achieved CR respectively. At last contact, 44 (88%) of 50 cases were alive and 6 cases were dead. With median follow-up of 3-4yrs, 5 years overall survival (OS) and event-free survival (EFS) for the 50 cases were, 87% and 56.5%. As per stage, the 5-years OS was 90%, 100%, 100% and 96.3% and 4-years EFS was 91.7%, 100%, 74.7% and 17% for stages 1, 2, 3 and 4 respectively (p-value = 0.001, < 0.001).

Conclusion: Compared to NWTS-3, we noticed higher percentage of our patients with stage 3 and 4 disease. However, the rate of relapse in our patients (15/48) 31.2% is comparable to that observed in the SIOP-EFS-3 figure (27%). In the light of presentation, the OS of our patients is still comparable to the Western experience.

PH044

Rhabdoid Tumours of the Kidney: A retrospective analysis of patients treated in Germany

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Purpose: Malignant rhabdoid tumours of the kidney (MRTK) have a dismal prognosis. To identify specific characteristics of this rare tumour type, which may help to diagnose and to treat them better we performed a retrospective analysis of patients with MRTK.

Methods: Between 1993 and 2011 2079 patients with renal tumours were registered within the Renal Tumour Study Centre in Germany. MRTK-patients were treated according to SIOP protocols for high-risk renal tumours in 36 different German hospitals.

Results: 48 MRTK-patients were identified with a median age of 12 months at diagnosis (0–184 months). 13 patients were treated by initial surgery while 35 received pre-operative chemotherapy for 4 weeks using Acto-D and vincristine or 6 weeks in case of metastatic disease with the addition of doxorubicin. 20 patients had metastatic disease, 13 had isolated lung, 3 combined lung and liver, lung and abdomen or lung, mediastinum and extrabdominal lymphnode metastases. 3 had brain and combined soft tissue, bone or subpleural metastases, 1 patient had lymph node involvement. Local stage after surgery was stage I in 5 patients, for stage II and for 32 stage III, in 4 patients data are missing. Out of 48 patients 30 died, 14/16 with initial metastases. Due to the small number of patients 5-year survival was not significantly different between patients with and without initial metastases (EFS: 44% vs. 62%, p < 0.289; OS 20% vs. 42%, p < 0.074).

Conclusion: MRTK-patients are younger, tend to present more commonly with metastatic disease and do worse when compared to other high-risk renal tumours. There is a demanding need to enroll all these patients into prospective trials or registries such as EU-RHAB. This registry is open to all patients with rhabdoid tumours independent of tumour location. Basic research is fundamental for the elucidation of new targets a subsequently improved treatment options.

PH045

THE ROLE OF FINE NEEDLE ASPIRATION CYTOTOLOGY IN EVALUATION OF PAEDIATRIC ABDOMINAL MASSES: INDICATIONS, CONTRAINDICATIONS, BENEFITS AND COMPLICATIONS SEEN OVER 8 YEARS AND 276 ASPIRATIONS

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Purpose: Malignant paediatric abdominal masses are amenable to chemotherapy. Early diagnosis of rare variants helps in correct treatment.

Methods: Aspiration cytology performed in paediatric abdominal masses were evaluated for adequacy, diagnosis and complications.

Results: There were 147 renal aspirates (114 Wilms tumor, 7 clear cell sarcoma of kidney, 4 renal cell carcinoma, 1 rhabdoid tumor of kidney and 4 others). 34 liver aspirates (25 hepatoblastoma, 5 hepatocellular carcinoma, 2 undifferentiated embryonal sarcoma and 2 infantile hemangiendothelioma) and 95 aspirates from abdominal masses (38 neuroblastoma, 16 non Hodgkin’s lymphoma, 13 germ cell tumour, 12 non-specific.
malignant round cell tumour, 8 primitive neuroectodermal tumour, and 13 others. There were 14 unsatisfactory aspirates (5.1%) Most aspirations were performed in large palpable masses abutting on the anterior abdominal wall. Aspiration cytology is indicated in all palpable paediatric renal masses under 5 years of age, for diagnosis of rare variants. Careful risk benefit analysis is needed in paediatric renal tumours between 5 and 10 years while it is contraindicated in patients above 10 years since chances of renal cell carcinoma are higher. Small renal tumours requiring ultrasonographic guidance should preferably undergo core needle biopsies. Aspirations are indicated in all retroperitoneal and liver tumours regardless of age, for diagnostic and prognostic tests, before starting chemotherapy.

PD046 LONG-TERM RENAL FUNCTION IN PATIENTS NEPHRECTOMIZED FOR UNILATERAL RENAL TUMOR: CROSS-SECTIONAL STUDY

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Purpose: The aim of this study was to investigate the prevalence of renal dysfunction and the associated risk factors in patients nephrectomized for childhood unilateral renal tumor (RT) and treated following SIOP protocols.

Methods: From 1978, 81 pts with RT were treated following four consecutive SIOP protocols at Pediatric Oncology Unit University ‘Sapienza’ of Rome (22 pts were nephrectomized at another center). Out of 81 pts, 13 (2 RCC and 11 WT) died of disease (EFS 84%), 2 died of accident, 66 are alive without disease. Out of survivors we excluded 13 pts treated with neophron sparing surgery, 3 pts with short term follow-up (<5 yrs) and 1 pt with BWT. Eight pts refused to participate, thus 41 pts were studied with chemistry, kidney ultrasound, blood pressure measurement and urine analysis. The estimated glomerular filtration rate (eGFR) values were calculated by MDRD study equation and Schwartz equation following the KDOQI guidelines. The prevalence of eGFR <90 ml/min/1.73 m² at diagnosis, site, time of follow-up, radiotherapy and chemotherapy were investigated.

Results: Out of 41 pts (25 M/16 F), median age at diagnosis 3.7 yrs (range13–0.1), median follow-up 17 yrs (range 33–5), 14 pts (34%) presented with eGFR < 90 ml/min/1.73 m² and 9 pts (22%) with eGFR < 60 ml/min/1.73 m². Moreover, 1 pt presented with hypertension, 8 pts (19.5%) with proteinuria (>160 mg/L), 5 of these with normal eGFR, 3 pts (7.3%) had ultrasound anomalies. eGFR less than 90 ml/min/1.73/m² resulted associated to the time of follow-up (p = 0.03) and, although not statistically significant, to the left site (p = 0.22).

Conclusion: A subset of pts treated for childhood unilateral RT presents minor renal dysfunction related to the time of follow-up. Prospective follow-up must be planned to assess eventual risk of deterioration of the single kidney function in RT survivors.

PD047 DEFECTS IN THE DNA MISMATCH REPAIR SYSTEM DO NOT CONTRIBUTE TO THE DEVELOPMENT OF CHILDHOOD WILMS TUMORS

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Purpose: Wilms tumor is the most common pediatric renal malignancy. Mutations in different genes like WT1, WTX, CTNNB1, TP53 or epigenetic alterations at locus 11p15 are involved in the pathogenesis of Wilms tumors. However, the majority of Wilms tumors do not harbor aberrations in these known genes, indicating that more insight into other underlying mechanisms is needed to further unravel the biology of the disease. Little is known about the role of defects in the DNA mismatch repair system in the etiology of Wilms tumors.

Methods: To detect mismatch repair deficiency in a full cohort of Wilms tumor patients, we combined immunohistochemistry for the expression of mismatch repair proteins and microsatellite instability (MSI) analysis by a fluorescent multiplex PCR-based assay.

Results: Of the 121 Wilms tumor patients treated between 1987 and 2010 in our institution, 100 were evaluable for MSI analysis, and 2 were considered unsuitable for analysis due to decreased expression of MLH1. Of these 100 patients, 35 (35%) had MSI high (MSI-H) tumors, 57 (57%) had MSI low (MSI-L) tumors, and 8 patients (8%) did not meet the diagnostic criteria for MSI-H or MSI-L tumors. The distribution of MSI-H tumors was similar in four groups classified according to the International Classification of Retinoblastoma (IRSS): 37.8% in group A, 37.9% in group B, 46.6% in group C, 37.9% in group D, and 37.9% in group E. The overall survival rate was 100% in group A (International Classification of retinoblastoma), 70.4% in group B, 46.6% in group C, 37.5% in group D, and 8.0% in group E. The overall survival rate was 98.8%. One patient was cured of CNV metastasis during local therapy. The reasons for early and late emaciation were papillary residual tumors or vitreous bleeding, and refractory or therapy-related complications, respectively.

Conclusion: Reduced cycles of VEC systemic chemotherapy combined with more focused local treatments can achieve an adequate ocular salvage rate.

PD002 IMAGING FEATURES OF CHILDREN WITH EXTRAOCULAR RETINOBLASTOMA (EORB)

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Purpose: Timely diagnosis and initiation of treatment in retinoblastoma is associated with high chances for preservation of vision, globe and disease free survival for the patient. In developing countries like ours, retinoblastoma is often diagnosed at a later stage with intraocular invasion, thus leading to a significantly more mortality and morbidity. Since imaging is a vital diagnostic aid for EORB, we studied the imaging profile of patients presenting with extraocular invasion and correlated this with the post enucleation histopathological features.

Methods: Prospective analysis of imaging features of EORBs (stage III and IV) in 98 children presenting to the pediatric oncology services of our institute over one year. For those eyes which were enucleated after receiving neo-adjuvant chemotherapy, haematoxylin and cosin stained sections were analysed for presence of histopathological high risk features.

Results: Over a period of one year, 98 children with retinoblastoma had presented, among them 37.8% (37/98) were EORB: mean age 3.4 ± 1.7 yrs, 70.3% males, 70.3% unilateral, 86.5% with no family history, 29.7% with metastasis. On imaging, there was isolated extraocular invasion in 21.6% (20/93), isolated invasion of orbital part of optic nerve in 32.4% (31/96), involvement of the central nervous system in 27.9% (27/98), recurrence in anophthalmic socket in 2.7% (3/110) and orbital wall involvement in 2.7% (3/110). On histopathological analysis of enucleated eyes post chemotherapy, all tumours were poorly differentiated and 52.3% had no microscopic residual disease.

Conclusion: There are very few human malignancies where definitive treatment is started without any confirmed pathological diagnosis and imaging is a must to do investigation for appropriate staging before initiation of treatment. A pictorial illustration of the varied imaging profile of EORB is presented. Chemotherapy has a variable effect on EORB, about 50% of eyes with documented extraocular invasion had no residual disease when enucleated after receiving 3–6 cycles of neoadjuvant chemotherapy.
PI003
CRANIO-FACIAL SECOND PRIMARY TUMORS IN RETINOBLASTOMA PATIENTS PREVIOUSLY TREATED BY RADIATION THERAPY: A MULTICENTER CLINICAL AND RADIOLOGICAL STUDY OF 42 PATIENTS
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Purpose: Hereditary retinoblastoma survivors treated with external beam radiation therapy (EBRT) have an increased risk for cranio-facial second primary tumors (SPT). This multicenter retrospective study provides an overview of clinical and imaging findings of cranio-facial SPTs in irradiated retinoblastoma patients.

Methods: Clinical and radiological data of 42 retinoblastoma patients with 44 second and third tumors in 38 cases were reviewed. Radiological data included anatomic location and CT and MR characteristics. Cox regression and likelihood ratio chi-square test were used to evaluate differences in patients’ survival rates.

Results: Cranio-facial SPTs were diagnosed at a median age of 13 years. Histological types included osteosarcoma (43%), thymus carcinoma (6%), RMS (20%) and embryonal, 4% alveolar and other types of SPT (37%). Predilection sites were: temporal fossa (39%), ethmoid sinus (23%), orbit (18%), superior maxillary (16%) and intracranial dura mater (4%). In patients with EBRT performed in the first year of life 78% of osteosarcoma and 80% of RMS occurred. Treatment of SPTs with a microscopically complete resection led to a significant better 5-year overall survival (P = 0.017) and event free survival (P = 0.012) compared to patients treated without surgery or incomplete surgical resection (OS: 83% versus 52%, EFS: 80% versus 47%, respectively).

Conclusion: Osteosarcomas and thymus carinoma are the most common cranio-facial SPTs in irradiated hereditary retinoblastoma patients, which develop in specific locations and occur predominantly in patients irradiated in their first-year of life. Microscopically complete surgical resection is a major prognostic factor, suggesting the potential benefit of early detection by imaging.

PI004
SPORADIC UNILATERAL RETINOBLASTOMA OR FIRST SIGN OF BILATERAL DISEASE?
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Purpose: A small number of children with primary diagnosis of sporadic unilateral retinoblastoma develop later a retinoblastoma in the contralateral eye. It is important to recognize these metachronous tumors early to preserve eyes and vision using adequate treatment and follow-up. This study determines the clinical and genetic characteristics of patients with metachronous bilateral retinoblastoma to identify risk factors present at the time of primary diagnosis.

Methods: Clinical and genetic data of 417 children with initial diagnosis of a sporadic unilateral retinoblastoma and ophthalmological follow-up examinations until age 5 years were retrospectively analyzed.

Results: Twenty-four of 417 children (5.0%) with unilateral retinoblastoma developed later a bilateral retinoblastoma. The tumor in the second eye was diagnosed at a median of age of 1.6 years (range 0.32–16 years). In 20/21 children, the latent period from initial diagnosis to detection of the tumor in the second eye was less than 2.3 years. The genetic cause of tumor development (the causative RB1 mutations) was clarified in 24/24 children: 52 carried a mutation in blood DNA and 194 children showed no concordant mutations in tumor with normal RB1 alleles in blood DNA. All 14/246 (5.7%) children with metachronous bilateral retinoblastoma carried a heterozygous RB1 germ line mutation. For children with germline mutation and primary diagnosis of unilateral retinoblastoma, the risk to develop a metachronous bilateral retinoblastoma is inversely related to age at diagnosis. Eight of 15 patients (53%) with an early age at diagnosis (<0.5 years) developed bilateral disease.

Conclusion: The overall risk for children with germline RB1 mutation to develop a tumor in the other eye is estimated at 26.9% (14/52). By contrast, children without a mutation in blood DNA carry a very low risk for second retinoblastoma (0/194). Early genetic analysis may identify those children at risk and guide treatment decisions and frequency of follow-up examinations.
**SIOP ABSTRACTS**

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**PJ001**

**ROLE OF POLYCOMB PROTEINS EZH2 AND BMI-1 IN PATHOGENESIS OF PEDIATRIC SOLID TUMORS**

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**Purpose:** The polycomb group (PcG) proteins BMI-1 and EZH2 are key regulators of function, in particular those associated with cell fate, self-renewal and ageing. A high repression of downstream genes. Their activity controls numerous aspects of mammalian cell progress, in particular those associated with cell fate, self-renewal and ageing. A high repression of downstream genes. Their activity controls numerous aspects of mammalian cell

**Methods:** We recruited 284 children with retinoblastoma over six years (141 boys and 143 girls); 72 were bilateral at diagnosis, 6 with family history (3 from 1 sibship). Histology was available for 92% and all case presented with advanced disease. Follow up was available for 262 (92%). At the end of the study, 144 were alive, 128 were dead and for 12, the vital status was unknown. At the beginning of the study, therapy involved enucleation and radiotherapy if indicated (cut end of optic nerve positive) and the majority of children died. The introduction of chemotherapy – both neoadjuvant and adjuvant – improved survival substantially with 70% surviving to the end of follow up.

**Conclusion:** Children with retinoblastoma in Uganda present with advanced disease and survival was poor. Marked improvements in survival followed the introduction of chemotherapy.

**PJ002**

**EXPRESSION AND GENOMIC STATUS OF ALK RECEPTOR TYROSINE KINASE IN A MEXICAN INSTITUTION EXPERIENCE IN A MEXICAN INSTITUTION**

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**Purpose:** As part of an investigation of the epidemiology of retinoblastoma in Uganda, we recruited a cohort of children with the tumour from several centres and actively followed them over time to establish outcomes.

**Methods:** We assessed status and function of ALK in 87 RMS tumours and 9 cell lines, by means of quantitative RT-PCR, DNA sequencing, immunohistochemistry and Western blotting, analyzing ALK gene expression, copy number variation and mutational status in association with clinical and molecular features of RMS patients.

**Results:** We demonstrated that PAX-FKHR positive ARMS tumours and cell lines express higher ALK mRNA and protein levels than the PAX-FKHR negative counterpart and that ALK regulates phosphorylation and activity of several growth and survival signalling proteins in RMS cells. Our study indicates that approximately one-third of RMS tumours have high levels of ALK expression, of which 92% are PAX-FKHR-positive ARMS with high disease stage and large tumour size, whereas 68% of PAX-FKHR negative RMS have low ALK expression. ALK transcript levels correlated significantly with primary tumour histology and staging (P < 0.0001), and resulted an unfavourable phenotype feature in RMS, in the absence of mutation and amplification events. When ALK was activated in vitro by agonistic antibodies, multiple signalling pathways were concomitantly induced, including those involved in maintenance of the transformed phenotype.

**Conclusion:** Our study suggests that high ALK mRNA expression can be used to discriminate RMS patients with different outcome, while ALK receptor signalling appears to be important for the oncogenicity of this malignancy.

**PJ003**

**VALIDATION OF SERUM MIR-206 EXPRESSION LEVEL AS A DIAGNOSTIC BIOMARKER FOR RHABDOMYSARCOMA: A REPORT OF THE CHILDREN'S ONCOLOGY GROUP STUDY ARST12B1**

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**Purpose:** Presently there is no established serum biomarker of rhabdomyosarcoma (RMS). We previously showed that a muscle-specific microRNA, miR-206, could be used to differentiate between RMS and non-RMS tumors with a sensitivity of 1.0 and a specificity of 0.913. However, the results were based on only 8 RMS serum specimens. Here, we tested the assay using 30 RMS and 9 non-RMS serum specimens.

**Methods:** Total RNA was extracted from serum samples (200μL) from 39 patients (12 alveolar RMS (ARMS), 16 embryonal RMS (ERMS), 2 unclassified RMS, 9 non-RMS). miRNAs were quantified by real-time quantitative RT-PCR. Both relative and absolute microRNA levels were determined, by normalizing to miR-16 and by using a dilution series of synthetic miR-206, respectively.

**Results:** Serum miR-206 expression levels were higher in RMS patients than in non-RMS patients (p < 0.001) with a sensitivity of 0.733 and a specificity of 1.0 (relative quantification) and 0.889 (absolute quantification). The absolute serum miR-206 expression levels were higher in patients with ARMS than in patients with ERMS (p = 0.023). The serum miR-206 expression levels differentiate between ARMS and non-RMS tumours with a sensitivity of 1.000 and a specificity of 1.000 (relative quantification), and with a sensitivity of 0.917 and a specificity of 0.889 (absolute quantification).
**P1004**

**SARCOMA CELLS MIMIC IMMUNOSUPPRESSIVE MECHANISM OF MESENCHYMAL STEM CELLS BY T CELL INHIBITION IN AN INDOLAMINE 2,3-DIOXYGENASE DEPENDENT MANNER**

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**Purpose:** Tumor-dependent immunomodulation is known to influence treatment outcome even beyond immunotherapy. Yet little is known about immunosuppressive mechanisms in pediatric cancer. Previously we delineated interferon (IFN)-dependent expression of indolamine 2,3-dioxygenase (IDO) as a critical T cell inhibitor mediator in mesenchymal stem cells due to depletion of tryptophan from the microenvironment. Here we demonstrate that mimicry of this immunosuppressive property in sarcoma correlates with a stem cell phenotype.

**Methods:** Sarcoma of different histology, 2 rhabdomyosarcoma, 1 synovial sarcoma and 8 Ewing sarcoma lines were screened for IDO activity by the rate of tryptophan-to-kynurenine metabolism in a colorimetric assay. Flow cytometry was applied to assess stem cell phenotype (CD24+/CD117+ and/or CD133 positive) in sarcoma as well as T cell proliferation and apoptosis by CFSE and Annexin V staining respectively. Prior to co-culture with sarcoma cells for 3 days, healthy donor T cells were isolated and co-culture was performed with 2×10^5 T cells and 1×10^5 sarcoma cells. 

**Results:** Indeed sarcoma cells are highly T cell suppressive in an IDO-dependent manner. IDO activity, ranging from constitutive (3/11 lines) to inducible expression with up to 6.5 fold higher tryptophan-metabolism after IFN-γ induction. The level of IDO-activity was independent of sarcoma histology, but strongly associated with a stem cell phenotype as IDO+ cells displayed a CD24+CD117+ and/or CD133 positive expression. Higher activity correlated with increased T cell death (29.84% ± 3.8 vs. 4.76% ± 1.86, Mean ± SEM, p<0.0005). Also, proliferation of surviving T cells was further reduced by 16.53% ± 2.57, p<0.0005. Addition of the IDO-specific inhibitor 1-methyltryptophan effectively reversed these T cell suppressive effects. Yet as in MSC, cell contact dependent inhibitory mechanisms such as IFN-γ-inducible PDL-1 surface expression also play a role on most sarcoma lines (8/10).

**Conclusion:** Identification of immunosuppressive mechanisms is a prerequisite to establish counteracting therapeutic strategies. In future, blockade of IDO, delineated here as a critical mediator of immunomodulation, may serve to improve efficacy of clinical immunotherapy in pediatric sarcoma.

**References:**

**P1006**

**HOW CRITICAL IS THE PATHOLOGY REVIEW OF PEDIATRIC SARCOMA REFERRED TO A CANCER CENTER IN A DEVELOPING COUNTRY**

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**Purpose:** Most pediatric soft tissue and bone sarcomas are rare. This rarity makes it more likely to label these tumors with erroneous diagnoses that can affect significantly the plan of care and the ultimate outcome of affected patients.

**Methods:** In our center, all patients referred from other hospitals are required to have their pathology reviewed by a board-certified pathologist. Difficult cases are discussed in the daily pathology meeting and if necessary cases are sent for international consultation. In this retrospective study, we reviewed medical records of all referred children under the age of 18 years at time of referral, who were diagnosed with bone or soft tissue sarcoma in other institutions. All patients who were referred from January 2003 till December 2011 were reviewed. Major changes in pathology diagnoses were considered if they potentially affected patients’ management or prognosis.

**Results:** During the study period a total of 312 pediatric patients were diagnosed with sarcoma. Of these 215 patients had their diagnosis done outside. The following referral diagnoses and percentages of patients with major changes were noticed: Ewing Sarcoma (N = 60, 25%), osteosarcoma (N = 41.7%), rhabdomyosarcoma (N = 70, 8.5%) and other soft tissue sarcomas (N = 44, 31.8%). The overall pathology change occurs in 19.5%. From patients with pathology change, 73.8% and 26.2% were referred from the private and academic public sectors, respectively, while in patients with no change 59.5% and 40.4% were referred from the private and academic public sectors respectively.

**Conclusion:** Major discrepancy in pathological diagnosis was noticed in a significant number of referred patients. Central pathology review should be done for all pediatric sarcomas and building local expertise is probably the most important element in establishing pediatric sarcoma care.

**References:**
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**P1007**

**EXTRASKELAL Ewing Sarcoma (EES) AND SKELETAL Ewing’s Sarcoma – ARE THEY DIFFERENT ENTITIES?**

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**Purpose:** Extraskeletal Ewing Sarcoma (EES) comprises 15% –20% of Ewing Sarcoma (ES). However, it’s not known if EES behaves differently. This study was done to analyze and compare clinicodemographic profile, prognostic factors and outcomes for non metastatic EES and skeletal ES.

**Methods:** We reviewed charts of patients seen at The MD Anderson Cancer Center from 1990 to 2011 with a diagnosis of initial or relapsed Ewing’s sarcoma to evaluate novel targeted therapy especially the new kinase inhibitor, pazopanib, and PEG-interferon. 

**Results:** Among the 81 pts (88% male; 12% female) median age at diagnosis was 25 (67% of pts < 30 yrs). Neoadjuvant chemotherapy included Ewing’s sarcoma-like chemotherapy (VDC alternating with IE or VIDE or VAE). Local control attempted was surgery in 39/81. For unresectable metastatic disease, 21 (25%) received radiotherapy. Twenty-four pts had Hyperthermic-Peritoneal-Perfusion with cisplatin (current dose in ongoing phase II trial = 100 mg/m²) after extensive abdominal surgery. After standard second line standard sarcoma therapies (e.g. temozolomide + irinotecan) some DSRT patients have benefited from novel targeted therapies like insulin like growth factor 1 receptor (IGF1R) + mTOR inhibitor therapy, new vascular endothelial growth factor (VEGF) inhibitors including the multi kinase inhibitors (pazopanib 3/3 PR), sunitinib, sorafenib and immunotherapy (PEG-interferon, n = 8, 1 CR). Current clinical trials with pazopanib, an agent that is expected to be FDA approved in 2012 for sarcoma, with other agents will be updated.

**Conclusion:** Even with aggressive chemotherapy and regional local control measures DSRT patients usually relapse within 1–2 years. Novel targeted kinase inhibitors, especially pazopanib, and immune therapies have high potential for additional benefit. Best combinations of targeted therapy agents remain to be determined.

**References:**
Methods: Retrospective review of prospectively maintained database of non metastatic ES patients diagnosed and treated on an institutional protocol at Tata Memorial Hospital (TMH) from January 2001 to December 2010 was done. Clinical characteristics, treatment, and outcomes of EES were studied and compared to skeletal ES.

Results: Of 409 cases of non metastatic ES, 90 (22%) were extra skeletal. Median age for skeletal ES (n = 319) was 15 (1–55) yrs and for EES (n = 90) was 17 (1–49) years. Axial tumors were significantly more in the EES group (57%) compared to skeletal ES (26%) (p = 0.000). Of EES patients, only radiotherapy was done in 24 (27%), only surgery in 22 (25%) and surgery followed by radiotherapy in 43 (48%) patients. Of these, 14 (15.5%) tumors were significantly more in the EES group (57%) compared to skeletal ES (26%) (p = 0.014). Also, baseline albumin (< 4 g/dl) (p = 0.007) and baseline albumin (< 4 g/dl) (p = 0.05) affected EFS significantly. On multivariate analysis, only percentage necrosis (p = 0.028) and baseline serum albumin (0.031) were significant. Outcome of patients treated with radiotherapy alone, surgery alone or radiotherapy with doxorubicin did not differ. Event Free Survival (EFS) of EES was not significantly different from skeletal ES (p = 0.156).

Conclusion: Though there were differences in clinicodemographic profile, outcomes and prognostic factors of EES are similar to skeletal ES. Radiotherapy and surgery have equivalent results in this subgroup of patients.

P1008

MULTIDISCIPLINARY APPROACH INCLUDING EXTENSIVE SURGERY OF PTERYGOPALATINE/INFRACTEMPORAL FOSSA SOFT TISSUE SARCOMA

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Purpose: To evaluate a strategy by which extensive surgery ± external radiotherapy (RT) could improve local control in pterygopatine/infratemporal fossa (PITF) sarcoma.

Methods: 41 patients with a diagnosis of parameningeval sarcoma involving the PITF and referred in Gustave Roussy Institut from 1984 to 2009 were included in the analysis. All patients received multidisciplinary chemotherapy ± radiotherapy ± surgery.

Results: Median age at diagnosis was 7-6 years (range: 1 month to 22 years). There were 38 RMS, 3 undifferentiated sarcoma and 2 other soft-tissue sarcoma. Sixty-eight percent of patients had malignant risk factors. Local treatment consisted of RT alone in 19 patients (n = 8/19 in local complete remission (CR)), and surgery ± radiotherapy in 22 patients (n = 46 cm in CR after limited resection; n = 11/16 in CR after extensive surgery). The 41 patients had a local progression rate of 19% at 5 years for the whole population, 50% for the 19 patients treated with RT alone and 34% for the 22 patients who underwent surgery as part of their treatment. All local failures after extensive surgery occurred on the skull base and/or leptomeningeal spaces. Functional and cosmetic sequelae of extensive surgery were limited.

Conclusion: Multidisciplinary approaches, including extensive surgery for PIF sarcoma, can be feasible, safe, and yield good local control. Future studies are warranted to confirm these promising results, to evaluate the possibility to avoid or to limit the field of RT to the skull base, especially in young children, and to extent the indication of extensive surgery to other “worse” sites of PM sarcoma such as paramasal sinuses.

P1009

OUTCOME OF INFLAMMATORY MYOFIBROBLASTIC TUMOURS (IMF) REGISTERED ON THE EPSSG NRSTS 2005 STUDY

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Purpose: Inflammatory myofibroblastic tumours are rare soft tissue lesions with more than half occurring in children and young adults. There are few paediatric series describing in detail the treatment received and outcome. The EpSSG NRSTS 2005 study therefore set out to prospectively register cases and achieve this aim.

Methods: Treatment was recommended as guidelines only with wide surgical resection for all cases but due to the lack of evidence base no specific guidance was given for the type of chemotherapy.

Results: Twenty six subjects were registered from 6 European countries, 11 (42%) between 1 and 9 years of age, 11 (42%) between 10 and 17 years, 3 (11%) between 1 and 18 years. Following surgery at presentation the majority were IRS group I (n = 17, 65%), 3 were IRS II and the rest (n = 6, 23%) were IRS III. Most had small tumours ≤5cm (n = 18, 69%). Complete treatment data is available in 23 subjects following surgery either as resection or biopsy only. No subjects received radiotherapy with only 3 receiving chemotherapy. Two subjects received vincristine and oral cyclophosphamide, one progressing on treatment and a third subject received vincristine, actinomycin D and ifosfamide. Outcome data were available in 25 patients. Median follow up was 28.9 months (range 0.1–60.5). Five patients developed an event: 3 progressed, 2 with a local relapse and 1 a second malignant tumour resulting in death. Twenty-two patients were alive at last follow up and two patients are lost to follow-up. The 3-yr EFS was 82.4 (95%C1 71.1–89.5) %.

Conclusion: This series of subjects with IMT from the EpSSG NRSTS 2005 study demonstrates that the majority have complete surgical resection at diagnosis. The numbers receiving chemotherapy are too small to draw any conclusions but the overall excellent outcome confirms the surgical based approach to treatment.

P1010

CLINICAL PROFILE AND OUTCOMES OF RHABDOMYOSARCOMA PATIENTS TREATED AT TATA MEMORIAL HOSPITAL: A RETROSPECTIVE ANALYSIS

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Purpose: Rhabdomyosarcoma is the most common soft tissue sarcoma in the first two decades of life. However there are hardly any reports on the pattern of its occurrence and features from India. Our present study is a retrospective analysis of the epidemiological pattern, clinical features, and pathology of rhabdomyosarcoma patients (0–18 years) who underwent treatment at Tata Memorial Hospital from January 2003 to December 2007.

Methods: Design: We retrospectively studied 162 cases of histologically proven rhabdomyosarcoma in children aged 0–18 years treated at our centre from January 2003 to December 2007. We evaluated the histological subtype, site, clinical group, risk stratification and treatment received of RMS patients.

Results: There were a total of 162 patients in our study. The male to female (MF) ratio was 3.1:1. The most common histology was embryonal in 122 patients (74.5%). The primary site of disease was head and neck in 71 cases (43.8%), abdominal 25. Fifteen patients of the 162 defaulted treatment before chemotherapy, all the remaining patients received chemotherapy, however 30% of the patients defaulted before completion of therapy. 87 patients had surgery in the treatment schedule. Radiotherapy was given in 71% of the patients. 77 patients were in CR at the end of treatment (48.8%). 67 patients are still alive after at least 4 years of completion of therapy.

Conclusion: The epidemiology, pathology and clinical features of rhabdomyosarcoma in our patients are different to that reported from other areas, but there are certain differences. However a major problem remains abandonment of treatment due to socioeconomic and other factors.

P1011

SYNOVIAL SARCOMA: REPORT OF A SERIES OF 30 CHILDREN AND ADOLESCENTS FROM A SINGLE INSTITUTION

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Purpose: Synovial sarcoma (SS) is the most common subtype of nonrhabdomyosarcoma soft tissue sarcoma in children and adolescents. Aggressive management is necessary to achieve cure. The best treatment, however, remains uncertain. We evaluate clinical features, treatment, and outcomes of children and adolescents with SS.

Methods: We reviewed the records of 30 patients with synovial sarcoma treated at the Instituto Nacional de Cancer, Brazil from 1996 to 2010. Follow up extended to December 2012.

Results: The mean age at diagnosis was 15 ± 4 years (4–21 years). The male to female ratio was 1.3:1. The most common primary tumor sites were lower extremities n = 21 (70%), upper extremities n = 5 (16.7%), head and neck n = 3 (10%) and trunk n = 1 (3.3%). Disease groups, according to Intergroup Rhabdomyosarcoma Study (IRS) surgicopathologic staging system were: GI, n = 14 (46.7%); GII, n = 3 (10%); GIII, n = 8 (26.7%) and GIV, n = 5 (16.7%). Tumor size was greater than 5 cm in 19 (73.1%) patients and local invasiveness was present in 21 (71.5%) pts. At admission, 15 (43.3%) patients were newly diagnosed, 8 (26.7%)
that both were located in the same site in nucleus, suggesting that both proteins were co-
E-cadherin did not. In advanced HBLs, double stain analysis of TERT and
CTNNB1 were significantly activated in the tumors with telomerase activation (P = 0.013).

Results:

Methods:

Purpose: To describe the radiological features of alveolar soft part sarcoma (ASPS) in the pediatric population to allow early diagnosis and treatment.

Results: Between 1997 and 2011, 4 females and 2 males aged 7 to 17 years at diagnosis (median 11 years), were referred to our institution for ASPS. The histopathological pattern was typical in 5/6 patients, high nuclear TFE3-expression was present by IHC in the 4 tumors tested and the ASPL-TFE3 gene fusion was positive by RT-PCR in the 3 tumors tested. In 5/6 patients the tumor was deeply located within muscles (5 in the quadriceps femoralis, 1 in the triceps brachii and 1 in the pectoralis minor) and 1 tumor occurred in the orbit. The median largest tumor diameter was 60 mm (range: 24–90 mm). High-flow feeding arteries, large drainage veins and intense enhancement after contrast agent injection were constant findings by all imaging modalities. By MR, all tumors demonstrated a high-signal intensity on T2-weighted MR images and high- or iso-signal intensity on T1-WI compared to the muscles. In tumors larger than 70 mm (3/6), large vessels converging toward the tumor center led to a “vascular hilum” appearance. Five patients demonstrated synchronous (4/5) or metachronous (1/5) lung metastases.

Conclusion: The radiological pattern of ASPS in children and adolescents is highly suggestive. The diagnosis of ASPS should be suggested in front of a highly-vascularized, intramuscular mass demonstrating large feeding/drainage vessels or a “vascular hilum” pattern, especially if synchronous lung metastases.

LIVER TUMOURS

MECHANISM OF WNT SIGNAL PATHWAY ACTIVATION IN HEPATOBLASTOMA

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Purpose: The abnormal Wnt/β-catenin signaling plays a key role in hepatoblastoma (HBL) development. In HBL, CTNNB1 (β-catenin) gene mutation or deleted at hot-spot regions including exon 3 stimulates this pathway. Recently, we identified that Wnt/β-catenin signaling was activated by high expression of TERT in the HBLs without CTNNB1 mutations. In this study, we investigated the location of β-catenin in HBL with or without CTNNB1 mutations and the expression levels of the Wnt signal genes downstream of β-catenin.

Methods: Tumors derived from 56 HBL cases treated with the JPLT-2 protocol were analyzed for oncogenic mutations (missense mutations and interstitial deletions in the third exon) of the CTNNB1 gene encoding β-catenin and for the expression levels of TERT (telomerase reverse transcriptase) and the Wnt signal genes downstream of β-catenin (cyclin D1 and E-cadherin) using Real-time PCR.

Results: Oncogenic mutations of CTNNB1 were detected in 42 cases (75%). The expression levels of TERT were significantly higher in 14 cases without mutation (P < 0.05). Interestingly, Wnt/β-catenin target genes including cyclin D1 and E-cadherin were significantly activated in the tumors with telomerase activation (P < 0.003). Therefore, β-catenin staining distinguished the CTNNB1 mutated tumors from others but cyclin D1 and E-cadherin did not.

Conclusion: The Wnt/β-catenin signaling in the HBLs without CTNNB1 mutations was activated by telomerase activation. The clinical courses in HBLs with mutated β-catenin and/or high TERT expression seemed to be unfavorable due to highly activated Wnt/β-catenin signaling. This pathway might become molecular targets for advanced hepatoblastoma.

REFERENCE


PK002

EXPRESSION OF GATA4 IN EPITHELIAL LIVER TUMORS IN CHILDREN AND ADOLESCENTS

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Purpose: Epithelial liver tumors in older children are rare and usually include hepatocellular carcinoma (HCC). The differential diagnosis between HCC and hepatoblastoma (HB) is challenging, also considering the existence of transitional forms (hybrid tumors). GATA4, member of a family of zinc-finger-DNA binding proteins regulating cell growth and differentiation, has been recently reported to be highly expressed in pediatric HCC and HB, whereas it is constantly absent in adult HCC. The expression of GATA4 has been evaluated in a series of epithelial liver tumors either in children and adolescents, in order to investigate its potential role in distinguishing HCC from HB and transitional tumors.

Methods: Nine children older than 5 years, affected by epithelial tumors, and 7 younger children affected by epithelial HB were examined. HE stain section and available immunostains were reviewed and tumors reclassified in HB, HCC and hybrid tumors, according to WHO 2010 Classification. Immunostain for GATA4 were performed and graded as weak (scattered nuclear positivity) or strong (majority of nuclei positive).

Results: GATA4 was expressed in 90% of HB: in 6 cases, patients were less than 5 years, in 3 older. In patients with hybrid tumors and HCC (all older than 5 years), GATA4 was mostly not expressed.

Conclusion: Lack of GATA4 expression in hybrid tumors and HCC suggests a possible pathogenetic relationship between these two entities and may represent the expression of an adult type” phenotype in these lesions.

PK003

PRELIMINARY EXPERIENCE USING HIGH INTENSITY FOCUSED ULTRASOUND COMBINED WITH TRANSATHERETER ARTERIAL EMBOLIZATION FOR THE TREATMENT OF CHILDREN WITH ADVANCED HEPATOBLASTOMA

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Purpose: The purpose of this study was to assess the effectiveness of high-intensity focused ultrasound (HIFU) combined with transarterial chemoembolization (TACE) in treating pediatric hepatoblastoma.

Methods: 12 patients with advanced-stage hepatoblastoma were enrolled in the study. All patients received chemotherapy, TACE and HIFU ablation. Follow-up materials were obtained in all patients. The tumor response, survival rate and complication were analyzed.

Results: Completely ablation was achieved in 10 patients (83.3%), the AFP level was also decreased to normal in these patients. The mean follow-up time was 13.3 ± 1.8 months (range, 2–25 months). At the end of follow-up, 2 patients died from tumor progression, the rest 10 patients were alive. One patient was found to have lung metastasis after HIFU and had an operation to remove the lesion. The median survival time was 14 months, and the survival rates of 1, 2-year were 91.7% and 83.3%, respectively. Complication included fever, transient impairment of hepatic function and mild malformation of rib.

Conclusion: HIFU combined with TACE and chemotherapy can maximize its benefits and achieve a higher clinical impact in hepatoblastoma treatment.

PK004

HEPATOCELLULAR CARCINOMA IN CHILDREN: 13 YEARS EXPERIENCE OF A PEDIATRIC ONCOLOGY GROUP IN PERU

Ana Gloria Paredes Guerra

Pediatric Oncology, Rebagliati Hospital, Lima, Peru

Purpose: The purpose of this study was to assess the effectiveness of high-intensity focused ultrasound (HIFU) combined with transarterial chemoembolization (TACE) in treating pediatric hepatoblastoma.

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Conclusion: HIFU combined with TACE and chemotherapy can maximize its benefits and achieve a higher clinical impact in hepatoblastoma treatment.

Hepatocellular carcinoma in children: 13 years of experience of a pediatric oncology group in Peru

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Pediatr Blood Cancer DOI 10.1002/pbc
Purpose: To describe the epidemiology, treatment and outcome of hepatocarcinoma in children from Peru.

Methods: A retrospective review of children less of 18 years old with the diagnosis of hepatocarcinoma treated in our institution (Rebagliati Hospital) from January 1999 to March 2012. Data collected included demographic, clinical, radiologic, pathologic, treatment and outcome.

Results: There were 19 patients with the diagnosis of hepatocarcinoma. Their median age was 8 years old (range 1–17). There were 5 girls and 14 boys. The main signs were hepatomegaly, abdominal mass, vomiting, weight loss, anemia and pain. Only 7 patients (37%) received hepatitis B vaccine, 6 patients (31.7%) had chronic hepatitis B and 4 (22%) had cirrhosis. The alpha-fetoprotein in median level at diagnosis was 86,940 ng/ml. The SIOP results were: Pretext 4: 26%, Pretext 3: 58%, Pretext 2: 15% and none Pretext 1. Five patients had metastasis (lung, brain and skin). The histology was epithelial hepatocarcinoma in all cases. Four patients had primary surgery (one patient submitted to partial hepatectomy and three patients had liver resection) and 15 patients had unresectable disease at beginning; of this patients, 4 received chemotherapy alone (based in SIOPEL protocols), 5 patients received systemic chemotherapy and hepatic intra-arterial doxorubicin; and six patients received systemic chemotherapy and sorafenib. At the moment, there are 6 patients alive without disease and 13 patients died (5 had disease progression, 5 relapsed, 2 post- chemotherapy complication and 1 liver failure).

Conclusion: Hepatocarcinoma is a bad prognosis disease. The initial approach and multidisciplinary treatment is very important in improving the outcome. The role of sorafenib in children with hepatocarcinoma is still uncertain, even the patients with this drug didn’t have relapse.

PK005 HEPATOBLASTOMA ASSOCIATED WITH BECKWITH-WIEDEMANN SYNDROME IN JAPAN: THE JPLT EXPERIENCE

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Purpose: To describe the epidemiology, treatment and outcome of hepatoblastoma in children less than 18 years old with the diagnosis of Beckwith–Wiedemann syndrome (BWS) treated in our institution (Rebagliati Hospital) from January 1999 to March 2012.

Methods: We reviewed the clinical data of patients with hepatoblastoma associated with BWS who were enrolled to JPLT-2 study. In this study, primary chemotherapy consisted of cisplatin and pirabacine (CTA), and for unresectable or unresponsive disease, the combination of ifosamide, pirabacin, etoposide, and carboplatin (ITEC) was used.

Results: Of 279 patients, seven (2.5%) had BWS, 3 were males and 4 were females. The median age at diagnosis was 6 months, range (2 to 10 months). Tumors were classified as PRETEXT I (2), II (3), III (2). All had metastatic disease and two were ruptured. The median α-fetoprotein level was 211,820 ng/ml (range, 70,651.9 to 837,305 ng/ml). Two underwent initial resection and adjuvant chemotherapy, and five had partial hepatectomy after neoadjuvant chemotherapy followed by postoperative chemotherapy. For resection by partial hepatectomy, there were only two cases, however, children needed additional chemotherapy (ITEC in one, ITEC and high-dose actinomycin in the other). Two patients experienced relapse, which were successfully salvaged by surgery and chemotherapy. One child had therapy-related acute leukemia, but remained in complete remission after chemotherapy. All patients were alive without evidence of disease with median follow-up of 6 years (range, 2–10 years).

Conclusion: Hepatoblastoma is a bad prognosis disease. The initial approach and multidisciplinary treatment is very important in improving the outcome. The role of sorafenib is still uncertain, even the patients with this drug didn’t have relapse.

RARE TUMOURS

PL001 ADRENOCORTICAL TUMOURS IN CHILDREN: A 25 YEAR EXPERIENCE

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Purpose: Adrenocortical tumours (ACTs) are rare in children and their management requires a multi-disciplinary approach. Our aim was to investigate the prognostic significance of the histopathology and other outcome variables.

Methods: Twenty-nine cases of ACTs treated at our institution between 1987 and 2011 were identified from a histopathological database. The case notes were reviewed for presentation, management and outcome. For tumour staging, the UKCCSG staging system was used. Weiss score was applied for the histological evaluation. Kaplan-Meier estimate was used for the statistical analysis.

Results: Twenty-nine patients (14 boys, 15 girls) with a median age of 2.2 years (range, 5 months–15.8 years) at presentation were identified. 96% (28/29 patients) presented with signs of a secreting tumour: virilisation or Cushing’s syndrome or both. Fifteen patients (52%) had systemic hypertension. Eight patients had an underlying genetic condition; e.g. Beckwith–Wiedemann syndrome, Li–Fraumeni syndrome. All patients underwent surgical excision with intraoperative tumour rupture/capsule breach documented in 7 patients. Median tumour weight was 61g (range, 4–156g). Histopathologically large tumour showed high Weiss score with bad outcome. Atypical mitoses and confluent necrosis were the independent predictive variables in Weiss categories. Seven patients died from recurrent disease, 1 patient with intra-atrial and intra-hepatic extension of tumour died immediately post op because of MOF (multiple-organ failure), and 2 died from a secondary tumour. Six out of 7 patients who had rupture during the operation died from recurrent disease despite subsequent chemotherapy. Relapse free survival was 65% with a median survival of 32 months (range, 3–165 months).

Conclusion: Tumours with a high Weiss score were associated with a poor outcome. Complete surgical excision without rupture is mandatory and upstaging should be considered when tumour rupture occurs.

PL002 CLASS II HISTOCOMPATIBILITY ANTIGENS (HLA) IN CHILDHOOD ADRENOCORTICAL TUMOURS (ACT); LOW EXPRESSION IS RELATED TO A POOR PROGNOSIS

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Purpose: To describe the epidemiology, treatment and outcome of children diagnosed with hepatic tumors at our centre between 2005 and 2012. Hepatoblastoma and hepatocellular carcinoma (HCC) were treated as per SIOPEL-3 protocol and undifferentiated embryonal sarcoma (UES) as per the IRS-V protocol.

Methods: This is a retrospective review of the clinical presentation, diagnosis and outcome of children diagnosed with hepatic tumors at our centre between 2005 and 2012. Hepatoblastoma and hepatocellular carcinoma (HCC) were treated as per SIOPEL-3 protocol and undifferentiated embryonal sarcoma (UES) as per the IRS-V protocol.

Results: Of 825 pediatric malignancies 14 children (1.7%) were diagnosed with primary hepatic tumors. Median age at diagnosis was 6 years (2 months–15 years). M:F ratio was 5:2. In 12 cases (85%) a malignant neoplasm was present of which hepatoblastoma was the commonest, seen in 9 (64.2%) cases. HCC was diagnosed in 2 patients (14.2%) and UES (group III) in 1 patient (7.1%). Seven of these 12 patients (58.3%) opted for treatment of which 5 (35.7%) were alive and well at a median follow up of 2 years. In 2 patients the disease relapse in median lefity (14.2%) Five (35.7%) abandoned treatment following diagnosis owing to financial constraints and distance from treatment centre. Their outcome is not known. Benign tumors were diagnosed in 2 patients (14.2%) and included hepatic mesenchymal hamartoma in 1 and hemangiomia in the other. Both were managed primarily by surgery and are doing well on follow up.

Conclusion: The incidence of hepatic tumors diagnosed at our centre was found to be higher than reported in literature. Hepatoblastoma comprised the highest proportion of malignant liver tumors. In patients who underwent treatment, a multidisciplinary approach resulted in reasonably good outcome. In a resource constrained country treatment abandonment is a major hurdle yet to be overcome.
OVEREXPRESSION OF IGFR1 BUT NOT IGF2 IS ASSOCIATED WITH UNFAVORABLE EVENT AND METASTASIS IN ADRENOCORTICAL CARCINOMAS

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Purpose: Although pediatric adrenocortical tumors (ACTs) are very rare malignancies, in Southern of Brazil their incidence is 10–15 times higher and related to TP53 mutation p.R337H. Overexpression of IGFR2 has been found in adults and pediatric ACTs and IGFR1 was described in pediatric adrenocortical carcinomas as overexpressed in a very small series of cases. In this study we evaluated the expression profile of IGFR2 and IGFR1 in pediatric ACTs and non-neoplastic adrenal and its association with clinical and biological features.

Methods: We analyzed 57 ACTs, 11 non-neoplastic adrenal samples, 11 adenomas and 46 carcinomas according to Weiss criteria. Gene expression was analyzed by RT-qPCR and Immunohistochemistry (IHC) to IGFR1 was performed to 25 patients.

Results: A significant overexpression of IGFR2 was observed in ACTs when compared with non-neoplastic samples (p < 0.0001). No differences were observed in adenomas versus carcinomas (p = 0.56). To IGFR1 no significant difference was observed between ACTs and non-neoplastic samples (p = 0.58), neither between adenomas and carcinomas (p = 0.55), which it was confirmed by the IHC (p = 0.66). No significant differences were observed between IGFR2 and IGFR1 genes and the variables analyzed: age, tumor weight and size, clinical presentation, TP53 p.R337H status, metastasis and event (death/relapse versus remission) (p > 0.05). When we analyzed only patients with carcinomas, significant association was observed between higher levels of IGFR1 and unfavorable event (p = 0.041) (HR: 1.256, IC 95%: 1.055 to 1.524, p = 0.021) and also presence of metastasis (p = 0.049) (HR: 1.308, 95% IC: 1.047 to 1.633, p = 0.018).

Conclusion: We observed a significant overexpression of IGFR2 in ACTs when compared to non-neoplastic adrenal samples, however no difference was observed between carcinomas and adenomas to the IGFR1. The overexpression of IGFR2 in carcinomas was associated with higher risk of unfavorable event and metastasis. These results need to be viewed with caution due to the relative small number of cases analyzed.

DIFFERENTIAL MICRONARAS EXPRESSIONS ARE ASSOCIATED WITH RELAPSE AND TP53 P.R337H MUTATION IN PEDIATRIC ADRENOCARCINOMAS

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Purpose: Adrenocortical tumors (ACTs) in childhood correspond only 0.2% of all pediatric tumors, however, ACT in children and adolescents presents high mortality rate in advanced stages. In Brazil, their incidence is 10–15 times higher and related to TP53 mutation p.R337H. Disturbed microRNAs (miRs) expressions have been shown to play an important role in development and progression of different types of cancer. The present study aimed to evaluated let-7e, miR-92a, miR-126a and miR-196a gene expression and try to correlate with diagnosis features and patients’ course.

Methods: The miRs expressions were evaluated by qRT-PCR in 34 pediatric ACTs patients (26 Weiss > 3, 26 TP53 p.R337H mutation and 8 relapse) and statistical analyses were performed by Mann-Whitney and Spearman correlation tests.

Results: Our results showed a significant association between lower expression of let-7e and relapse (p < 0.05). The expression of miR-92a, miR-126a and miR-196a were significantly higher in TP53 mutated samples compared to those without mutation (p < 0.05). The miR-196a presented a positive correlation with all miRs analyzed (p < 0.01).

Conclusion: Our study suggests a potential role for miRs in the development of different clinical outcomes and may be associated with TP53 mutation p.R337H in ACTs.

ENDOGLIN AS A PROGNOSTIC MARKER IN PEDIATRIC ADRENOCARCINOMAL TUMORS

Pediatr Blood Cancer DOI 10.1002/pbc

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Purpose: Adrenocortical tumors (ACTs) are a rare disease in the pediatric age group worldwide except in the southern area of Brazil. Except for the tumor weight, there isn’t any reliable prognostic fact or nowadays. Endoglin is a immunohistochemical marker for endothelium in newly formed blood vessels. Its over expression has been detected in other tumors such as liver, lung and stomach. The aim of this paper is to analyze the endoglin expression in pediatric ACT and its correlation with clinical and pathological features.

Methods: Twenty seven patients with adrenocortical tumors, from 0 to 19 years of age, over the last thirteen years, had their records reviewed and their tumor specimens blocked in paraffin were processed for immunohistochemical endoglin reaction. Normal pediatric adrenal tissue was acquired from renal tumors resection, when en bloc removal was necessary, they were similary processed as the control group.

Results: Endoglin expression was statistically higher in ACT samples than in control group (p < 0.05). When correlated with clinical and pathological features, endoglin expression was significant (p < 0.05) augmented in tumors with bigger diameters, higher mitotic index, higher incidence of intraoperative rupture, need of en bloc necrectomy, higher necrosis rate, elevated incidence of venous and capsule invasion. Tumor staged III and IV had higher endoglin expression than that staged I and II (p < 0.05). In the logistic model, endoglin expression was related with death probability (ODDs ratio = 6.22; p < 0.05) and inversally, with cure (ODDs ratio = 0.11; p < 0.05).

Conclusion: Endoglin immunohistochemical expression is a reliable prognostic marker in pediatric adrenal cortical tumor. Its expression is higher in tumors with worse prognosis.
Results: Among the 107 patients with TAC, 19 patients showed metastasis at diagnosis or had relapse and were selected for analysis. Six were female and 13 male. The median age was 3.3 years. Eight patients had primary metastasis to lungs, liver, lymph nodes or association and 11 (57.9%) had relapses. All but one patient had their primary tumor as well as their relapses completely resected. All patients received chemotherapy with Mitotane, cysplatin, doxorubicin and etoposide. Regarding the staging, 3 were stage I, 5 stage II, 3 stage III and 8 were stage IV. There were 12 cases of relapse and 6 are alive and 6 are dead. The overall survival for this series is 35.9% and when analyzed by stage, the survival was 33% for stage I, 50% for stage II, 33% for stage III and 30% for stage IV. There were no differences between these groups (p > 0.05).

Conclusion: Children with TAC still have a bad prognosis with advanced or relapsed disease with survival of 30 to 50% with aggressive treatments. From the analyses we have seen that after 5 years from the diagnosis, if the child is alive, he/she can be considered cured from the disease.

PI.007

CLINICAL CHARACTERISTICS AND EPIDEMIOLOGY OF GASTROINTESTINAL ADENOCARCINOMAS IN CHILDREN: EXPERIENCE IN SOLCA HOSPITAL, QUITO

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Purpose: Worldwide, gastrointestinal carcinomas in children are rare. This study describes the epidemiological and clinical characteristics of our patients.

Methods: We analyzed the medical records of children, aged less than 18 years, with gastrointestinal carcinomas from January 2006 to February 2012.

Results: We identified 8 cases diagnosed with gastrointestinal adenocarcinoma. Average age was 14.5 years (13–17). Six were female. Regarding ethnicity, 7 were mixed and 1 Indian who also had peritoneal tuberculosis. Seven patients came from the mountain regions of Ecuador. Forty percent of the patients had a previous diagnosis of gastritis and paraspites. In half of the cases, there was a close relative with history of gastric cancer. The main complaints were abdominal pain (100%), weight loss (60%) and gastrointestinal bleeding (50%). The mean interval between onset of symptoms and diagnosis was 3.6 months (range 1–5 months). Fifty percent patients had elevated DHL. The predominant type was signet ring cell (6). Tumors were located in the stomach in 5, colon in 1 and rectum in 2. Ninety percent of the cases were stage IV with retroperitoneal nodes, carcinomatosis and hepatic metastasis. Only 40% of the patients we attempted curative treatment according to adult protocols (the rest received palliative care). Treatment consisted on surgery, chemo and radiotherapy. The mortality rate is 80%. Two patients are alive, one on treatment and the other on palliative care.

Conclusion: Our patients showed pathological features and advanced stages associated poor prognosis. Due to the precarious clinical conditions at diagnosis, only 40% of patients received curative treatment. Despite this, most had progression and finally died. It is important to have a high index of suspicion in order to implement early diagnosis and more effective treatment.

PI.008

LYMPHANGIOGENESIS IN PEDIATRIC ADRENOCORTICAL TUMORS

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Purpose: The monoclonal antibody anti-podoplanin, D2-40, is a known selective marker for lymphatic vessels. Previous studies, in other types of neoplasms, have implicated its overexpression with tumor ability of lymphatic spread (lymphatic metastasis). The aim of this paper is to analyze the D2-40 expression in pediatric ACT and its correlation with clinical and pathological features.

Methods: Twenty seven patients with adrenocortical tumors, from 0 to 19 years-old, over the last thirteen years, had their records reviewed and their tumor specimens blocked in paraffin were processed for immunohistochemical D2-40 reaction. Normal pediatric adrenal tissues were acquired from renal tumors resections, when in block removal was necessary, they were similarly processed as the control group.

Results: D2-40 expression was higher in ACT samples than in control group (p < 0.05). All older patients than 8 years-old had a D2-40 smaller than 1. From the 27 patients, only two had lymphonodal metastasis. The local recurrence of the tumor occurred in 10 out of 27 patients. When correlated with clinical and pathological features, D2-40 expression was significant (p < 0.05) augmented in tumors with that required en bloc necrofomy. Tumor staged III and IV had higher D2-40 expression than that staged I and II (p < 0.05). In the logistic model, D2-40 expression was not related with death probability or cure.

Conclusion: The lymphatic spread is not the preferable way for recurrence in pediatric adrenocortical tumor, the local recurrence is. Therefore, lymphangiogenesis does not play an important role in the progression of this disease.

PI.009

FOLLOW-UP OF CHILDREN WITH GENETIC MUTATION FOR ADRENOCORTICAL TUMORS IN WESTERN PARANA

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Purpose: The adrenal tumor or tumor of the Adrenal Cortex (TCA) is a relatively rare tumor accounting for only 0.1% of malignancies, being the fourth most common malignant abdominal tumor of childhood. Despite its rarity, in South and Southeast regions of Brazil the incidence of (TCA) is 3.4 to 4.2 cases/1,000,000 approximately 15 times higher than the worldwide incidence is considered an endemic problem in southern Brazil mainly in children under 5 years. In a study by Dr. Ronald Figuredo (in press), using genomic screening (screening test for newborns) were able to identify the genetic mutation (R337T TP53) in newborns of Parana since 2005. The risk of developing tumors in patients with the mutation in Parana is around 9.9%, as shown penetrance studies conducted by the same author in cases of TCA in Parana. Due to the importance of early diagnosis and initial therapeutic approach in children who eventually could develop this type of tumor, children’s western regions, were followed up at the outpatient clinic of Pediatrics, University Hospital of Parana in Cascavel. The objective was to monitor healthy children carrying the genetic mutation for R337T p53 tumor of the adrenal cortex (TCA).

Methods: Follow-up was performed in 29 children with genetic mutation (R337T TP53). This monitoring was conducted at the clinic of Pediatrics, University Hospital of Parana, Cascavel.

Results: Of the 29 children evaluated, 18 were female (62.0%) and 11 males (38%). Of these, three (10.3%) developed TCA, with clinical and hormonal compatible with the initial tumor development. Conclusion: Children must be accompanied by genetic mutation for early diagnosis possible in tumor development. The genomic screening in Parana may contribute to alert the pediatrician to follow healthy children with a potential to develop the tumor.

PI.010

K-RAS MUTATION AND COLORECTAL CARCINOMA IN CHILDHOOD

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Purpose: Colorectal cancer is extremely rare in childhood and has a poor prognosis in young patients. The aim in this study was to investigate the features and outcomes of childhood colorectal carcinoma and examine the frequency of K-RAS mutation of colorectal carcinoma (CRC) in children and adolescents.

Methods: 28 children with CRC diagnosed between 1974 and 2010 were analyzed according to clinical, pathologic features, prognostic factors and outcomes. Out of these 28 patients, paraffin-embedded tissues of 18 were available and these tissues were analyzed by using pyrosequencing method for detecting K-RAS mutation. Results: The most frequent symptoms of patients were abdominal pain (57.1%) and weight loss (42.8%). It was mostly located in the rectum (42.9%) and sigmoid colon (25%). Mucinous adenocarcinoma (71.4%) was the most common histology. At presentation 89.2% of patients had metastatic disease, especially on peritoneal surface (39.3%). The overall survival rate at 5 years was 10.1%. Advanced stage (p = 0.045), macroscopic tumor due to incomplete resection (p = 0.0001) were significant poor prognostic factors. K-ras mutation was identified in two of 18 patients (11.1%). The patients who had K-RAS mutation were 13 and 16 years old. The location of disease was sigmoid and hepatic flexure. The histopathologic types were mucinous adenocarcinoma and stages were C and B (Dukes). Survival times of the two patients were 25 and 14.5 months, respectively.

Conclusion: Childhood colorectal carcinoma has a different biology and a worse outcome than adults. It is significant that 2 patients of 18 showed K-RAS mutation at an early age. Further studies are necessary with larger series of patients to investigate and understand the biology of childhood CRC and the relevance of the K-RAS mutation on the prognosis.

PL.011

RETROSPECTIVE ANALYSIS OF HISTOLOGY AND EVALUATION OF prognostic MARKERS OF PANCREATOBLASTOMA

Pediatric Blood Cancer DOI 10.1002/pbc

SIOP ABSTRACTS 1071
Purpose: Pancreatoblastoma is a rare neoplasm of infancy and childhood comprising <0.5% of pancreatic non-endocrine neoplasms. Though a round cell tumour, its prognosis is considered to be favourable as compared to other round cell tumours. Correct diagnosis is essential for appropriate therapy. Present study is a retrospective analysis of 8 cases of pancreatoblastoma aiming towards review of histomorphology and immunohistochemistry along with an attempt to determine prognostic parameters.

Methods: Clinical data and imaging findings of 8 cases were retrieved from medical records. Haematoxylin-Eosin stained slides were reviewed along with immunohistochemistry.

Results: One of eight patients was an adult. On review, conventional histology of pancreatoblastoma inclusive of squamous moles could be seen only in 3 of 8 cases. Correlation with imaging findings and application of a wide panel of immunohistochemistry was mandatory to differentiate between pancreatoblastoma and other malignant round cell tumours of the retroperitoneum. The epicenter of tumour was difficult to determine in 2 of 8 cases. On immunohistochemistry, CEA, EMA and beta catenin were positive in all cases. Four patients had local recurrence at the time of presentation, 2 patients developed metastasis, 2 patients died of disease. Resection of tumour was possible in only 4 patients. Mitotic activity and nuclear pleomorphism was seen in all five recurrent and metastatic cases. MIB 1 labeling index was less than 1% in 3 of 5 cases.

Conclusion: Lack of conventional histology and equivocal imaging findings pose diagnostic difficulty in pancreatoblastoma. A wide panel of immunohistochemistry is required to rule out other malignant round cell tumours. All our patients with pancreatoblastoma had experienced aggressive clinical course in terms of local recurrences, metastasis and death. Mitotic activity and nuclear pleomorphism can be considered as adverse prognostic features to help prognosticate a given case.

PL012
EXOME SEQUENCING REVEALS GENETIC PREDISPOSITION IN PEDIATRIC COLORECTAL CANCER

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Purpose: Infantile myofibromatosis (IM) is a benign fibrous tumour, typically occurring in infancy and early childhood. Conflicting evidence exist with regard to the inheritance pattern.

Methods: A retrospective review of case records and data extraction was done. Results: Patient 1: Presented at 10 days of age with firm rubbery flesh-colored nodules involving the right orbit, upper and lower limbs, back, and skin of the abdomen. MRI ruled out vesicular and intracranial involvement. Histology, immunohistochemistry (smooth muscle actin + + +, NSE +, desmin, S-100, GFAP and Leu-7 negative), and electron-microscopy investigations supported the diagnosis of multicentric cutaneous IM. She was treated with vincristine and methotrexate protocol over 6 months to salvage the eye. She is disease free at 6 years of clinical and imaging follow up. Patient 2: A first cousin of patient 1 presented in 2004, soon after birth, with lesions on the scalp and right thigh without visceral and intracranial involvement. A diagnosis of IM with similar histology was made. The thigh lesion was surgically resected. The scalp swelling resolved spontaneously. He is well at 5 years of follow up. Patient 3: Recently the younger full sibling of patient 2 presented with isolated swelling on the scalp. An excision biopsy of the lesion was carried out and a diagnosis of IM was made. Patient 4: The mothers of these children are known to be identical twins and one (mother of patient 2, 3) was diagnosed with IM of the tongue and forearm as a child.

Conclusion: This family history points to an AD pattern of inheritance. Both twins are genetically identical and represent a unique event with variable penetrance. Differential clinical manifestations and severity in these individuals further point to variable penetrance. Recognition of inheritance pattern can have prognostic implications and could identify ‘at risk’ individuals.

PL014
MYOPHTHALMIC CARCINOMA OF THE SOFT TISSUE IN PEDIATRIC AGE: A REPORT FROM THE TREP PROJECT

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Purpose: Myophthathelial Carcinoma (MyC) of the soft tissue is very rare in children. Recently its histologic characteristics have been better defined and it is expected that a larger number of cases will be recognized. Treatment has not been defined and prognosis remains poor. As part of the TREP (Rare Tumors in Pediatric Age) project we analyzed a series of patients treated in the Italian Centers. Methods: From 2005 to 2011 6 patients (5 male) aged 1.3–9.2 years (median 6.8) were registered in the TREP database. Tumor site was: nuchal area (2 pts), extremities (2 pts), orbit (1), sacral area (1). Maximum diameter varied from 1 to 5.5 cm. All tumors were localized but regional nodes were involved in one child. The second child we registered was treated with a combination of ifosfamide, cisplatin and etoposide (IfCE) with evidence of tumor reduction. We consequently decided to use ICP/E to treat the following 4 patients. Results: The tumor was grossly resected in 3 patients and biopsied in the other 3. All children received radiotherapy. One patient is still on treatment. 4 children are in complete remission (follow up 1–4.1 years). The child with nodal involvement developed lung metastasis and died.

Conclusion: Our preliminary results seem better than what is reported in the series published so far and we hope this experience may be useful to better define the treatment for this rare tumor. The management of patients with MyC poses a challenge for pediatric oncologists: due to its rarity it may take many years to gain enough information to establish an effective treatment. National and international networks dedicated to very rare tumors, such as the TREP Group, should be able to take charge of these “new tumors” to formulate recommendations.

PL015
CAN WE USE THE TORONTO EXTREMITY SALVAGE SCORE TO MEASURE FUNCTIONAL OUTCOME IN PAEDIATRIC DESMOID FIBROMATOSIS?

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Purpose: Desmoid fibromatos (DF) is a heterogeneous condition with lack of consensus regarding therapy. Fatality is rare but repeated surgery prevalent. Functional assessment for this group is not well established, although we believe it to be an important marker of treatment success. No validated self-assessment score exists for non-malignant limb tumours and this may explain why no previous reports exist in the literature. We elected to use the

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Toronto Extremity Salvage Score (TESS) 1. The London Sarcoma Service, one of the largest centres in Europe, set out to retrospectively review self-assessed functional outcome using the TESS.

Methods: All young people (< 21 years), with a histological diagnosis of DF in an extremity, from 2003 to 2010 were included. Nineteen children were assessed by telephone or post using the TESS questionnaire.

Results: Median time from diagnosis to TESS was 97 months and was not correlated with score. TESS was lower in children who underwent surgical resection compared with those who did not, although this was not significantly significant (p = 0.12). Median TESS of those children receiving cytotoxic and non-cytotoxic therapies was high (median TESS 75.9%), despite a trend towards advanced inoperable disease. TESS was lower in those receiving radiotherapy (median 52.5%). TESS analysis in this cohort took place greater than 2 years from treatment in all children except one at 15 months. We found children with progressive disease, 5 or more treatment modalities, or greater than 6 events had the lowest outcome scores.

Conclusion: Longitudinal data may aid optimisation, validation and development of function assessment. We suggest an annual formal objective assessment of function with additional assessment prior to a new therapeutic modality. To facilitate ease of completion, we propose a touch screen electronic tablet interface for patient input of questionnaires while waiting for outpatient clinical review.

References

PL.016 NEUROENDOCRINE TUMORS IN CHILDREN AND YOUNG ADULTS: THE M. D. ANDERSON CANCER CENTER EXPERIENCE

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Purpose: Neuroendocrine tumors (NETs) are rare in the pediatric population, and the treatment of NETs is dependent upon factors such as primary site and tumor grade. The purpose of this study is to report the clinical characteristics and outcome of pediatric patients treated for NET at our institution.

Methods: Retrospective record review of patients less than age 22 years at diagnosis and treated for NET from January 1, 2000 to December 31, 2010 at MD Anderson Cancer Center. Results: There were 33 evaluable patients with median age of 17.9 years (range 9.9–21.9 years) and more females (58%). The most common tumors encountered were well-differentiated appendiceal carcinoids (N = 17). The pancreas was the most common non-appendiceal site (N = 4) while unknown primary site was seen in 6 patients. The majority of tumors were low-grade (N = 24; 75%) and small (T1; N = 22; 67%). However, patients with non-appendiceal tumors had higher prevalence of high-grade tumors (5/16; 31%) and metastasis (8/16; 50%). All patients with appendiceal tumors only required surgical therapy, and 11 of those patients required second surgery due to tumor invading the muscularis layer as the most common indication. All 9 patients that experienced treatment failure had non-appendiceal tumors, and 8 of those patients had received prior chemotherapy. Six patients died of disease (Pancreas, N = 3; Unknown primary, N = 3). The 5-year overall survival rates for patients with appendicetal and non-appendicetal tumors were 66% (95% CI 45%–95%; P = 0.006) respectively; and the 5-year relapse-free survival rate for patients with appendicetal and non-appendicetal NETs were 100% and 41% (95% CI 22%–75%; P = 0.002) respectively.

Conclusion: Well-differentiated appendicetal carcinoid tumors were the most common pediatric NET encountered, and their overall prognosis is excellent. Better therapies are needed for patients with pancreatic NETs and NET of unknown primary site.

PL.017 NON-AIDS DEFINED MALIGNANCIES AMONG CHILDREN LIVING WITH HIV/AIDS IN UGANDA AND CO-ASSOCIATION WITH HHV-8 AND EBV

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Purpose: Among children living with HIV/AIDS as a complication of immunodeficiency have been well described in different settings. In the early beginning of the HIV/AIDS epidemic was observed marked rise in the incidence of Kaposi’s sarcoma, non-Hodgkin’s lymphoma and invasive cervical carcinoma, which strongly suggested a causal relationship between immunodeficiency and the development of these kind of cancer. The Centers for Disease Control (CDC) later defined list of indicator conditions for malignancies in the AIDS definition where called ‘AIDS-defining’ malignancies (ADM). In the era of highly active antiretroviral therapy (HAART) the epidemiology of malignancies among this group has changed and today, several other non-AIDS-defined malignancies (NADM) are observed with increasing incidence.

Methods: Between 1/2009 and 3/2012 data collected from 4 HIV/AIDS Centres in Central region of Uganda was analysed on the development of malignancy in HIV positive children. There were enrolled 64 HIV-positive children with cancer. In these studies the majority of patients had B cell & NHL, however 19% of the patients were identified with NADM which was demonstrable in most (83%) of the tested tumors and (25%) had both HIV-8 and EBV. CDC; 8UPMP; 9Surgical Department, National Hospital Mulago, Kampala, Uganda; 10St. Vincent's University Abbotsford Hospital, Abbotsford, Canada.

Conclusion: Other studies have reported similar EBV findings in NADM among AIDS patients. Thus EBV appears to be an important cofactor in development of malignancy in paediatric AIDS patients.

PL.018 COMPLICATIONS AFTER THYROIDECTOMY AND NECK DISSECTION IN CHILDREN WITH THYROID CARCINOMA

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Purpose: To analyse the rate of complications after thyroidectomy (TE) with lymph node dissection (LND) in children with thyroid carcinoma (TC).

Methods: 60 children (5–18 years old) have been included in research from 2005 to 2011 years. All patients were staged using the UICC classification 1997. TE + CLND (central lymph node dissection) was performed in 24 patients, TE + CLND + ipsilateral MND (modified radical neck dissection) - in 19 patients. TE + CLND + bilateral MND - in 16 cases. Histopathology types included papillary carcinoma in 58 cases, follicular carcinoma in 2.

Results: There were postoperative complications which included: 1 case of larynx edema (1.6%) after TE + CLND + bilateral MND (T1N1M0); 4 (6.6%) cases of permanent unilateral recurrent laryngeal nerve paresis (T1N2M0 - 2; T1N3M0 - 1; T1N3M1-1 case after TE + CLND + bilateral MND), 1 case (1.6%) of recurrent laryngeal nerve paralys (T1N1M0 after TE + CLND + bilateral MND), temporary hypoparathyroidism in 23 (38.3%) patients (T1N1M0-13, T1N1M0-1, T1N2M0-4, T1N3M0-5) which TE + CLND + ipsilateral MND was carried out in 6 cases, TE + CLND + bilateral MND - in 5 cases, and TE + CLND + in 12 cases. The chronic hypoparathyroidism revealed in 2 children (3.3%) from which 2 have T1N2M1 stage, after TE + CLND + bilateral MND.

Conclusion: Postoperative complications were not noted in patients with stage T3, without lymph node metastasis on neck and stage T4 with metastasis in central lymph node. Complications were registered in 14 cases with T1N1M0 stage and in 2 patients with T1N1M1 stage. All patients with stage T1N1M0 have complications. Persistent postoperative complications were revealed in 4.9% of cases of which chronic hypoparathyroidism was noted in 2 patients (3.3%), recurrent one-sided laryngeal nerve paralysis in 1 patient (1.6%).

OSTEOPONTIN AS A POTENTIAL CLINICAL TUMOUR MARKER FOR CHILDHOOD CANCER

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Purpose: In clinical oncology there is a lack of biomarkers that distinguish highly aggressive tumours from moderately aggressive and non-aggressive ones. The cancer metastasis gene Osteopontin (OPN) has been investigated intensively and found to be associated with 34 different cancer types in adults. Our purpose was to compare OPN blood and cerebral fluid (CSF) levels in children of all age groups to analyse whether OPN levels are evaluated in children with cancer-diseases (cancer group; n = 47) in comparison to children with non-cancer-diseases (controls; n = 202) within the same age group.
Methods: Plasma and CSF samples of all children had been collected in the Children’s Hospital of Saarland University in Homburg/Saar. In controls we obtained 164 blood and 46 CSF samples; in cancer group 34 blood and 24 CSF samples. Children were divided into 5 different age groups (0–1, 1–5, 6–10, 11–14 and > 14 y). ELISA was used for the measurement of OPN blood and CSF levels.

Results: Within the cancer group blood and CSF samples were distributed as follows: Acute leukemias 16/15, brain tumours 5/7, lymphomas 6/2 and other solid tumours 7/0. In the cancer group median age was 8 years with a range of 0–21 years. Gender was equally distributed in cancer and control group. Significant higher blood OPN-level was found in children with cancer-disease in comparison to controls of the same age group (all p < 0.001). CSF levels in children within the cancer group were higher compared to controls, without reaching significance. OPN blood levels were significantly decreasing with age within controls (Spearman r = −0.754; p < 0.001).

Conclusion: Our study is the first one analysing blood and CSF levels in children with and without cancer. Our data indicate that OPN may play a role as a biomarker in childhood malignancies. Further research is needed to define in which cancers OPN serves as a biomarker.

BRAIN TUMOURS

PM001

BRAIN TUMOUR IN CHILDHOOD: THE IMPACT OF CRANIAL IRRADIATION AND TUMOUR LOCATION ON FERTILITY

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Purpose: While the 5-year survival rate has risen to 75% in childhood brain tumor patients, side effects of treatment are attracting increasing interest. The present analysis focuses on the impact of irradiation to the hypothalamic-pituitary-axis and of brain tumor location on fertility.

Methods: In 2008 the German nationwide survey “Fertility after Chemo- and Radiotherapy in Childhood and Adolescence, FeCe” was conducted. A questionnaire was sent to 4689 adult former patients.

Results: Among 2754 participants of the nationwide survey 1110 received cranial irradiation. In female survivors, a dosage of ≥30 gray to the pterygoid plate was associated with an increased risk of permanent amenorrhea of 16.7% (636) compared to 1.7% (3180) and 0% (0/180) in females with radiation doses of 18–29 gray and 0–17 gray, respectively (p < 0.001). A dosage of ≥30 gray to the hypothalamic-pituitary-axis was associated with a decreased number of pregnancies of 7.4% (10/135) in female participants or partners of male participants compared to 32.8% (157/478) and 12.4% (60/482) in those receiving 18–29 gray and 0–17 gray, respectively (p < 0.001). 203 brain tumor survivors were classified. 16% of the female survivors (9/57) reported transient and 7% (4/57) permanent amenorrhea. 82% (>151/182) of brain tumor survivors expressed the desire to have children and 12 pregnancies were reported.

Conclusion: High irradiation dosages administered to the hypothalamic-pituitary axis are associated with an increased risk for permanent amenorrhea and fewer pregnancies. For these patients in particular, special attention should therefore be given to fertility development.

PM002

IS IT TIME TO REVISE THE RECIST CRITERIA TO INCORPORATE STEREORECULATION? A COMPARATIVE STUDY OF MANUAL PLANIMETRY, CALLIPER MEASUREMENTS AND MODERN STERELOGICAL METHODS IN THE MEASUREMENT OF TUMOUR SIZE IN PAEDIATRIC BRAIN TUMOUR IMAGING

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Purpose: The effectiveness of chemotherapeutic strategies in paediatric oncology is measured using modified RECIST categories of Complete Response (CR), Partial Response (PR), Stable Disease (SD) and Progressive Disease (PD) originally based on two-dimensional calliper measurements of tumor x-rays. Modern 3D imaging (i.e. MRI/CT) and computer interfaces to support image analysis require the guidelines to be updated.

Methods: This study compared three techniques for measuring tumour size over time in the scans of two paediatric patients. 3D reconstruction involved painstaking manual segmentation (i.e. painting) of the tumor on every slice and drawing around it by computer mouse. Next callipers were used to obtain the major axis representative of the RECIST measurement and the product of minor and major axis representative of the WHO guidelines. Lastly, stereology was used with systematic point counting on images obtained from a random starting position.

Results: Tumour changes can be measured with acceptable precision using stereology methods in one of the third for 3D reconstruction. Stereology and 3D reconstruction showed similar results. Calliper measures under-estimated the volume change in both cases. (Tumour 1: percentage change by 3D 43.3%, Stereology 47.1% and Callipers 6.3%. Tumour 2: percentage change by 3D 38.57%, Stereology 45.24% and Callipers 23.%) Both stereology and 3D reconstruction resulted in the same RECIST categories (generalised kappa 0.67).

Stereology showed excellent intra-observer repeatability (ICC = 0.91, F = 0.18) and inter-observer reproducibility (ICC = 0.98, F = 0.63) and took on average 4 minutes to scan compared to 14 minutes for 3D reconstruction and 1 minutes for callipers.

Conclusion: Stereological methods appear to offer a substantial time saving compared to traditional 3D reconstruction and much improved reliability and precision compared to calliper measures, however this needs to be validated within Paediatric Oncology.
We performed a retrospective, international multi-center (N = 10) study to evaluate the indications for treatment and the visual outcomes following chemotherapy in children with NF1-OPG. Subjects underwent initial treatment with chemotherapy between January 1997 and December 2007. Results: In 59 evaluable subjects, the 3-year post-treatment VA was improved (31%), stable (42%) or worse (27%), compared with their pre-treatment VA. Most importantly, when compared with subjects without VA deterioration, the low likelihood of treatment failure or subsequent significant vision loss was maintained. Conclusion: Visual acuity either continued to improve or deteriorate in over half of subjects in the 3 years following completion of initial chemotherapy. Continued monitoring of vision is crucial in the first few years following treatment.

EXCELLENT LONG-TERM VISUAL PROGNOSIS FOLLOWING CHEMOTHERAPY FOR NF1 ASSOCIATED OPTIC PATHWAYS GLIOMAS WITH NORMAL BASELINE VISUAL ACUITY

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Purpose: Although optic pathway gliomas (OPGs) arise in 15–20% of children with neurofibromatosis type 1 (NF1), no more than half will develop vision loss. There is little information in the literature regarding the indications for treatment. Some recommend treatment solely for patients with documented visual deterioration, while others treat for completion of initial chemotherapy in 88 children with NF1-OPG. 32% improved, 40% remained stable, and 28% declined. We now report VA outcomes 3 years after completion of initial therapy.

Methods: We performed a retrospective, international multi-center (N = 10) study of visual outcomes following chemotherapy in children with NF1-OPG. Subjects underwent initial treatment with chemotherapy between January 1997 and December 2007. Results: In 59 evaluable subjects, the 3-year post-treatment VA was improved (31%), stable (42%) or worse (27%), compared with their pre-treatment VA. Most importantly, when compared with subjects without VA deterioration, the low likelihood of treatment failure or subsequent significant vision loss was maintained. Conclusion: Visual acuity either continued to improve or deteriorate in over half of subjects in the 3 years following completion of initial chemotherapy. Continued monitoring of vision is crucial in the first few years following treatment.
**PM010**

**IN VIVO EVALUATION OF THE PATHOGENIC AND THERAPEUTIC RELEVANCE OF BRAF FUSION GENE VARIANTS IN JUVENILE PILOCYTIC ASTROCYTOMA**

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**Purpose:** Pilocytic astrocytomas (PAs) typically show a benign behavior. Nevertheless, treatment of tumors in critical anatomic locations remains challenging, since tumors often respond to conventional chemo and radiotherapy poorly. BRAF fusion genes, rendering the MAPK pathway constitutively active, were shown to comprise a hallmark genetic event in many GBM patients. The study aims at the in vivo characterization of BRAF fusion gene variants found in PA thus suggesting a promising tumor-specific therapeutic target. This study aims at the in vivo characterization of BRAF fusion gene variants found in PA thus suggesting a promising tumor-specific therapeutic target. This study aims at the in vivo characterization of BRAF fusion gene variants found in PA thus suggesting a promising tumor-specific therapeutic target.

**Methods:** Participants were 25 BT patients (M age = 10.6; SD = 3.0; 52% White; M age months from diagnosis = 20.8; SD = 41.1) and 21 comparison traumatic brain injury (TBI) patients (M age = 13.2; SD = 4.5; 56% White; M age months from injury = 1.8; SD = 42.6). The LANSE is a brief (20–25 minute) measure of patient orientation, attention, executive functioning, language, verbal and visual memory, and visual-spatial functioning normed on children with TBI. BT and TBI patients 6 to 17 years were administered the LANSE by trained psychology staff. Caregivers of BT patients completed the Child Behavior Checklist (CBCL), a parent-report measure of child emotional, behavioral, and cognitive functioning.

**Results:** Common domains of impairment for BT patients were attention, executive functioning, and verbal memory. BT patients (M = 3.56, SD = 3.00) exhibited a similar number of domains of probable impairment as TBI patients (M = 4.71, SD = 3.18).

**Conclusion:** Screening results from the LANSE are consistent with full neurocognitive examination results reported in the literature. The LANSE appears to be a sensitive screening measure that can be feasibly administered during regular clinic visits. For pediatric BT patients, the LANSE may be a valuable tool for early detection of neurocognitive impairment. Data collection is ongoing.

**PM011**

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**Purpose:** Research on pediatric brain tumor (BT) patients has identified long-term neurocognitive deficits in areas such as attention, memory, and executive functioning. With this knowledge comes the need for brief neurocognitive screening measures that can readily detect impairment and be easily administered in clinical settings so as to guide early intervention. The purpose of this study was to examine the feasibility and sensitivity of the Lebby-Asbell Neurocognitive Screening Examination (LANSE) for pediatric BT patients in a regular clinical setting.

**Methods:** Participants were 25 BT patients (M age = 10.6; SD = 3.0; 52% White; M age months from diagnosis = 20.8; SD = 41.1) and 21 comparison traumatic brain injury (TBI) patients (M age = 13.2; SD = 3.6; 56% White; M age months from injury = 1.8; SD = 42.6). The LANSE is a brief (20–25 minute) measure of patient orientation, attention, executive functioning, language, verbal and visual memory, and visual-spatial functioning normed on children with TBI. BT and TBI patients 6 to 17 years were administered the LANSE by trained psychology staff. Caregivers of BT patients completed the Child Behavior Checklist (CBCL), a parent-report measure of child emotional, behavioral, and cognitive functioning.

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**Conclusion:** Screening results from the LANSE are consistent with full neurocognitive examination results reported in the literature. The LANSE appears to be a sensitive screening measure that can be feasibly administered during regular clinic visits. For pediatric BT patients, the LANSE may be a valuable tool for early detection of neurocognitive impairment. Data collection is ongoing.

**PM012**

**FEASIBILITY OF LONG-TERM INTRAVENTRICULAR THERAPY ALTERNATING ETOPOSIDE AND LIPOSOMAL CYTARABINE: EXPERIENCE IN 41 CHILDREN WITH MALIGNANT BRAIN TUMORS**

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**Purpose:** Embryonal brain tumors carry a high risk for leptomeningeal dissemination and tumor cells floating in the CSF are often not amenable to systemic and/or antiangiogenic chemotherapy. We report on our experience with an intraventricular therapy consisting of alternating courses of liposomal cytarabine and etoposide.

**Methods:** Between 2004 and 2012, 41 patients aged 0.5 to 21 years (median age: 8 years) with various malignant brain tumors received intraventricular etoposide 0.25 mg (median 200 mg) cumulative dose, 1-19 (median 4) per patient were given. 905 mg (median 200 mg) cumulative dose, 1-19 (median 4) per patient were given. Immediate toxicities such as transient headaches, nausea, and vomiting were more frequent after liposomal cytarabine (11 versus 4). In addition, 9 patients receiving liposomal cytarabine developed visual disturbances and 6 intracranial hypertension requiring lumbar puncture. Since all patients received some sort of concurrent anti-cancer therapy, the efficacy of intrathecal therapy cannot be assessed independently. However, 16/41 patients died of local recurrences and only 1/25 surviving patients developed metastases under intrathecal therapy.

**Conclusion:** In conclusion, alternating intraventricular liposomal cytarabine and etoposide is feasible, allows for a more dose dense schedule and may produce responses.
**PM014**

**CHANGES IN THE PATTERNS OF CARE OF CENTRAL NERVOUS SYSTEM TUMOURS AMONG 16–24 YEAR OLDS AND THE IMPACT ON SURVIVAL IN YORKSHIRE BETWEEN 1990–2009**

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**Purpose:** To describe the influence of patterns of care on survival for teenagers and young adults with primary Central Nervous System tumours.

**Methods:** We used high quality data from one population based cancer registry in Yorkshire, UK to describe primary central nervous system tumours in teenagers and young adults (16–24 yrs) diagnosed between 1990 and 2009. The Ritch classification scheme was used to identify differences by tumour subgroup. Incidence, patterns of care, and survival trends were described using Poisson and Cox regression.

**Results:** There were 163 cases comprising 98 Astrocytomas, 17 “other gliomas”, 14 Ependymomas, 11 Medulloblastomas and 23 “other intracranial and intraspinal neoplasms” yielding an overall incidence of 18.1 million person years. Care varied significantly over time and by Principal Treatment Centre (Leeds 77%, Hull 23%), coordinating specialty (Neurosurgery 53%, Clinical Oncology 22%, Paediatrics 17%, Other Adult Services 8%), and treatment received. Cox regression showed no significant difference in survival by age, sex, treatment centre, level of deprivation, year of diagnosis or coordinating specialty, but a significant difference by tumour grade and diagnostic group. Survival improved for all diagnostic groups except astrocytoma, although only the Medulloblastoma group showed a significant change over time.

**Conclusion:** The lack of any significant improvement in survival over time in most diagnostic groups warrants further investigation and provides justification for a more collaborative regional approach to the care of central nervous system tumours, perhaps through the development of regional guidelines for this unique population. More detailed analysis of relapse patterns and pre-diagnostic symptoms would also be informative for this cohort.

**PM015**

**WHAT IS THE REAL INCIDENCE OF PEDIALRIC BRAIN TUMORS? EXPERIENCE IN THE GERMAN NATIONAL PEDIATRIC TUMOR NETWORK HIT**

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**Purpose:** The HIT-network was established in the year 2000 in Germany as a consortium of prospective nation-wide studies or registries with concerted central reference institutions for neuropathology, neuroradiology, CSF diagnostics, radiotherapy, and biometrics, aiming to improve diagnostic assessments, therapeutic recommendations, and ultimately the prognosis of childhood effects of Actinomycin-D and studied the resulting molecular effects.

**Methods:** TP53 mutation status of 130 primary ependymomas and the two ependymoma cell lines was assessed by Sanger sequencing of exons 2−11. p53 immunohistochemistry was performed on a tissue microarray of 398 primary tumours. Cell viability was assessed via MTS assay and proapoptotic effects of Actinomycin-D treatment and adriamycin were analysed by flow cytometry. Changes in the gene expression profile after treatment were evaluated by Agilent 44K microarrays and validated by Western blotting and quantitative PCR.

**Results:** TP53 sequencing of primary ependymomas confirmed the low rate of somatic mutations (3%) yet p53 accumulation occurred much more frequently (22%) and was associated with worse progression-free and overall survival. After treatment of the cells with different concentrations of Actinomycin-D we proved the IC-50 to be in the low nanomolar range for both cell lines. Transcriptome analyses of high-dose (100 nM), low-dose (5 nM) and untreated cells revealed many differentially expressed genes including several p53-associated candidates (i.e. PUMA, TP53I3). At protein level we validated the Actinomycin-D induced upregulation of p53 interaction partners (MDM-2, p21). Flow cytometric analysis of Actinomycin-D treated cells demonstrated the high apoptotic potential of low-dose application of the agent.

**Conclusion:** We demonstrate here that Actinomycin-D can restore a functional p53 response and induce apoptosis. Treatment with this agent could therefore be a very promising novel therapeutic option for high-risk ependymoma patients, who frequently exhibit p53 inactivation by mechanisms other than mutation.

**PM016**

**AURORA KINASE INHIBITION DECREASES PROLIFERATION AND DIMINISHES CLONOGENIC CAPACITY IN PEDIATRIC MEDULLOBLASTOMA CELL LINES**

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**Purpose:** Medulloblastoma (MB) is the most common malignant childhood brain tumor. Because aggressive multimodal therapy, a significant proportion of medulloblastomas have proved largely refractory to treatment. Aurora kinase family (A, B and C) have been studied in several tumors. These proteins act in different cell cycle processes such as centrosome maturation, mitotic spindle assembly, chromosomal bi-orientation and cytokinesis. Aurora-A and Aurora-B have been found overexpressed in different types of malignancies, inclusive in MB, and the pharmacological activation of inhibition of them has shown promising results for cancer therapy. In this work it was evaluated the effects of Aurora kinase inhibitor ZM447439 (ZM) (Tocris Bioscience, Avonmouth, United Kingdom) on pediatric MB cell lines UW402 and UW473.

**Methods:** Cell proliferation was measured by XTT assay (XTT II; Roche Molecular Biochemicals, Indianapolis, IN). IC50 analyses were calculated using the CalcuSyn program. Cells were treated with ZM at concentrations of 2−20 μM and incubated for 24, 48 and 72 h for proliferation assay and at concentrations of 200−1000 nM and incubated for 48 h for clonogenic assay. The experiments were performed in triplicate.

**Results:** ZM caused inhibition of cell proliferation in a time and dose dependent manner in both cell lines studied (p < 0.05). IC50 values were 15.17 μM and 6.99 μM for UW473 and UW402 cells, respectively. ZM also caused diminution of clonogenic capacity in a dose-dependent manner in the two cell lines (p < 0.05).

**Conclusion:** These results showed that inhibition of Aurora kinases by ZM447439 leads to antineoplastic effects on pediatric MB cell lines. Thereby, these data suggest that Aurora kinase inhibition may be a target for MB treatment. Other functional studies are being conducted to expand these results.

**PM017**

**CARBOPLATIN AND VINCISTINE AS TREATMENT FOR PROGRESSIVE HYPOTHALAMIC/OPTIC PATHWAY GLIOMAS IN CHILDREN WITH NEUROPHIROMATOSIS TYPE 1 (NF1) AND RISK OF SECOND MALIGAN NT NEUROPLASMS: REPORT FROM THE CHILDREN’S ONCOLOGY GROUP (COG)**

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**Purpose:** The HIT-network was established in the year 2000 in Germany as a consortium of prospective nation-wide studies or registries with concerted central reference institutions for neuropathology, neuroradiology, CSF diagnostics, radiotherapy, and biometrics, aiming to improve diagnostic assessments, therapeutic recommendations, and ultimately the prognosis of childhood
**PM018**

**A PROSPECTIVE STUDY OF CEREBRAL, FRONTAL LOBE AND TEMPORAL LOBE VOLUME AND NEUROPSYCHOLOGIC PERFORMANCE IN CHILDREN WITH PRIMARY BRAIN TUMORS TREATED WITH CRANIAL RADIATION**

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**Purpose:** Cranial radiation (RT) can result in long-term effects on the developing brain. This prospective study aims to assess the effects of cranial RT on cerebral, frontal lobe, and temporal lobe volume and its association with higher cognitive functioning.

**Methods:** Ten pediatric patients (median age 9.0 years; range: 1.2–15.3) with primary brain tumors treated with cranial RT were evaluated. The primary brain tumors consisted of medulloblastoma, ependymoma, and supratentorial PNET. The group consisted of 14 age- and sex-matched controls. Quantitative MRIs and neuropsychologic (NP) tests were performed at baseline and at 6, 15, and 27 months following RT and at corresponding time points for the controls. Linear mixed-effects (LME) models were used for analyses. NP tests evaluated language (Retrieval Fluency), memory (Bead Memory), processing (Sound Blending), and intelligence (Wechsler Intelligence Scale for Children [WISC-III]).

**Results:** Cerebral volume increased with age in all children (p = 0.01). A significant relationship was found between cerebral volume and performance on PPVT-3 (p = 0.05), suggesting that a reduced growth rate of cerebral volumes were associated with lower measures of intelligence. There was also a significant relationship between cerebral RT dose and performance on PPVT-3 (p = 0.003) with higher RT doses associated with lower scores in patients. Right frontal lobe, left frontal lobe, and left temporal lobe volumes were also found to increase with age in all children (p = 0.05). However, it was only the right frontal lobe and right temporal lobe volumes which differed significantly over time with patients having lower volumes than controls (both p < 0.05).

**Conclusion:** This prospective study found a significant relationship with cerebral volumes and RT dose on measures of intelligence. There was also a significant effect of treatment on development of the right frontal and temporal lobes. The results of this study provide further support to clinical trials aimed at reducing cranial RT dose in the pediatric population.

**PM020**

**FEASIBILITY, TOXICITY AND PRELIMINARY RESULTS OF HELICAL TOMOTHERAPY IN PEDIATRIC MEDULLOBLASTOMA**

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**Purpose:** Current practice in the management of completely resected medulloblastoma in children is to deliver reduced-dose craniospinal irradiation in combination with chemotherapy. The purpose of this study was to assess the feasibility, toxicity, and outcome of helical tomotherapy (HT) for pediatric medulloblastoma.

**Methods:** From May 2007 to July 2010, 21 consecutive pediatric patients (11 male; 10 female) with diagnosis of standard (N = 11) or high risk (N = 10) medulloblastoma were treated with HT, all in supine position. Median age was 5 years old (range, 3–14). Two patients were treated with 2 sessions per day. All the other patients received a standard fractionation regimen with one fraction per day. The total dose delivered to the craniospinal axis was 23.4 Gy (N = 12), 36 Gy (N = 8), or 39 Gy (N = 2); and 54 Gy to the posterior fossa except for the 2 patients who were treated twice per day (60 Gy). The Kaplan-Meier method was used to provide estimates of the overall survival (OS) and disease-free survival (DFS). Toxicity was evaluated using the Radiation Therapy Oncology Group scale.

**Results:** The median follow-up was 23 months (range, 3–58). Median OS was 27 months (range, 6–60). There were 2 local failures, 2 distant failures, and 3 both local and distant failures. Two-year DFS and OS rates were 86% and 91%, respectively. Early severe (grade ≥ 3) toxicity was mostly hematologic (47.6% of patients) with grade IV neutropenia, 1 grade IV thrombocytopenia, and 1 grade IV anemia experienced by severe long-term toxicity. The average dose received by the critical organs was acceptable. **Conclusion:** HT in pediatric medulloblastoma is well-tolerated. In our series, no patient had long-term severe toxicity. HT seems to be ideally suited to plan such long and complex-shaped target volumes, avoiding any junction, field-matching and abutment dosimetry.

**PM021**

**DIFFUSE INTRINSIC PONTINE GLIOMAS IN CHILDREN: RESULTS FROM A SINGLE CENTER**

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**Purpose:** The prognosis of children with diffuse intrinsic pontine gliomas (DIPG) is dismal. This study aims to evaluate characteristics and treatment outcome of children with DIPG. **Methods:** We retrospectively reviewed the characteristics and treatment outcome of children with DIPG treated at Istanbul University, Oncology Institute from 1999 to Feb 2012. We also evaluated the group that prospectively received RT with concurrent and adjuvant temozolomide after 2004.

**Results:** 51 children (26 female, 25 male) with the median age of 7 years (6 months–16 years) were analyzed. The median duration of symptoms was 30 days (2–630 days). The frequent clinical findings were ataxia, strabismus and motor weakness. All patients received RT. 12 received only RT. 39 had concomitant and/or adjuvant chemotherapy with RT. Since 2004, 20 patients received the institutional protocol consisting of temozolomide (TMZ)
PM022
INITIAL HYPOTHALAMIC INVOLVEMENT IS A MAJOR RISK FACTOR FOR IMPAIRED PROGNOSIS AND QUALITY OF LIFE IN CHILDHOOD CRANIOPHARYNGIOMA REGARDLESS OF CHOSEN TREATMENT STRATEGIES - RESULTS OF KRA NIOPHARYNGEOM 2000

Herrmann Lothar Müller1,2, Ueli Gallehy1, Christian Fischbach2, Andreas Faldum2, Monika Warmuth-Metz3, Torsten Pittsch3, Gabriele Calaminus3, Niels Sörensen3, Study Committee KRA NIOPHARYNGEOM 2000/2007

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Purpose: Hypothalamic obesity has major impact on prognosis and quality of life (QoL) in childhood craniopharyngioma (CP). The pathogenetic relevance of initial hypothalamic involvement versus treatment-related hypothalamic lesions is a matter of controversy.

Methods: 120 patients were recruited prospectively during 2001 and 2007 and evaluated after 3 yrs of follow-up. Body mass index (BMI) and QoL, at diagnosis and 36 mo after diagnosis were analyzed based on reference assessment of tumour localization and post-surgical hypothalamic lesions using a standardized grading system (no, anterior, posterior involvement/lesion). Treatment was analyzed regarding neurosurgical strategy of 50 participating neurosurgical centres and the centre sizes. Based on patient load during the 6-year recruitment period, participating centres were categorized as small (≤1 ptys/year), middle (2.5–5 ptys/year) or large-sized centres (>5 ptys/year).

Results: BMI SDS at diagnosis was similar in patients with or without hypothalamic involvement. Surgical lesions of anterior and posterior hypothalamic areas were associated with higher increases in BMI SDS during 36 mo post-diagnosis compared to patients without or only anterior lesion (+1.8±1.3MSD, p = 0.013; +2.1±1.3MSD, p = 0.011), negatively impacting QoL in patients with posterior hypothalamic lesions. Surgical strategies varied between the 50 neurosurgical centres and the centre sizes. Based on patient load during the 6-year recruitment period, participating centres were categorized as small (1 ptys/year), middle (2.5–5 ptys/year) or large-sized centres (>5 ptys/year).

Conclusion: Radical strategies leading to posterior hypothalamic lesions are not recommended due to potential to exacerbate hypothalamic obesity and impaired QoL. Because our results show that initial hypothalamic involvement has a priori effect on prognosis, our recommendations are based on recognizing CP as a chronic disease. Supported by German Childhood Cancer Foundation.

PM023
SIOP CHOROID PLEXUS TUMOR INITIATIVE - INTERIM REPORT 2012

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Purpose: The Choroid Plexus Tumor (CPT) group aims to improve survival and quality of life of patients with choroid plexus tumors including choroid plexus papilloma (CPP) and choroid plexus carcinoma (CP). Because our results show that initial hypothalamic involvement has a priori effect on prognosis, our recommendations are based on recognizing CP as a chronic disease. Supported by German Childhood Cancer Foundation.

PM024
PROTON THERAPY FOR LOW GRADE GLIOMA: EARLY CLINICAL OUTCOMES

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Purpose: By limiting exposure of non-target normal tissues to radiation, proton therapy (PT) may reduce side effects in children with low grade glioma (LG). The purpose of this study was to report acute toxicity and early disease control in patients treated with PT.

Methods: From 2007 to 2012, 40 patients with a median age of 8.5 years (range, 2.1–21.6 yrs) were treated with PT for non-metastatic LGG. 50% of tumors were located in the optic pathway/hypothalamic region. Two patients had known NF-1. Eight patients were treated based on radiographic criteria alone: Of the remaining 32 patients, 19 and 13 had WHO grade I and II glioma, respectively, and 10, 5, 10, 4, and 1 patients received PT for LGG, PA, T, I, 2, 3, and 4, respectively.

Results: 38/40 patients survive. One patient has died of locally progressive disease and one of intercurrent illness. Two living patients are receiving salvage chemotherapy for local recurrence. No patients have developed metastatic disease. Two patients had acute grade 2 toxicity (partial seizure and emesis). One patient (18 yrs old) had grade 3 toxicity: Brainstem necrosis approximately 5 months following 54 CGE for a brainstem pilocytic astrocytoma. This resolved following steroids and hyperbaric oxygen treatment. At early time points, 1 patient had partial ipsilateral hearing loss; we have not observed vision decline or radiation vasculopathy.

Conclusion: PT allows highly conformal radiation delivery without compromising early tumor control or increasing toxicity. To date, this is the largest cohort of children with LGG treated with PT and provides the foundation for the long-term outcome studies necessary to accurately characterize the therapeutic ratio of PT.

References:

PM025
PHASE 2, SINGLE ARM TRIAL OF IRINOTECAN AND CISPLATIN IN CHILDREN WITH HIGH-RISK GLIOMAS

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Purpose: After a pilot study suggesting that irinotecan/cisplatin (IC) may be effective for pediatric gliomas, we conducted this phase II trial (EudraCT:2009-010742-59).

Methods: Patients diagnosed with high-risk (HR) gliomas (HGG, DIPG, or HR-LGG) received sixteen weekly outpatient iv. cycles of C (30 mg/m2) and I (65 mg/m2). Malignant gliomas received radiation at the end. Objective response was assessed with MRI plus volumetric analysis and [11C]MET-PET, along with performance/psychological tests, MGMT-promoter-methylation, MSI (IHC), BRAF analysis (V600E-mutation and BRAF-family fusion) were used. Statistical analysis was performed with the chi-square test. Results: Since November/2009, 29 patients aged 7-17y (mean = 8.4yrs), diagnosed with DIPG (n = 4), HGG (n = 4), atypical gangliocytoma (n = 5), LGG n = 15 (PA = 4, Atrocytoma NOS = 7, Pilomyxoid A = 1, Ganglioglioma = 1, NFI = 2), were included. Four patients died of disease (2HGG, 2DIPG). Clinically significant responses (PR + SD) were found in 14 (51%) patients (EpitT 9LGG/1AA), progressive disease in 8 (3DIPG/3AA/2LGG), 7 pts remain on treatment. High

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SUV in [11C]MET-PET correlated with progressive HGG. CSF and plasma samples were analyzed for free and encapsulated cytarabine, plasma samples were selected. Ingenuity Pathway Analysis (IPA, www.ingenuity.com) was used to identify enriched biological functions among differentially expressed genes between the ATRT and MB. Genes with FC > 2 and p-value < 0.05 were selected. Ingenuity Pathway Analysis (IPA, www.ingenuity.com) was used to identify enriched biological functions among differentially expressed genes.

Results: Among the 1,002 transcripts differentially expressed between ATRT and MB, 39 present therapeutic properties and hold target drugs that are already in test for different types of diseases including cancer. Among them, 21 were significantly up-regulated and therefore urgently needed. This study aims to identify new potential therapeutic targets for ATRTs.

Methods: We analyzed the gene expression (GE) profiles of 14 untreated ATRT and 2 cell lines (MON, kindly granted by Dr. Delattre, Institut Curie - Paris and G401, America Type Culture Collection-ATCC), compared to 6 untreated medulloblastomas (MB). Samples were snap frozen and stored at -80 °C. Illumina HT-12 whole-genome-expression-arrays were used for GE profiling. Fold changes (FC) were calculated and t-test was applied to assess the significance of differentially expressed genes between the ATRT and MB. Genes with FC > 2 or FC < 2 and p-value < 0.05 were selected. Ingenuity Pathway Analysis (IPA, www.ingenuity.com) was used to identify enriched biological functions among differentially expressed genes.

Conclusion: The identification of genes that might represent new therapeutic targets for ATRTs gives new hope for patients suffering from this disease. Funded by the Rally Foundation for Childhood Cancer Research in memory of Hailey Trainer and Dr. Ralph & ATRTs gives new hope for patients suffering from this disease. Funded by the Rally

Conclusion: The administration of 25mg liposomal cytarabine in children less than 3 years of age, 35mg in children 4 to 7 years, and 50mg in older children shows sufficient drug exposure and appears to be safe and well tolerated with concomitant dexamethasone.

Purpose: Optimal treatment of ependymoma remains controversial. Prognostic value of histological grade is also questioned. In our historical patients with anaplastic ependymoma (AE) treated with surgery and craniospinal radiotherapy survival was 32%. We have thus introduced a new treatment protocol.

Methods: Between 2003 and 2011, 40 patients aged 7 m-17.5 yrs/median 5 yrs were treated with this protocol (surgery, chemotherapy and focal radiotherapy (patients > 3 yrs). AE was defined when high mitotic activity (5-10/hpt), microvascular proliferation and foci of necrosis were present. There were 26 pts over and under 13 yrs of age, 25 pts had infratentorial and 15 supratentorial tumors. Complete resection was performed in 17 pts, 23 had subtotal or partial resection. EFS and OS were assessed, correlated with age, localization, resection (assessed by neurosurgeon’s MRI at 72 hrs).

Results: 36 out of 40 patients (11 < 3 yrs and 25 > 3 yrs of age) were alive with 5 yrs EFS and OS of 62% and 88%. Eleven out of 14 pts < 3 yrs of age are alive, 10m-7yrs5yrs from diagnosis. Twenty-five out of 26pts > 3 yrs of age are alive, 6m-8.5yrs4yrs9m from diagnosis. All patients with supratentorial localization are alive 5m-8.5yrs6yrs from diagnosis. Twenty-one out of 25 patients with infratentorial tumors are alive from 9m-8yrs m/4yrs m. All 17 patients with complete tumor resection are alive with 5 yrs EFS of 100%. There was favorable correlation between EFS and supratentorial patients (p=0.025), complete resection (p<0.001) and age over 3yrs (p<0.006) whereas age did not correlate with OS.

Conclusion: Introduction of our protocol resulted in improved survival of children with AE. Excellent results in completely resected supratentorial AE indicate a change in the treatment strategy which we are now considering. Supported by The National Centre for Research and Development.
CONCLUSION: Our analysis shows that CNS tumours were more frequent in children than in adolescents and that the most common malignant tumours in younger children and adolescents were medulloblastoma and high-grade glioma respectively. Adolescents with high-grade glioma, medulloblastoma/PNET and brain stem glioma had a worse outcome comparing to younger patients. Supported by The National Centre for Research and Development.

PM030

TREATMENT RESULTS OF METASTATIC MEDULLOBLASTOMA (M2 AND M3 ACCORDING TO CHANG CLASSIFICATION) IN CHILDREN OVER 3 YEARS OF AGE: EXPERIENCE FROM ONE INSTITUTION

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Purpose: Analysis of treatment results of patients with M2 and M3 medulloblastoma treated according to Polish Pediatric Neurooncology Group protocol.

Methods: Between 1999 and 2009 153 patients older than 3 years with medulloblastoma were treated in the Children’s Memorial Health Institute. 59 presented with metastases (19 M0&1 and 40 M2&3). 

Results: 5year OS was 87% in M0&1 group and 62% in M2&3 (p = 0.005); Seyer PFS was 86% and 59% respectively (p = 0.003). There was no correlation between age, sex and disease stage (mean 9.4 in either group, 105 boys, 68 M0&1, 40 M2&3; 48 girls 29 M0&1, 19 M2&3), metastases were localized in brain in 7 pts, spine 35 and in 17 pts in both. There was a higher proportion of LCA subtype in the metastatic group (3.8% vs 16.9, p = 0.007). Seyer OS was 64.3% in classic medulloblastoma and 29% in anaplastic medulloblastoma, PFS was 62% and 0 respectively. Seyer OS was 71% in pts with brain, 67.7% in pts with spine and 47.5% in pts with metastases in both sites. The molecular analysis is ongoing and the results will be presented.

Conclusion: The strategy of conventional chemotherapy administered both before and after individualized irradiation is an option of treatment that offers long time remission to approximately 60% of M2&3 patients, but is ineffective in patients with LCA Medulloblastoma.

PM031

MANAGEMENT OF CRANIOPHARYNGIOMA: THE LIVERPOOL EXPERIENCE FOLLOWING INTRODUCTION OF CCLG GUIDELINES: INTRODUCING A NEW RISK ASSESSMENT GRADING SYSTEM

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Purpose: In 2005 the Children’s Cancer Leukaemia Group (CCLG) proposed a management pathway for cranioopharyngioma that advocated limited surgery followed by upfront radiotherapy for large tumours with hypothalamic involvement and a radical resection only for smaller tumours without hypothalamic involvement. This strategy is not proven to provide optimum care or to be risk-free. The aim of this study is to review our experience of the management of cranioopharyngioma diagnosed since the introduction of the CCLG guidelines.

Methods: All children diagnosed with cranioopharyngioma at Alder Hey Children’s NHS Foundation Trust in the period between 1st January 2005 and 30th June 2011 were included. Management was based on presence of hypothalamic syndrome, hydrocephalus, tumour size and radiological Paris grading system. Endoscopic drainage of tumour cyst was performed prior to formalizing risk grade and surgical strategy. Definitive surgery was performed in 4–6 weeks-time. In this respect we developed a grading criteria.

Results: Twenty patients were included. Ten of the children underwent endoscopic cyst drainage prior to definitive surgery. The results of the subsequent surgical excision were complete resection, near total resection or sub-total resection in 30%, 25% and 45% patients respectively. There was no surgical related mortality and no new neurological deficits. Nine patients underwent radiotherapy at some stage.

Conclusion: In this study we tried to develop an advanced model for the management of cranioopharyngioma with a new risk grading system. This may have a direct impact in the surgical strategy and outcome and could be able to improve morbidity.

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SIOP ABSTRACTS 1081

PM032

THE ROLE OF SURGERY IN OPTIC PATHWAY & CHIASMAL- HYPOTHALAMIC GLIOMAS IN CHILDREN

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Purpose: Optic-Chiasmatic-Hypothalamic tumours are benign tumours situated in an exquisitely sensitive region of the brain. The tumour location and resultant symptoms have lead to much debate about optimal treatment. In particular the role of surgery has received a particular focus due to the difficulties of access and potential complications.

Methods: We present a cohort of patients managed by the neuro-oncology team at Alderhey and a single surgeon. Data were collected retrospectively until 2009, then prospectively. Tailored treatment strategies were used including observation, and combinations of surgery chemotherapy and or radiotherapy. Tumour control rates and outcomes are reviewed.

Results: Forty-three patients were treated between 1998 and 2010. Mean age at diagnosis was 7years 5months (range 1yr1m to 16yr8m, median 5yr9m), with slight female predominance. Follow-up ranged from 6 months to 1years 7months (mean 5yr 2m, median 4yr 9m). Surgical debulking was required for a total of 21 patients (19 NonNF1, 2 NF1) - 15 new patients and 6 from other centres. An additional 2 patients only had biopsies performed (1 endoscopic and 1 via craniotomy). The extent of tumour debulking achieved was > 70% for 16 patients, 50–70% for 4 patients and < 50% for 4 patients. 13 of the patients had chemotherapy at some point in their management and only 5 patients had radiotherapy. PFS was 67% over 5 years with Overall survival of 95% at five years.

Conclusion: Good long-term survival and functional outcomes can be achieved in children with OPCHG. Surgery via a midline transcallosal approach can safely debulk the centre of third ventricular tumours whilst preserving hypothalamic and visual function. Due to high rates of long-term survivors we recommend observation or chemotherapy for initial treatment. Surgery has a role for diagnosis, tumour control, relief of mass effect, and optic decompression. We prefer to limit radiotherapy to older children due to late effects.

PM033

TRANSCRIPTIONAL PROFILES OF MEDULLOBLASTOMA TUMOURS: CORRELATION WITH CLINICAL AND HISTOPATHOLOGICAL FEATURES. AN EXPERIENCE FROM A SINGLE INSTITUTION

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Purpose: Since the biological heterogeneity of medulloblastoma is clearly of clinical relevance, molecular sub-types of tumours were identified and further tested in the cohort of uniformly treated patients.

Methods: Fifty-one patients with known transcriptional profiles of tumours based on RNA analysis were investigated for clinical and histopathological correlations. Subsequently, using a panel of representative antibodies for identification of transcriptional sub-types, extended analyses was performed in the groups of uniformly treated patients. Further, an association between the biological type of tumour and the site on diagnosis was assessed using MRI analysis.

Results: Our analysis revealed two groups of patients with an excellent survival rate who belonged to either the WNT group or to the group of infants with desmoplastic/nodular or MBEN histopathology. All the latter patients were spared intracranial irradiation and 30% of them relapsed; however, after the introduction of second line therapy, all are disease free. This result is in striking contrast with the outcome for infants with classic or anaplastic histopathology, who performed badly on the same treatment (p < 0.0001). Among older patients, those with transcriptional group C tumours had a worse survival rate and on average relapsed one year earlier than patients from group D. Almost half of the group C tumours displayed anaplastic histopathological features. MRI images indicate that all three WNT tumours analysed so far were attached to the dorsal surface of the brain stem pointing to this region as a potential site of origin for tumours of the WNT type.

Conclusion: Our preliminary analysis confirmed that the biological characteristic of the medulloblastoma tumour is related to other clinical and histopathological parameters and should be taken into account in treatment stratification schemes.

PM034

EFFECTS OF RESVERATROL AND 5- AzA-2' DEOXYCYTIDIN ON DOUBLE-STRAND BREAK REPAIR AND CLONOGENIC SURVIVAL AFTER IRRADIATION OF HUMAN MEDULLOBLASTOMA CELL LINES

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PM036
ANALYSES OF CANCER INCIDENCE AND CAUSES OF DEATH IN CHILD-PARENT TRIOS: CLUES TO AETIOLOGY OF CHILDHOOD CENTRAL NERVOUS SYSTEM (CNS) TUMOURS

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Purpose: In most childhood CNS tumours aetiology is unknown. However a small proportion of cases occur with heritable syndromes. Familial cancer patterns may give pointers to environmental as well as genetic causes.

Methods: CNS tumour cases from North West England, diagnosed under age 15 years, 1954–2008, and their parents were traced and flagged at the National Health Service Information Centre. This provides continuous, prospective notification of incident cancers and causes of death. Expected numbers (E) of cancers within the cohort were calculated from national cancer incidence rates and compared with the observed (O) using Poisson regression.

Results: The cohort included 1389 case children, 1178 mothers and 1078 fathers. There were 297 cancers in parents below the age of 80 years. (E = 266, P = 0.03) including 18 CNS tumours (E = 7.45, P = 0.001) and 3 bone sarcomas (E = 0.58, P = 0.02). 31 cancers occurred between ages 15 and 39 years (E = 17.2, P = 0.002) including 8 breast cancers (E = 3.7, P = 0.04). There were 44 subsequent primaries in case children (E = 9.3, P < 0.001) including 23 CNS tumours, some of which may be therapy related (E = 0.57, P < 0.001) and 3 breast cancers under 40 years (E = 0.51, P = 0.02) which may be syndrome related. Analyses of clustering of cancers in parents with subsequent primaries and other factors in case children, together with causes of death in parents, will be conducted to explore putative genetic and environmental factors.

Conclusion: Cancer excesses in case children and their parents may be syndrome-associated but might also relate to environmental agents relevant to aetiology of childhood CNS tumours.

PM037
CHANGING FAILURE PATTERN WITH CHANGING RADIOTHERAPY TARGET VOLUME IN EPENDYOMA?

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Purpose: Management of ependymoma includes aggressive surgery and RT. The RT target volume has been progressively decreased from whole posterior fossa to anatomically targeted CTV. We reported 3 breast cancers in a case child treated between 1996 and 2006. With the further reduction of target volumes and changes in RT technique, we undertook an analysis of the failure pattern in a consecutive series of 94 children with histologically confirmed ependymoma treated with high-dose RT at our center from 2006-2016.

Methods: The following steps were undertaken: retrospective analysis of children with CNS tumours from our center treated before 1996 was performed to serve as a reference since it was the era of whole posterior fossa RT. The primary goal of reducing the margins for RT is to reduce the exposure of normal tissue and the related side effects. This case illustrates the potential for geographic miss with these new RT target volumes and points out the need for optimal imaging techniques.

Conclusion: The use of a reduced CTV margin in PF ependymoma mandates especial care these new RT target volumes and points out the need for optimal imaging techniques.

PM038
THE TREATMENT OF AVERAGE RISK MEDULLOBLASTOMA WITH CHEMOTHERAPY, REDUCED DOSE CRANIOSPINAL IRRADIATION, AND TUMOR BED ONLY BOOST: THE UNIVERSITY OF WASHINGTON EXPERIENCE 1990–2008

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Purpose: To report a single institution's experience with a prospective protocol for the treatment of average risk medulloblastoma using craniospinal and tumor bed irradiation.

Methods: Between 1990 and 2008, 1735 patients were registered in the SIOP 99-3 trial. Since 2002 1735 patients were registered. LGG were the most common- 42.8%, MB-PNET- 58.8 HGG-26.2%, Anaplastic GCT-3.4%. Interdisciplinary approach and unified treatment protocols resulted in the following 5 yrs OS survival: LGG - 95.2%, MB/PNET- 58.8% HGG-26.2%, Anaplastic GCT-3.4%. Interdisciplinary consultations at our center were available for all patients diagnosed with primary CNS tumours from our center treated before 1996 was performed to serve as a reference since it was the era of whole posterior fossa RT. The primary goal of reducing the margins for RT is to reduce the exposure of normal tissue and the related side effects. This case illustrates the potential for geographic miss with these new RT target volumes and points out the need for optimal imaging techniques.
SIOP ABSTRACTS

1083

PM040

MEDULLOBLASTOMA CELL LINE EXPOSED TO HYPOXIA ENVIRONMENT AND MIMETIC REAGENTS EXPRESS HIF1A AND VEGF WITHOUT AFFECTING CELL VIABILITY

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Purpose: Medulloblastoma is the most common brain tumor in children. Hypoxia is a state of oxygen reduction that often occurs in pathological processes like cancer. Both the reduction in oxygen concentrations and hypoxia mimetic reagents can induce hypoxia inducible factor (HIF1A) and trigger the expression of downstream transcripts, particularly VEGF, related to cancer invasiveness. The objective is to activate the HIF1A expression through the mimetic reagents desferrioxamine (DFX) and Cobalt Chloride (CoCl2). To compare the expression profile of HIF1A, VEGF and cell viability with these reagents.

Methods: The cell line UW402 was kept in HAM F10 medium and exposed to hypoxia 2% condition during 12 hours. A fraction of UW402 was treat with hypoxia mimetic reagents CoCl2 and DFX in 50μM, 100μM and 150μM at times 4, 8 and 24 hours. The qRT-PCR and XTT proliferation assays were performed. Statistical analyzes obtained by One-way ANOVA.

Results: Cell exposure to true hypoxia resulted in higher expression (3.5 folds) of HIF1A and VEGF when compared to normal oxygen conditions. The hypoxia expression of these genes was observed following treatment with CoCl2 at 50μM (2 folds for both genes). For DFX cell treatment, HIF1A expression was as high as 16-fold in 50μM concentration at 8h. Cell viability was not reduced in proliferation assay by the hypoxic mimetic reagents. Interestingly, for CoCl2 exposure of 50μM for 24hs, UW402 proliferation was higher than the untreated control (p < 0.05).

Conclusion: Both hypoxic mimetic reagents can trigger HIF1A and VEGF expression in medulloblastoma cell model. The chemical-induced hypoxia with CoCl2 shows similar pattern of expression of HIF1A and VEGF when compared to the true hypoxia. This model suggests that CoCl2 could be a suitable model for mimicking hypoxia due to its low impact on cell viability and its comparable profile of HIF1A and VEGF expression.
OPTIC PATHWAY GLIOMA: INDICATIONS OF TREATMENT

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Purpose: Optic pathway glioma is a slow growing lesion that can cause blindness. It is a difficult disease to monitor. Moreover, there is no consensus on the treatment threshold. This study analyses the reasons and rationale behind treatment of optic pathway glioma, with the intention of sharing our experience of managing the same.

Methods: Retrospect data collection.

Results: 20 year data of Leeds teaching Hospitals was analysed. 34 patients were diagnosed with optic pathway. 23 patients were treated due to visual deterioration, 11 were treated due to neurological or radiological progression of the disease.

Conclusion: Visual deterioration was the most common reason for OPG treatment. On average a 2 line vision drop on Snellen or logMar chart is considered significant in our hospital. Contrast sensitivity and colour vision are not as sensitive as visual acuity. However, in patients with reduced vision, contrast sensitivity was shown to precede radiological progression. Analysis of optic nerve function revealed that visual acuity is the first parameter to be affected in a progressive disease, followed by colour vision and then contrast sensitivity.

PM043

MICRorna Sinaitures in a BROAD COHOrt OF PAEDiATric BRAiN TuMOURS

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Purpose: Genetic alterations have been widely studied in paediatric brain tumours, but it is likely that epigenetics also plays a key role in the aetiology of these tumours. MicroRNAs are short RNA molecules involved in post-transcriptional regulation of gene expression. Aberrant microRNA expression has been identified in a number of cancers but few studies have examined paediatric brain tumours. The aim of this study is to improve our understanding of the role of miRNAs in paediatric brain tumours, with a focus on low grade astrocytomas and ependymomas.

Methods: MicroRNA and mRNA expression were analysed in a range of paediatric brain astrocytomas and ependymomas.

Results: 20 year data of Leeds teaching Hospitals was analysed. 34 patients were diagnosed with optic pathway. 23 patients were treated due to visual deterioration, 11 were treated due to neurological or radiological progression of the disease.

Conclusion: Visual deterioration was the most common reason for OPG treatment. On average a 2 line vision drop on Snellen or logMar chart is considered significant in our hospital. Contrast sensitivity and colour vision are not as sensitive as visual acuity. However, in patients with reduced vision, contrast sensitivity was shown to precede radiological progression. Analysis of optic nerve function revealed that visual acuity is the first parameter to be affected in a progressive disease, followed by colour vision and then contrast sensitivity.

PM045

DHMEQ INHIBITS IN VITRO MIGRATION AND INVASION IN ADULT AND PEDIATRIC GIOBLASTOMA CELLS

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Purpose: Glioblastoma (GBM) is the most aggressive primary brain tumor accounting for 50% of adult gliomas. In children is much rarer comprising only 5%-10% of childhood intracranial neoplasms. The standard treatment is based on neurosurgery followed by radiotherapy, and adjutant temozolomide (TMZ), nevertheless the median survival remains around of 12 months. One of the causes responsible for the low effectiveness of this treatment is the high capacity of cells to invade the surrounding tissue. Recently, a new inhibitor of the NF-kappaB transcription factor called dehydroxymethylepoxyquinomicin (DHMEQ) has shown notable antitumor effects. To study the effects of NF-kB inhibition on migration and invasion processes in pediatric and adult GBM cell lines.

Methods: Six adult (T98G, LN319, U343, U138 and U87) and one pediatric (SF188) GBM cell lines were treated with different DHMEQ concentrations (2.5, 5, 10 and 20 µg/mL) and analyzed after 24 hours. Invasion in matrigel and migration assays were performed as described by the standard protocols.

Results: Treatment with DHMEQ 20 µg/mL showed a medium decrease of 73% in the invasion process for all cell lines when compared with controls, (p < 0.05). At lower concentrations a significant reductions in invasion were also observed for four lines (T98G, U251, LN319 and SF188). Migration rates were likewise significantly attenuated in all cell lines when compared with control (p < 0.05). These results corroborate the antitumor action of DHMEQ and the participation of NF-kB in tumor invasion process, pointing this transcription factor as a possible target in GBM combat.

PM046

DUAL CONTRAST PERFUSION MRI IN A SINGLE IMAGING SESSION FOR ASSESSMENT OF PEDIATRIC BRAIN TUMORS

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Purpose: For tumors, an iron nanoparticle used as an intravascular contrast agent for perfusion magnetic resonance imaging (MRI), has never been explored the pediatric population. The purpose of this prospective study is to characterize the vascular and permeability properties of pediatric brain tumors using two contrast agents during a single imaging session: ferumoxytol for dynamic susceptibility weighted contrast (DSC) MRI and gadoteridol for dynamic contrast enhanced (DCE) MRI.

Methods: In a single imaging session, patients received intravenous ferumoxytol for DSC MRI followed by gadolinium for DCE MRI. Relative cerebral blood volume (rCBV), relative cerebral blood flow (rCBF), transfer coefficient (Ktrans), and extravascular extracellular space

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volume fraction \(v_c\) of the brain lesions were calculated. Patients underwent serial imaging sessions over the course of two years.

Results: Most of the seven patients enrolled thus far, none has experienced an adverse event. Two patients with medulloblastoma were enrolled preoperatively. In the first, \(c\text{CBV}_{\text{max}},\) \(c\text{CBF},\) \(K^{\text{trans}}_{\text{max}},\) and \(v_c\) max values were 3.74, 3.12, 0.47 \(\text{min}^{-1}\), and 0.08, respectively, while in the second patient, \(c\text{CBV}_{\text{max}},\) \(c\text{CBF},\) \(K^{\text{trans}}_{\text{max}},\) and \(v_c\) max values were 7.42, 3.47, 0.60 \(\text{min}^{-1}\), and 0.05, respectively. Four patients were enrolled after a second-gate scan enhancement was noted in the tumor resection cavity. In 80% of these tumors, \(c\text{CBV}\) was < 1 suggestive of pseudopseudosignificant progression secondary to radiochemotherapy.

Conclusion: These preliminary results demonstrate that use of ferumoxytol and gadoteridol contrast agents during a single imaging session is feasible, safe, and appears useful for assessing tumor perfusion and permeability characteristics in children.

**PM047**

**TREATMENT OF EXTRANEURAL MEDULLOBLASTOMA - A REVIEW AND SURVEY OF UK ONCOLOGY PRACTICE**

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**Purpose:** Extranuclear medulloblastomas have a dismal outlook despite multimodal therapy. There is currently no consensus on optimal management.

**Methods:** We searched PubMed for all cases of extraneural medulloblastoma with explicit details of treatment and survival. Demographic data were extracted with details of initial treatment, management at relapse and survival. An online survey was performed of current UK oncology practice in extraneural disease.

**Results:** 46 reports detailed 102 individuals with adequate data. In total, 90% were diagnosed with extraneural disease at relapse. Most cases were managed with chemotherapy +/- irradiation. A proportion were given several sequential chemotherapy regimens. High dose therapy was given in a minority (n = 13), using various conditioning regimens. Median survival was 1.01 years. Of 13 disease-free survivors, all were given conventional dose chemotherapy including combinations of vincristine, cyclophosphamide, doxorubicin and etoposide, compared to 29/68 non-survivors (p = 0.025). 4/13 disease-free survivors had high dose therapy. Experience of extraneural disease is limited. Of 18 respondents, most would treat extraneural disease at initial presentation with intensive induction therapy and myeloablative therapy. Extraneural disease at relapse was more likely to be treated with low-dose oral chemotherapy or symptom control only.

**Conclusion:** Extraneural disease is rare and most cases are diagnosed at relapse. Outlook is poor but long-term survival is described, principally following conventional dose chemotherapy +/- irradiation. Most UK oncologists would treat new extraneural disease with intensive chemotherapy and myeloablative therapy. At extraneural relapse, most would use low-dose oral chemotherapy or symptom control only.

**PM048**

**IMMUNOTHERAPY FOR (RELAPSED) GBM WITH AUTOLOGOUS DENDRITIC CELLS LOADED WITH TUMOR LYSATE: CURRENT CLINICAL EXPERIENCES**

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**Purpose:** Immunotherapy is emerging as a novel treatment approach in children and adults with GBM.

**Methods:** Based on preclinical data, we are running a cohort comparison trial HGG-IMMUNO-2003 for patients with relapsed HGG. In the HGG-2006 trial, feasibility, toxicity and clinical efficacy of the full integration of DC-based tumor vaccination into standard of care therapy was studied in adults with newly diagnosed GBM.

**Results:** 25 patients < 20y with relapsed GBM had a median PFS of 2.75m and median OS of 12.72m. Most importantly, the survival curve flattened at 19.3% after 41.8m, with patients in FU for more than 10y. For adults, we observed an shift towards improved survival from cohort C, confirmed in cohort D. Both cohorts together consist of 98 adults with relapsed GBM. Median PFS and OS are 3.57m and 10.36m. 18m OS is 21.52% and the curve flattened down to 8.8% survival beyond 48.7m. There is no difference in median PFS and OS in the E cohort (closed cultures), compared to the combined C and D cohort (open cultures). Toxicity was minimal and most patients were treated in an ambulatory setting. Plans for cohort F are in development and will be discussed at the meeting.

**Conclusion:** In adults with (relapsed) GBM when required criteria can be fulfilled, like minimal residual disease, we conclude that immunotherapy is a novel effective treatment option for children aged 7–17 years (median age - 11 years). The treatment included surgery (mainly biopsies), 4 courses of chemotherapy with standard-dose Etoposide and Cisplatin, and local radiation to ventricular area in dose 24 Gy for localized tumor cases. The historical group (Group 1) included all infants aged 0–7 years of age (median age - 3 years). They received: 3 courses of chemotherapy (Etoposide + Carboplatine and Etoposide + Ifosfamide) followed by 24 Gy cranio-spinal irradiation + 40 Gy local boost. All patients had residual tumor at the start of therapy. The progression free survival (PFS) and early toxicity of treatment in both groups were compared.

**Results:** In patients in both groups are alive and have complete remission. The observed PFS was 95 ± 5% (median - 18 months) in Group 1 and 84 ± 8% (median - 77 months) in Group 2. Log-rank test did not show difference in the results (p = 0.46). The hematological toxicity grade I-IIW was much less in Group 1 (30%) compared to Group 2 (95%).

**Conclusion:** The moderate regimen of chemotherapy followed by reduced and restricted radiation therapy had the same high effect and was better tolerated than more severe regimen of combined therapy in children with CNS germoma.

**PM050**

**OUTCOMES OF RADIOTHERAPY ALONE VS. CHEMOTHERAPY FOLLOWED BY RESPONSE-BASED RADIOTHERAPY FOR NEWLY DIAGNOSED PRIMARY CNS GERMINOMA (COG ACNS 0232)**

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**Purpose:** Primary CNS germoma is readily curable with wide volume and high dose radiotherapy. Late effects of radiotherapy upon neuropsychological functioning amongst this population remain limited. Children’s Oncology Group (COG) study ACNS 0232 examined the addition of pre-radiotherapy chemotherapy and response-based reductions in radiotherapy fields aimed at long-term disease control of childhood CNS Germinoma while striving to improve neuropsychological outcomes and quality of life.

**Methods:** Enrolled patients were treated with either standard radiotherapy alone (Regimen A) or chemotherapy followed by response-based radiotherapy (Regimen B). Patients included 21 children and adolescents (17 males, 4 females) who were randomized to either Regimen A (n = 10) or Regimen B (n = 11) and treated according to extent of disease: disseminated disease (n = 12) or localized disease (n = 9). Measures of intelligence, memory, executive functioning, academic achievement, quality of life, and social-emotional functioning were to be administered at 9- (T1) and 30-months (T2) post diagnosis.

**Results:** At T1, 18/21 (86%) of patients (age range, 111–249 months) were evaluated and 6/13 (46%) of patients (age range, 111–249 months) were evaluated and data collection is underway for T2 (age range, 139–221 months), which has currently collected 92/45% of patients, who are on average 31.77 months post-diagnosis. Patients evaluated at T1 and T2 demonstrated no significant declines on measures of intelligence (mean FSIQ T1 = 100, SD = 9.8, mean FSIQ T2 = 101, SD = 10.7), or memory, executive functioning, academic achievement, quality of life, and social-emotional functioning.

**Conclusion:** Preliminary findings reveal no significant deficits on measures assessed and stable functioning across all neurocognitive and quality of life domains was noted at T2 follow-up. With the acquisition of the remaining survivor assessment data, analyses will investigate whether deficits are noted over time and whether the addition of pre-radiotherapy chemotherapy and reductions in radiotherapy will account for neurocognitive differences in survivors, which may have implications for future treatment recommendations.

**Pediatt Blood Cancer DOI 10.1002/pbc**
Purpose: To evaluate the feasibility and toxicity of HART (1.24 Gy b.i.d.) followed by chemotherapy for M1-3 MB. The aim of HART was to improve the therapeutic ratio for RT by introducing acceleration in addition to hyperfractionation to minimise tumour cell repopulation during RT.

Methods: Between February 2002 and May 2008 36 patients were entered into the study. 2 were ineligible for RT, leaving 34 patients (22 male, 12 female) aged 3–15 (median: 7) with metastatic MB (M1: 23, M2: 11). Following maximum resection of the primary, patients were treated by HART followed by 8 cycles of chemotherapy. Craniospinal radiotherapy (CSRT) dose was 39.68 Gy in 32 fractions, followed by a whole posterior fossa boost of 22.32 Gy in 18 fractions and where appropriate, boosts to metastases of 9.92 Gy in 8 fractions. Chemotherapy comprised Vincristine (VC) 1.5 mg/m², CCNU 75 mg/m² and Cisplatin 70 mg/m². The first 7 patients did not receive VCR concurrent with RT. The remainder received VCR 1.5 mg/m²weekly x 8 doses starting during the first week of RT. Results: HART was delivered with a median duration of 34 days, range 31–38 days. Common grade 3–4 toxicities during HART included mucositis (8 patients), nausea (10), anaemia (5), thrombocytopenia (2), leukaopenia (24). 22 patients received all 8 courses of adjuvant chemotherapy. 28 patients had carboplatin substituted for Cisplatin for at least 1 course. Exploratory analysis showed that with a median follow-up of 4 years EFS and OS were 69% and 81% at 2 years and 59% and 71% at 3 years. Of 10 relapses, 1 was outside the CNS, 1 posterior fossa alone and 8 leptomeningeal with 3 of these also associated with posterior fossa relapse.

Conclusion: The HART regimen was well tolerated and may have a place in the multimodality management of patients with high risk MB/PNET.

PM054 HYPERFRACTIONATED ACCELERATED RADIOTHERAPY (HART) WITH CHEMOTHERAPY FOR M 1–3 MEDULLOBLASTOMA (MB) – A CHILDREN’S CANCER AND LEUKAEMIA GROUP (CCLG)/NATIONAL CANCER RESEARCH NETWORK (NCRN) STUDY

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Purpose: To study an imaging based systematic analysis and scoring system for posterior fossa tumours devised. This was reverse applied to the imaging of 36 patients with posterior fossa tumours presenting to our institution between January 2008 and January 2012. The results were stored in a database with correlation to proven histology. Computerised decision tree analysis of the imaging database was performed to derive an imaging phenotype classification system for posterior fossa tumours. The system was then compared to the initial imaging reports. Results: In 28 patients (78%) the radiologist correctly identified the tumour when compared to histology findings. Six patients had discordant radiologic and histologic diagnoses. Two medulloblastomas were felt to be more closely resemble pilocytic astrocytomas, while two astrocytomas were felt to be cystic ependymomas/medulloblastomas. One medulloblastoma, invading the foramen of Luschka, was thought to be an ependymoma, while one brainstem ependymoma was thought to be a glioma. By contrast correct classification was obtained in more than 97% by the use of the systematic imaging model and decision support tree.

Conclusion: Posterior fossa tumours have a variable radiologic appearance with a significant crossover between tissue types. This study confirms the value of a systematic approach to posterior fossa tumour radiological phenotyping, demonstrating the potential of an automated decision tree classification system support. Validation will require the analysis of larger numbers of scans from patients with posterior fossa tumours of known and unknown aetiology.

PM052 NUTRITIONAL STATUS IN CHILDREN WITH HIGH-RISK BRAIN TUMOUR – DIAGNOSTIC AND THERAPEUTIC POSSIBILITIES

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Purpose: High risk CNS tumors requires intensive oncological treatment (surgery, radiotherapy, medetarepy). Illness and intensive care are often bring the child into a state of malnutrition. With the increased laboratory monitoring, treatment involves intensive supportive therapy.

Methods: In this study we analyzed 30 children with a diagnosis of high-risk malignant CNS tumors. We have monitored changes in body weight and body mass index during the implementation of treatment. Applied supportive nutritional therapy, we followed an implementation of supportive nutritional therapy, we followed an supportive therapy.


PM053 ZEBULARINE PROMOTES RADIosensitivity in Glioblastoma and is Less CytoToxic Than TemozolomIDE

Pediatr Blood Cancer DOI 10.1002/pbc

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Purpose: Glioblastoma (GBM) is the most frequent and aggressive central nervous system tumour. This type of tumor can occur at any age but it's rare in children. Actually, surgery, radiotherapy and adjuvant/concomitant temozolomide (TMZ) chemotherapy has been the standard treatment protocol but most patients do not respond to TMZ and survival remains extremely poor. Zebularine (ZB) is a DNA methyltransferase inhibitor, stable toxin that has showed promise effects in cancer but little is known about ZB in glioblastoma. So the objectives of this study were analyze citotoxicity and effects of ZB isolate and in combination with TMZ in irradiated and non-irradiated GBM cells.

Methods: In this study were included 5 GBM primary cultures, 3 GBM cell lines (U251, SF862 and SF188) and 1 fibroblast cell line (MRC5). Proliferation, clonogenic, radiation and apoptosis were realized as functional assays. Statistical analysis was made by SPSS15.

Results: We observed decrease of GBM cell proliferation from 50–100% of ZB and 250–500µM of TMZ on GBM cell lines and from media 40µM for primary GBM samples. It was not observed synergy in the most of combinations doses of ZB and TMZ. ZB and TMZ showed decrease of colony formation with doses from 10µM and 10µM respectively on U251 and SF188 cell lines non irradiated and irradiated with 2, 4, and 6Gy. T98G that express MGMT, do not respond to TMZ but showed response to ZB. It was also observed that 10µM of TMZ is more cytotoxic than 100µM of ZB in fibroblast cell line (p < 0.5).

Conclusion: ZB increase apoptosis from 100µM on the three GBM cell lines. Results obtained in this study can indicate that ZB may be an alternative therapeutic target effective and less toxic for glioblastoma treatment.

PM051 FORMALISED DESCRIPTIVE SET DECISION TREE CLASSIFICATION OF PAEDIATRIC POSTERIOR FOSSA TUMOURS

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Purpose: Pilocytic astrocytoma, medulloblastoma and ependymoma account for the majority of paediatric posterior fossa tumours. Imaging is crucial to diagnosis, staging and identification of complications. However, there is significant uncertainty with regards to the imaging appearances in a proportion of cases making radiological diagnosis difficult. We have developed a systematic descriptive imaging model underpinning a decision support system that facilitates radiological phenotyping of these tumours.

Methods: An imaging based systematic analysis and scoring system for posterior fossa tumours was devised. This was retrospectively applied to the imaging of 36 patients with posterior fossa tumours presenting to our institution between January 2008 and January 2012. The results were stored in a database with correlation to proven histology. Computerised decision tree analysis of the imaging database was performed to derive an imaging phenotype classification system the output of which was then compared to the initial imaging reports.

Results: In 28 patients (78%) the radiologist correctly identified the tumour when compared to histology findings. Six patients had discordant radiologic and histologic diagnoses. Two medulloblastomas were felt to be more closely resemble pilocytic astrocytomas, while two astrocytomas were felt to be cystic ependymomas/medulloblastomas. One medulloblastoma, invading the foramen of Luschka, was thought to be an ependymoma, while one brainstem ependymoma was thought to be a glioma. By contrast correct classification was obtained in more than 97% by the use of the systematic imaging model and decision support tree.

Conclusion: Posterior fossa tumours have a variable radiologic appearance with a significant crossover between tissue types. This study confirms the value of a systematic approach to posterior fossa tumour radiological phenotyping, demonstrating the potential of an automated decision tree classification system support. Validation will require the analysis of larger numbers of scans from patients with posterior fossa tumours of known and unknown aetiology.

PM054 HYPERFRACTIONATED ACCELERATED RADIOTHERAPY (HART) WITH CHEMOTHERAPY FOR M 1–3 MEDULLOBLASTOMA (MB) – A CHILDREN’S CANCER AND LEUKAEMIA GROUP (CCLG)/NATIONAL CANCER RESEARCH NETWORK (NCRN) STUDY

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Purpose: Medulloblastomas (MBs) are highly aggressive primitive neuroectodermal tumours (PNETs) usually located in the posterior fossa. Current treatment for MBs include a
PM056

PEDIATRIC GLIOMAS. ANALYSIS OF IDH1 MUTATIONS

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Purpose: Low grade gliomas are the most frequent tumours of the central nervous system in children. IDH1 mutations have been reported in a high percentage of secondary high grade glioma in adults and have been linked with a favourable prognostic significance. The aim of this study was to analyse the IDH1 mutations in paediatric gliomas and relate these results with p53 expression, Ki67 and clinical data.

Methods: We studied 57 samples of the central nervous system tumours in children aged from 3 months to 18 years. We obtained DNA in 25 cases, including; 9 pilocytic astrocytomas, 3 grade II astrocytomas, 2 anaplastic astrocytomas, 1 glioblastoma, 1 pilomyxoid astrocytoma, 3 SEGAs, 3 gangliogliomas, 2 pleomorphic xanthoastrocytomas and 1 high grade glioneuronal tumor, and in all of them IDH1 mutation was analyzed. We also investigated by Immunohistochemistry, p53 expression and Ki67 and were related with clinical data.

Results: Overexpression of p53 was observed in 6 of 57 cases analyzed. No mutations at aminocid 132 of IDH2 were detected, from the 25 cases analyzed, including patients over 14 years of age and tumours with p53 overexpression.

Conclusion: IDH1 mutations were not found in pediatric gliomas analyzed. These results suggest that the biology of high-grade gliomas in children differ from adults. Therefore, unlike adults, the IDH1 mutation analysis does not appear useful to detect possible progression to high-grade glioma in children.

PM057

NOVEL BIOMARKERS OF PROGNOSIS FOR MEDULLOBLASTOMA USING 1H MAGNETIC RESONANCE SPECTROSCOPY

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Purpose: Magnetic resonance spectroscopy (MRS) is known to provide non-invasive biomarkers of tumour aggressiveness but studies are lacking in elaborating on specific tumour types and with long term follow-up for survival. Medulloblastomas (MB) are the most common malignant brain tumours of childhood and in this study we investigate whether MRS metabolite profiles can identify prognostic biomarkers of this tumour.

Methods: Single voxel MRS (1.5T, TE 30ms, TR 1500ms) was performed on 36 children with MB prior to treatment; patients were followed-up for a median of 4 years and 15 had died by the end of the study period. MRS was analysed using TARIQUN software to provide metabolite concentrations. Wilcoxon signed rank test analysis was used to compare metabolite profiles of those MBs currently alive compared with those that progressed and died and Cox regression analysis with overall survival was used to test each metabolite. Kaplan Meier curves were then constructed of those metabolites that demonstrated significance in the Cox regression analysis.

Results: The poor prognosis group demonstrated lower levels of Creatine (Cr) (Wilcoxon signed rank test, p = 0.003) and near significant lower levels of total choline (tCho) (p = 0.06). Cox regression analysis also demonstrated only Cr and tCho to be significant with a lower hazard for those subjects with higher values. Kaplan Meier curves demonstrated significant differences in survival for both Cr (p = 0.000) and tCho (p = 0.01). Conclusion: Cr and tCho have been demonstrated as biomarkers of good prognosis and this may be useful for strategising treatment in MBs. The validation of these biomarkers with biological information is warranted.

PM058

SURGICAL PATHWAY AND MANAGEMENT OF PINEAL REGION TUMOURS IN CHILDREN

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Purpose: Pineal region tumours are rare, accounting for around 5% of childhood brain tumours. Surgery has historically been associated with high morbidity and there has been some reluctance to undertake resection of tumours in this area. Consensus on ideal management pathways remains variable. We report our single-centre experience on pineal region tumours.

Methods: Patients with pineal region tumours were identified from the neuro-oncology database and retrospectively reviewed. Data collection included: presentation, germ cell markers, tumour size and location, imaging, histology, treatment, and control/relation rates. Classic non-progressive tectal plate gliomas were excluded.

Results: Twenty four patients were treated at Alder Hey Children’s Hospital between 1998 and 2010. Median age at diagnosis was 12.7 years (range 3.6–17). Sixteen patients presented with hydrocephalus. Twelve were successfully treated with endoscopic third ventriculostomy, and 4 required shunt insertion at some point during follow-up. Fourteen patients had endoscopic biopsies (eleven were performed at the same time as third ventriculostomy and 3 patients without significant hydrocephalus had endoscopic image-guided biopsies), eight had stereotactic biopsies (either because of slit ventricles at diagnosis or because a VP shunt already in place). One patient only had open biopsy and one patient went straight for open resection. No morbidity or mortality was associated with biopsies. Thirteen tumours underwent resective surgery. They were 5 teratomas, 2 pineoblastomas, 5 progressive astrocytomas, 1 papillary parenchymal tumour. Significant tumour debulking was achieved in all patients, and a gross total resection was obtained in 70% of them.

Conclusion: A multi-disciplinary approach is required for this heterogeneous group of paediatric tumours. The mainstay of hydrocephalus management is endoscopic third ventriculostomy. In our experience, craniotomy and tumour resection is effective and safe.

PM059

SAFETY AND EFFICACY OF NIMOTUZUMAB IN THE TREATMENT OF CHILDREN AND ADOLESCENTS CENTRAL WITH MALIGNANT CENTRAL NERVOUS SYSTEM TUMORS

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Purpose: To evaluate safety and efficacy of the prolonged use of humanized anti-EGFR mAb Nimotuzumab in children and adolescents with brain tumors.

Methods: 85 patients aged 3–18 years from Juan M. Márquez Pediatric University Hospital with diagnosis of High Grade Glioma (HGG), Brain Stem Tumor (BST), Ependymoma and Low Grade Glioma were treated with Nimotuzumab 150mg/m2 IV weekly in induction phase during 12 weeks and every 2 weeks in consolidation phase until progression in combination with chemotherapy, radiotherapy or as monotherapy between 2005 and 2011. Safety and Efficacy were explored overall and in subgroups of patients.

Results: Most common drug-related adverse events were mucositis grade 1–2 (3 events) skin toxicity grade 1–2 (8 events). No renal, liver or cardiac dysfunction were found despite prolonged exposure to nimotuzumab (15 of 85 patients in treatment for more than 3 years with more than 80 doses received). Median overall survival for brain stem tumor was 8.3, and 52.2 for ependymoma. More than 50% of the patients with high and low grade glioma are alive.

Conclusion: Experience show that Nimotuzumab is safe and effective as a single agent and in combination with other treatments and might be an agent that suppresses the growth of these tumors.
POOR RISK SURVIVAL

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Purpose: Malignant germ cell tumors (GCTs) have a bimodal age distribution with a first peak during childhood and a second peak beginning at the onset of puberty that extends through early adulthood. The objective of this study was to understand whether peri-pubertal GCT has a clinical course more similar to children or to adults.

Methods: Using data from SEER 17 registries from 1998 to 2005, we estimated 3-year relative survival (RS) for testicular cancer patients, ages 0–39 years, which were classified as poor risk by the International Germ Cell Consensus Classification criteria. We compared the frequency of primary site, histology, sites of metastasis, stage and presence of elevated tumor markers (AFP, LDH, βhCG) by age category.

Results: Data from 626 male patients showed that the lowest RS was observed among the 16–19 age group (n = 83, 66.1%), vs the 20–39 age group (n = 506; 72.7% p = 0.21) and vs the 0–15 age group (n = 37; 78.1%, p = 0.24). Adverse risk factors were more common in the 16–19 year olds than in other age groups; mediastinum as primary site (38% vs. 30%, p = 0.02); presence of visceral metastases (53% vs. 46%, p = 0.25) and distant disease (70.6% vs 58.4%, p = 0.09).

Conclusion: Although not significantly different, there was a decrease in survival noted in late adolescence for men with poor risk testicular cancer that could be explained by more extensive metastatic disease. This difference should be explored in datasets with larger numbers. Contributing factors may be inherent biologic differences or/and due to health system issues such as lower rates of insurance coverage, delays in diagnosis and lower accrual to clinical trials.

TREATMENT OUTCOME OF CHILDREN WITH MALIGNANT GERM CELL TUMOR–A REPORT OF 62 CASES

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Purpose: This study was to analyze the clinical characteristics and treatment outcome of children with malignant ovarian germ cell tumor, and to investigate the therapeutic strategy.

Methods: Clinical characteristics, treatment outcome and follow-up of 62 children with malignant ovarian germ cell tumor, treated in Surgical oncology department of Chongqing medical university from Jan. 2001 to Dec. 2009, were analyzed.

Results: Abdominal pain and abdominal distension were the most clinical presentations. Elevated AFP was observed in 93.5% cases. Surgery + adjuvant chemotherapy was applied in 33 patients, other 27 patients received chemotherapy + surgery or surgery alone. 7 patients had malignant YST. Among testicular tumors we observed 10 yolk sac tumor (YST), 4 YST plus immature teratoma.

Conclusion: Teratomas with regions suspicious for YST were restained with lin28.

COMpletely RESEcted SACR0COCCYGEAL GERM CELL TUMORS WITH FOCI OF YOLK SAC TUMOR Are CURED WITH SURGERY ALONE

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Purpose: A successful treatment strategy for completely resected germ cell tumors (GCT) of the testes or ovary is observation only, reserving chemotherapy only for those who recur. This strategy has not yet been adopted extragonadal GCT. Yolk sac tumor (YST) can be difficult to diagnose pathologically. Lin28, a microRNA-binding protein that processes let-7 microRNA, has been identified as a new sensitive and specific marker for YST, detectable by immunohistochemistry. The study was undertaken to ascertain whether it was possible to identify in retrospect sacrococcygeal teratomas (SCT) with previously unidentified YST elements and to estimate risk of recurrence.

Methods: All SCT diagnosed between 1993 and 2008 at Children’s Hospital Boston were identified and reviewed by a single pathologist and corresponding clinical outcome data were abstracted. Teratomas with regions suspicious for YST were re-stained with lin28. Results: 43 SCT were identified. 3 tumors had malignant elements identified at diagnosis. Of the remaining 40 tumors, the pathologist identified 20 tumors with areas that were suspicious for YST (e.g. glands with or without basal vacuoles and/or hepatoid foci). 52/30 of these tumors, including the tumor that had a high level of positive cytoplasmic staining with lin28. All 5 patients were diagnosed antenatally with resection performed in the neonatal period. Initial pathology was immature teratoma in 4 (3-grade 3; 1-grade 2). One patient died intraoperatively of cardiac arrest. None of these patients had recurrence of their YST, although 25 patients recurred with teratoma.

Conclusion: Our data suggest that patients with completely resected extragonadal teratomas with YST elements may benefit from a conservative approach with surgery and observation, thus limiting the use of chemotherapy to those patients with disease recurrence. However, given the small numbers of our series, a prospective study is warranted.
OUTCOME OF RELAPSED INTRACRANIAL GERM CELL TUMOURS FROM A SINGLE CHILDREN'S HOSPITAL

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Purpose: Primary intracranial germ cell tumours (ICGCT) are rare and heterogeneous. Most children are treated with a combination of chemotherapy and radiotherapy. There are no agreed treatment regimens for relapse after such first line treatment. We report our results of salvage treatment for relapsed ICGCT.

Methods: Retrospective data were collected from all ICGCT diagnosed and treated at our centre, the largest children's hospital in the country, since the hospital started operating in May 1997. Data were collected until March 2012.

Results: From 1997 to 2011, 40 were diagnosed with ICGCT, 19 non-secreting GCT and 21 secreting GCT in our centre. Prior to 2000, treatment was with BEP±RT. After 2000, majority were treated on SIOP CNS GCT 96 protocol. Eight relapsed, 4 non-secreting and 4 secreting. One child returned to his home country and was lost to follow up. Interestingly, of the 4 non-secreting GCT who relapsed, 3 relapsed as secreting GCT. All 3 had normal serum HCG. Time to relapse ranged from 1.3 to 9 years; mean 3.5 years; median age: 2.5 years.

Conclusion: It is likely that the 3 non-secreting GCT which relapsed had secreting GCT initially and therefore it is important to obtain CSF markers at diagnosis and interpret accordingly. Although our numbers are small, salvage treatment with thiopeta-based ASCR has encouraging results.
PM069

IS THERE A ROLE FOR CARBOPLATIN IN THE TREATMENT OF MALIGNANT GERM CELL TUMORS? A SYSTEMATIC REVIEW OF ADULT AND PEDIATRIC TRIALS

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Purpose: While cisplatin is considered superior to carboplatin for the treatment of malignant germ cell tumors (MGCTs) in adults, pediatric oncology collaborative groups remain concerned about the late effects of cisplatin in children. We conducted a systematic review of studies that used carboplatin in the treatment of adults and children with MGCTs in order to gain insight into whether carboplatin may have a role in the treatment of pediatric MGCTs.

Methods: We performed a literature search to identify randomized controlled trials that used carboplatin for MGCTs in adults, and meta-analyzed results. Since no RCTs were available in children, we identified cohort studies of pediatric MGCTs treated with carboplatin. We compared the adult and pediatric trials in terms of study characteristics, doses of chemotherapy, and outcomes.

Results: Of 2,131 publications reviewed, five RCTs in adults (1,340 patients) and four cohort studies in children (219 patients) met inclusion criteria. All adult RCTs evaluated carboplatin versus cisplatin in regimens in men with good-prognosis metastatic MGCTs. Carboplatin regimens had a higher risk of events, defined as any outcome other than continuous complete remission (relative risk 2.95, 95% CI 1.92–3.27; p < 0.001) and of deaths (relative risk 2.21, 95% CI 1.41–3.48; p < 0.001). Across all five RCTs, 497/654 (76%) of adults who received carboplatin remained event-free at last follow-up. Three pediatric studies used carboplatin at a higher dose, frequency, and number of cycles than the adult trials. Across these three studies, 158/179 (88%) of children remained event-free.

Conclusion: Carboplatin is superior to carboplatin at the studied doses for the treatment of adult metastatic MGCTs. However, we observe that carboplatin has excellent outcomes when used for children with localized disease and at appropriate doses. We hypothesize that a risk-adapted approach utilizing cisplatin or carboplatin in the correct context may achieve the optimal balance between cure and late effects.

PM070

TREATMENT FAILURES AND RESULTS OF PROGRESSION/RELAPSE TREATMENT IN CHILDREN WITH EXTRACRANIAL GERM CELL TUMORS – LONG-TERM SINGLE CENTER EXPERIENCE

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Purpose: Evaluation of therapy failures and results of progression/relapse treatment in children with extracranial germ cell tumor (c-GCT) prospectively included and uniformly treated according to SFOP-TG95 protocol.

Methods: 38 children, aged 0–19 years (median 13.5 years), were treated between 1993 and 2011 according to SFOP-TG95. 2005/38 (53%) children were qualified for standard risk group (SRG), 183/38 (47%) for high risk group (HRG).

Results: Treatment failures occurred in 938/26 (26%) children, including 238/5% (5%) progressions (both in HRG and 73/18% (18%) relapses, which were diagnosed 1–29 months (median 6 months) from first complete remission (CR1) achievement in 5 children from SRG and in 2 children from HRG. Mixed tumor was found in 49/44.4% (cases, yolk sac tumor in 29/22.2%, immature teratoma in 29/22.2%, and mature teratoma in 1/38 (11.1%).

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Relapse in primary tumor site occurred in 377 (42.8%) patients, outside of primary site in 277 (28.6%), and in 277 (28.6%) originated from primary metastatic sites. Second line treatment was administrated according to SFOP-TG95. Two children demonstrating progression did not achieve CR and died. Out of 7 relapsed patients, all but one (14.3%) from HRG, achieved the CR2 (n = 6; 87.5%), and are alive in CCR (11 months–9.3 years; median 4.5 years).

Conclusion: (1) Progression and relapse were sole cause of therapy failure in studied children with c-GCT treated according to SFOP-TG95 protocol. (2) Therapy failures were observed with comparable frequency in SRG and HRG; however, progression was observed exclusively in children with high-risk e-GCT. Thus, additional prognostic factors are needed to identify children from SRG and from HRG with higher risk of relapse and progression, respectively.

(3) Results of first e-GCT relapse treatment were usually favourable. (4) Second line treatment according to SFOP-TG95 protocol for e-GCT progression usually fails, thus further optimization of progressive e-GCT therapy is needed.

PM071

PRIMARY MEDIASTINAL NON SEMINOMATOUS MALIGNANT GCT (PMNSGCT) IN CHILDREN: FINAL LONG TERM RESULTS OF THE FRENCH SFOP/SFCE TGM 95 PROTOCOL

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Purpose: To improve survival of PMNSGCT, with cisplatin-based chemotherapy adapted to initial conditions, quality of the resection, aFoetoproteine (AFP) level and presence of metastases (M).

Methods: Based on previous TG85/90 studies, SFOP developed TG95 protocol: for intermediate-risk(IR): non metastatic incompletely or unresectable tumor and AFP < 15000: VIP (Vincristine, Bleomycine, CDDP) regimen; for high-risk(HR): AFP 15000 and/or metastasis VIP regimen. 2 more courses after biological RC. 2nd line treatment if insufficient response.

Results: Among 239 patients registered between January 1995 and December 2005, 16 pts had a mediastinal site. Eight were less than 5 years of age: 7 girls; 5 needed initial emergency care, 1 murdullar compression, AFP always elevated (569–104,000 ng/ml), HCG always normal, 6HR(1+1M+) and 2IR pts, all received chemotherapy (3–6 courses) and had surgical removal. Histological examination after chemotherapy: 5 teratomas (one immature), no malignant cells. All were alive in 1st CR (median follow up 7, 6 years). Eight adolescents (> 9 years): all boys, with Kleinefelter syndrome (1pts) or nephro-ureteral malformation (1pt). 2 needed initial emergency care, AFP always elevated (125–32,300 ng/ml) and HCG 4 times; 3IR (2M+), 3IR pts, and 2 IR pts in the HR group. All received chemotherapy (5–7 courses) and surgical tumoral resection. Histological examination after chemotherapy: 5 teratomas (one immature), mixed with 2 Embryonal Carcinoma, 1 Yor Sac Tumor. Two patients had local failure after incomplete surgery of a residue containing embryonal carcinомa and died. Another patient had 2nd malignancy (after 8 years) and is alive.

Conclusion: There is a bimodal demographic distribution among PMNSGCT correlating with different histology and prognosis. Children with YST have an excellent survival rate. Adolescents with mixed PMNSGCT should be considered as high risk patients, and a complete resection of their tumor is needed for care, which may justify an aggressive surgical approach.

PM072

GERM CELL TUMOR: PRESENTING CHARACTERISTICS AND OUTCOME FROM A TERTIARY CANCER CARE CENTRE (INDIA)

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Purpose: Germ cell tumors (GCT) are relatively common solid neoplasms in children. They may occur in both gonadal and extra-gonadal locations. Most of the GCT's produce serum markers. Combined treatment modality makes them highly curable.

Methods: We analysed pediatric GCT registered in Tata Memorial Hospital (TMH), Mumbai, India from January 2001 to December 2008. Demographic, clinical and laboratory data were collected from hospital’s electronic medical record and patient’s files.

Results: 15 patients with confirmed diagnosis of GCT were registered during this period. Records of sixty one patients were available for analysis. Among 61 patients, 29 (48%) were male and 32 (52%) were female. Median age was 36 months (range: 9 months to 15 years). Primary site was: ovary-25 (41%), testis-17 (27%) and extra-gonadal 19 (31%) including 2 patients of CNS GCT. 9/25 (36%) of ovarian, 2/17 (11%) of testicular and 9/17 (47%) of extragonadal GCTs were presented with advanced stage disease (i.e. stage III and IV).
**NEW DRUGS/EXPERIMENTAL THERAPEUTICS**

**PN001**

**A PHASE I STUDY OF VINBLASTINE AND SIROLIMUS IN PEDIATRIC PATIENTS WITH RECURRENT OR REFRACTORY SOLID TUMORS INCLUDING CNS TUMORS**

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**Purpose:** To determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of IV Vinblastine (VBL) given weekly with daily oral Sirolimus. To determine the response rate and explore peripheral blood biomarkers of mTor inhibition and angiogenesis modulation in the confines of a phase I study.

**Methods:** Phase I multi-center 3 + 3 design study. Weekly IV VBL regimen (28 day cycles) with a starting dose of 4 mg/m² was given in combination with daily oral Sirolimus with target plasma concentration set at 10–15 ng/ml. Response was evaluated using RECIST criteria.

**Results:** Twelve of fourteen enrolled patients were evaluable for toxicity and eleven for response. No DLT was observed below 6 mg/m² (n = 8). At 6 mg/m² dose level of VBL, one of six patients experienced grade 3 mucositis and one developed an acute acalculous cholecystitis possibly attributable to sirolimus. Ten out of fourteen patients achieved the target sirolimus serum concentration between cycle 1 and 3 and four patients were taken off study before achieving the target concentration. Two patients receiving sirolimus by nasogastric tube required several dose increments to achieve the target concentration. Of eleven patients evaluable for response, one patient with metastatic alveolar rhabdomyosarcoma demonstrated a confirmed partial response lasting five cycles, one brain stem glioma patient had stable disease (eleven cycles) and one patient with neuroblastoma had a confirmed MBG response. Plasma VEGFR2 concentration at day 28 decreased significantly compared to baseline (p = 0.0012). VEGF, Endoglin and PI3K did not significantly change. mTor inhibition biomarkers are pending.

**Conclusion:** The combination of VBL and Sirolimus is well tolerated with no excessive myelosuppression. The phase II recommended dose of VBL is 6 mg/m². The 10–15 ng/ml target level of sirolimus is achievable. The response rate and prolonged stable disease warrant the conduct of a phase II study combining vinblastine with an mTor inhibitor.

**PN002**

**VALIDATION OF SRC FAMILY KINASES (SFKS) AND PHOSPHATIDYLINOSITOL 3-KINASES (PI-3Ks)/mTOR AS DRUG TARGETS IN PEDIATRIC OSTEO SARCOMA**

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**Purpose:** Src and PI-3Ks/mTOR signaling are constitutively active in osteosarcoma. The aim of this study was to investigate the importance of SFKs and PI-3Ks/mTOR in survival, proliferation, motility and invasion in pediatric osteosarcoma, and to test the hypothesis that combined inhibition of SFKs and PI-3Ks/mTOR would be more effective than either alone.

Methods: The response to inhibition of SFK and/or PI-3Ks/mTOR was investigated using small molecule inhibitors in osteosarcoma cell lines. An orthotopic mouse model of metastatic osteosarcoma was used to evaluate whether inhibiting SFK and/or PI-3Ks/mTOR was able to prevent pulmonary metastases in vivo.

**Results:** 24 hr incubation with >0.1 µM saracatinib inhibited SFK signalling as measured by the level of p-FAK in both cell lines. PI-3K signalling was inhibited by exposure to 1 µM PI-103 as measured by levels of p-AKT. At concentrations up to 10 µM saracatinib had no effect on proliferation whilst PI-103 was effective (IC50 < 0.8 µM in U2OS, 1.8 µM in 791T). Both agents inhibited motility (saracatinib IC50 1 µM in both; PI-103 IC50 < 1 µM in U2OS, 0.3 µM in 791T) and invasion through 8 micron pores in PET membranes (saracatinib IC50 0.54 µM in U2OS, 0.63 µM in 791T; PI-103 IC50 0.78 µM in U2OS, 0.71 µM in 791T). In our metastatic mouse model of osteosarcoma, oral daily dosing with saracatinib and/or BEZ2355 (20mg/kg) did not prevent the development of pulmonary metastases compared to animals treated with vehicle alone.

**Conclusion:** Inhibition of SFKs and/or PI-3Ks/mTOR reduced the motile and invasive capabilities of osteosarcoma cells in vitro. Inhibition of the same protein kinases in vivo, singly or in combination, did not prevent the development of pulmonary metastases.

**PN003**

**SORAFENIB ENHANCES THE ANTITUMOR EFFECT OF CHEMORADIATION TREATMENT ON HUMAN OSTEO SARCOMA CELLS**

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**Purpose:** As the survival of patients with osteosarcoma has reached a plateau, search for novel agents focused on different mechanisms is needed. Sorafenib is the first oral multi-kinase inhibitor originally developed to block the ERK 1/2 pathway by targeting Raf kinases, such as RAF-1 and B-RAF. We aimed to investigate the therapeutic potential of sorafenib in osteosarcoma cells and whether it enhances the efficacy of chemotherapy or radiation.

Methods: We evaluated sorafenib (BAY 43-9006, LC Laboratories, USA) for its effect on four osteosarcoma cells (HOS, KOHOS/NP, MG-63, U2OS) using MT3 (3.45. Dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide), flowcytometry and wound-healing assay. Changes of downstream pathway after sorafenib treatment were analyzed by western blot. Sorafenib and cisplatin were concomitantly administered at concentration ratios of 1:4 and the combination index was calculated using CalcuSyn software (Biosoft®, Cambridge, UK). We also assessed its combination effects with irradiation using colony-forming assay.

**Results:** At the concentration of 3 µM, sorafenib significantly inhibited the viability and proliferation and induced apoptosis of osteosarcoma cells. Wound healing assay showed that sorafenib prevented the migration of osteosarcoma cells. Sorafenib treatment decreased the phosphorylation of ERK1/2 and MEK1/2 of osteosarcoma cells. Combination of sorafenib and cisplatin showed synergistic effects on inhibiting cell proliferation, as indicated by the combination index value < 1. Colony-forming assay showed that sorafenib enhanced the radiosensitivity of osteosarcoma cells.

**Conclusion:** We found that sorafenib exerts therapeutic potentials in osteosarcoma cells and further studies are necessary to determine its downstream targets for clinical application.

**PN004**

**EARLY PHASE CLINICAL TRIALS IN PAEDIATRIC ONCOLOGY. THE ROYAL MARSDEN EXPERIENCE**

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**Purpose:** Early phase clinical trials in oncology are crucial in the development of new therapies for poor prognosis childhood malignancies. The outcomes and toxicities of children treated on Phase III trials at the Royal Marsden NHS Foundation Trust, RM), one of the largest paediatric oncology early phase trial units in Europe, were examined.

**Methods:** All patients recruited over a 10-year period to December 2011 were included and variables including baseline characteristics, time on study, survival, toxicities and admissions were collected.

Results: Overall, 72 patients with a wide variety of diagnoses were recruited to 21 trials (5 were Phase I, 16 Phase II; overall 12 involved molecularly targeted agents). Median age at consent was 12.4 years. Median overall survival was 3.6 months for patients on Phase I trials and 11.2 months for those on Phase II. Only 7.7% of patients on Phase I trials, compared to 33% in Phase II trials, remained on study at 6 months. Dose limiting toxicities were rare in Phase I trial participants (2 of 16 evaluable patients, 13%) and the most common reason for leaving trials was disease progression (76%), rather than drug toxicity (1.7%).

**Conclusion:** The prognosis of children recruited to early phase trials is poor. However, in our experience, such trials are safe and unexpected toxic side-effects are infrequent. There remains a clear demand from parents and patients for access to novel anti-cancer therapies and it will be necessary to continue to expand the early phase trial portfolio ultimately to improve the outcomes for those with the resistant disease.
POLO-LIKE KINASE 1 AS A POTENTIAL TARGET IN PEDIATRIC MEDULLOBLASTOMA

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Purpose: Medulloblastoma is a malignant cerebellar neoplasia, considered the most common solid tumor in childhood. Even though survival rates attain over 50%, current treatment strategies display long term severe sequelons on patients. Thus, alternative treatments are needed, especially for patients younger than 3 years old that cannot receive radiotherapy. Polo-like kinase 1 (PLK1) is a serine-threonine kinase involved in cell cycle progression that has already been associated with cell proliferation and tumor prognosis. The aim of this study was to evaluate the effects PLK1 inhibition by BI 2536 on medulloblastoma cell lines. Methods: The UW402 and UW473 medulloblastoma pediatric cell lines were treated with BI 2536 at different concentrations during 24, 48 and 72 hours. Proliferation, cellular viability, colony formation capacity, mitotic index, apoptosis and cell cycle dynamics assays were performed and results analyzed by one-way ANOVA. Results: The inhibition of PLK1 with BI 2536 showed an efficient decrease (p < 0.05) in cell proliferation and viability, with a corresponding increase in the apoptosis rate (p < 0.05). The clonogenic assay also demonstrated that BI 2536 causes a significant decrease in colony formation at concentrations as low as 50nM (p < 0.05). Moreover, cell cycle analysis demonstrated G2/M arrest, along with increased number of cells in mitosis (P < 0.05) as detected by cytogenetic analysis. Conclusion: These results point to PLK1 as a potential target to improve medulloblastoma outcome.

INHIBITION OF LIT1 GENE TRANSCRIPTION BY PYRROLE-IMIDAZOLE POLYAMIDE IN BECKWITH-WIEDEMANN SYNDROME FIBROBLAST CELL LINES

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Purpose: In Beckwith-Wiedemann syndrome (BWS), molecular confirmation of abnormal methylation of DMR1 (KIP2/LIT1) and/or DMR2 (KIP2/LIT1) has clinical utility to find epigenotype-tumor association. Demethylation of LIT1 in maternal allele, called loss of imprinting, occurs in several adult tumors and about half of the patients with BWS. Overexpression of LIT1 inhibits KIP2 and circumjacent genes, which predisposes patients to embryonal tumors in BWS and several adult tumors. KIP2 is a putative tumor suppressor gene. In BWS and several adult tumors, KIP2 expression is epigenetically reduced. Pyrrole-Imidazole (PI) polyamide can recognize a specific DNA sequence and bind the minor groove of DNA. PI polyamide designed against the transcription factor binding site, might artificially down-regulate the expression of a target gene. In this study, we analyzed the effect of PI polyamides targeting LIT1 in BWS fibroblast cell lines. Methods: We generated a PI polyamide for CCAAT box in LIT1 promoter regions. At first, the methylation status of LIT1 promoter regions in BWS fibroblast cells (BWS6, 7, 8, 9) were analyzed by MassARRAY EPITYPER procedure. Second, the expression levels of LIT1 mRNA was analyzed by real time RT-PCR. Third, BWS fibroblast cells showing demethylation of LIT1 and high expression levels of LIT1 mRNA were cultured with or without 1μM PI polyamides. Then finally, the expression levels of LIT1 and KIP2 mRNA were analyzed by real time RT-PCR. Results: BWS6 showed demethylation of LIT1 promoter regions and high expression levels of LIT1 mRNA. After 72 hours cultured with the PI polyamide, these cells showed the significant down-regulation of LIT1 expression (p < 0.05) and up-regulation of KIP2 expression (p < 0.05). Conclusion: We were able to down-regulate LIT1 and up-regulate KIP2 in BWS cell lines using the PI polyamide. This PI polyamide could be a therapeutic agent in BWS patients with tumors showing lower expression level of KIP2.

ZEBULARINE INDUCES CHEMOSENSITIZATION TO METHOTREXATE AND EFFICIENTLY DECREASE AIR GENE METHYLATION IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA CELL LINES

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Purpose: Acute lymphoblastic leukemia (ALL) is the most common hematologic malignancy in childhood. Despite the advances in treatment, about 20% of patients relapse and/ or die, indicating the need of different approaches to this group. Zebularine (ZB) is a potent inhibitor of DNA methylation and has been associated with gene demethylation and enhancing of tumor chemosensitivity. This study aimed to evaluate the effects of ZB, alone or combined with chemotherapeutics (methotrexate and vincristine) in childhood ALL cell lines.
Methods: Functional studies of cell proliferation, apoptosis, cell cycle and clonogenic capacity were performed in triplicate with Jurkat and Reh cell lines. Drug combination was analyzed by the median-effect method (Calcusoft software; Biosoft, Ferguson, MO). Bisulfite modification followed by MS-PCR was carried out in order to evaluate 5’A’r demethylation status, since its gene is involved with cell cycle progression and is densely methylated in ALL patients. Gene expression of TET1 status, since its gene is involved with cell cycle progression and is densely methylated in ALL patients. Gene expression of TET1 and DNMT3a and 3b was assessed using qRT-PCR. Statistical analysis was made by one or two-way ANOVA and Bonferroni post hoc and Student’s T-Test.

Results: Both cell cultures were sensitive towards ZB showing a response dose- and time-dependent (p < 0.05). Combination with methotrexate resulted in a synergistic effect, while combination with vincristine led to an antagonistic response in the two cell lines. ZB also induced an S-phase arrest in ReH cell line, caused apoptosis and decreased clonogenic capacity in both cell lines (P < 0.05). ZB treatment also decreased gene expression of the three DNMTs and induced 5’A’r gene promoter demethylation efficiently.

Conclusion: These results indicate that ZB may be a promising drug for the adjuvant treatment of ALL, mainly when combined with methotrexate and suggest that its demethylation may be therapeutically useful. Further studies should be conducted to confirm these findings.

PN010

DOUBLE ALKYLYATING AGENTS TREATMENT WITH IFOSFAMIDE (IFOS) AND CYCLOPHOSPHAMIDE (CYCLO) FOR RELAPSED PEDIATRIC SOLID TUMORS
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Purpose: CYCLO and IFOS are two of the most active agents in childhood cancer. There is no cross-resistance between CYCLO and IFOS and they have dissimilar toxic side effects. In vitro, tumor model systems document that alkylator resistance may be overcome by several fold increases in drug concentration. We developed a strategy in attempt to limit side effects and increase antitumor activity of high doses oxazaphosphorines therapy: an association of IFOS plus CYCLO, giving an equivalent to 20g/m2 of IFOS or 5g/m2 of CYCLO. The schedule is the association of these two drugs: CYCLO 2.5g/m2(corresponding to 10g/m2 of IFOS) plus IFOS 10g/m2.

Methods: Eligibility included recurrent/refractory measurable disease, life expectancy > 6 weeks, adequate renal, hepatic and bone marrow function. CYCLO (2.5g/m2) and IFOS (10g/m2) with Mesna, with interval of 21 days. Responses were evaluated after 2 cycles. So far, 9 patients were enrolled: median age 19 years (5–26), 6M:3F; 5 osteosarcoma, 1 Ewing sarcoma, 3 neuroblastoma, 1 rhabdomyosarcoma, 1 Wilms tumor. Five patients received IFOS previously (Total = 38–63 g/m2) and 4 CYCLO.

Results: Twenty four cycles were evaluated. Toxicity was tolerable with no death. Main adverse event was neutropenia grade (GR) 4 in all cycles, median duration of seven days (3–15), GCS-F was used in all cycles; anemia GR 3 and 4 and thrombocytopenia GR 4 in 19 cycles; infection GR 3 and 4 in 12 cycles; hemorrhage cystitis GR 1 in 2 cycles and 1 patient with Grade 4 neutropenia and thrombocytopenia. One patient showed increase of AST/ALT up to 36 times above normal value. At the end of the study, the complete response (CR) was observed.

Conclusion: This schedule is feasible with high response rate (CR + PR = 56%). Due to lack of new agents, innovative approaches for high-risk patients can have a potential benefit. More patients are warranted.

PN011

THE EFFECT OF RESVERATROL ON ARA-C INDUCED CEREBELLAR TOXICITY
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Purpose: To evaluate the protective effect of resveratrol on cytokine arabinoside ( Ara-C) induced cerebellar toxicity.

Methods: 28 female adolescent rats (Wistar) were randomly assigned to one of the four groups (7 rats/group). Group 1 control group intraperitoneal (IP) saline only, Group 2: treated with IP Ara-C 400mg/kg 5 days, Group 3: IP resveratrol 3mg/kg x 5 days, and Group 4: Ara-C 400 mg/kg and resveratrol 3mg/kg x 5 days. The rats' spatial navigation, learning and memory were evaluated with Morris water maze test. The rats were sacrificed at day 5. All layers of the cerebella were analyzed with light microscopy and immunohistochemistry.

Results: Light microscopy showed no difference between cerebellums. Immunohistochemical examinations showed a significant reduction of neurofilament (NF) heavy chain and light chain isoforms in the cerebellums of rats that received Ara-C. This reduction was more prominent at the granular layer. The reduction of NF isoforms was significantly less prominent in Group 4 rats' cerebellum, which were treated with Ara-C + resveratrol. In the Ara-C group, spatial navigation and swimming speed showed no difference compared to the control group, but spatial memory was impaired. In Ara-C + resveratrol group, spatial memory showed significantly less impairment.

Conclusion: In this model, Ara-C treatment resulted in reduction of NF isoforms in cerebellum representing a toxicity targeting cerebellar cytoarchitecture. It also leads to an impairment in spatial memory, which was consistent with cerebellar dysfunction. The addition of resveratrol to the Ara-C showed a neuroprotective effect. In rats that received resveratrol with Ara-C, the cerebellums showed significantly less reduction of NF isoforms and more preservation of the spatial memory. These findings suggest that resveratrol can show neuroprotective effect against Ara-C induced cerebellar toxicity. Further research is needed to show its neuroprotective effect without compromising the antitumor effect.

PN012

THE EFFECT OF MESENCHYMAL STEM CELLS AND RESVERATROL ON DOKOXRUBICIN CARDIOTOXICITY IN RATS
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Purpose: It has been suggested that anthracyclic cardiomyopathy is mediated by the depletion of cardiac stem cell pool and is rescued by restoration of progenitor cell function. The aim of this study was to determine the effects of adipocyte derived mesenchymal stem cells (AMSC) and cardioprotective polyphenolic compound resveratrol (RES) on cardiac tissue of rats treated with doxorubicin (DOX).

Methods: Forty-two female and 3 male Wistar-Albinos were included in the study. The study groups and the control groups were as follows: Group I: DOX; Group II: DOX + RES; Group III: DOX + AMSC; Group IV: DOX + RES + AMSC; Group V: Sham; Group VI: Normal saline. AMSC obtained from male rats were defined with stem cell markers (CD11b(−), CD45(−), CD90(−), CD44(−), CD10(−)). DOX 12mg/kg i.p. was injected as a single dose in female rats. Resveratrol 100 mg/kg was injected 3 times i.p. in Groups II and IV. AMSC ≥ 106cells/kg/dose were labeled with BrdU and injected i.p. for a total of 3 times in Groups III and IV. When the study was terminated after 4 weeks, the beating hearts were connected to a Langendorff set up and records were obtained for 30 minutes. Left ventricle developed pressure (LVDP) and left ventricle end diastolic pressure (LVEDP), ±dP/dt were measured via a latex balloon placed in the left ventricle. The hearts were then prepared for histopathological, immunohistochemical, and immunofluorescent examination with H&E, Troponin I, and BrdU stain.

Results: Langendorff-perfused rat hearts showed impaired LVDP, ±dP/dt were measured via a latex balloon placed in the left ventricle. The hearts were then prepared for histopathological, immunohistochemical, and immunofluorescent examination with H&E, Troponin I, and BrdU stain. Results: Langendorff-perfused rat hearts showed impaired LVDP, ±dP/dt were measured via a latex balloon placed in the left ventricle. The hearts were then prepared for histopathological, immunohistochemical, and immunofluorescent examination with H&E, Troponin I, and BrdU stain.

Conclusion: Based on Langendorff measurements and histopathological examinations, we can conclude that RES and AMSC were successful in the prevention/treatment of the doxorubicin cardiomyopathy in rats.

PN013

IRINOTECAN AND TEMOZOLAMIDE FOR CHILDREN WITH RELAPSED OR REFRACTORY RHABDOMYOSARCOMA, NEUROBLASTOMA AND EWING SARCOMA TUMORS: EXPERIENCE IN A SINGLE CENTER
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Purpose: Report our experience in use of Irinotecan and Temozolamide as rescue therapy for patients with relapsed refractory rhabdomyosarcoma, neuroblastoma and Ewing sarcoma. Estimate response rate (RR) and time to progression (TTP). Evaluate tolerance and efficacy. Methods: Retrospective review of 16 records of patients who received Irinotecan + Temozolamide between January 2007 and January 2012. Schema: Irinotecan 20mg/m2/day Temozolamide/100mg/m2/day for 5 days, every 5 weeks. Response rate: 75%, including 4 complete response (CR) and 8 partial response. One patient had stable disease. Progressive disease occurred in 3 patients. The 4 CR’s occurred in patients with neuroblastoma, 3 of whom had received I/T therapy for relapse, and 1 for lack of bone marrow remission before transplantation. From 13 patients who progressed, the mean TTP from the start date of I/T was 3.8 months (r:1-13). Three patients are alive and asymptomatic.

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 ROLE OF CYTOCHROME P450 ENZYMES IN THE METABOLIC FATE OF BUSULFAN AS EXPLORED IN PEDIATRIC PATIENTS UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Purpose: Busulfan (Bu) is a key component of myeloablative conditioning regimen used in pediatric patients prior to hematopoietic stem cell transplantation (HSCT). It is presumed that several cytochrome P 450 (CYP isoforms) might play a role in the metabolic pathway of Bu particularly in the oxidation of its metabolites. The present study is aimed at exploring the role of CYP2C9, CYP2C19 and CYP2B6 in the metabolic pathway of Bu.

Methods: Bu and sulfolane (Su, a metabolite of Bu) levels were measured from the plasma of 46 pediatric patients from St Justine Hospital, Montreal, Canada (22 females, 20 males of age range 0.1–19.9 years) collected immediately after dose 9 infusion of Bu using established liquid and gas chromatographic methods. The subjects were also genotyped for common alleles in CYP2C9 (2*, 3*), CYP2C19 (2*, 17*), and CYP2B6 (5*, 9*) genes using TaqMan® Drug Metabolism Genotyping Assays on a StepOnePlus™ Real-Time PCR System. These observations demonstrate a role of CYP2C9 in the metabolic pathway of Bu.

Conclusions: These observations demonstrate a role of CYP2C9 in the metabolic pathway of Bu. Future studies are needed to investigate the association of CYP2C9 genotypes, MRs and clinical outcomes of Bu treatment prior to HSCT in children.

PP001

DEVELOPMENT OF CHILDHOOD CANCER DATABASES IN LOW-MIDDLE INCOME COUNTRIES

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Purpose: 80% of the children who develop cancer are estimated to live in low- middle income countries (LMIC). Many are misdiagnosed, diagnosed too late, and a majority of families cannot afford the cost of treatment. Cancer emerges as other life threatening conditions are brought under control. Few countries have population based registries/databases documenting incidence, mortality and survival so how can we define the challenge each country faces and develop at least some services to cure the curable and provide good palliation for all the others.

Methods: SIOP has always advocated concentration of expertise in PCUs, registration of cases and development of country wide registries. Since its creation by ICCCP0 with the support of SIOP in 2007 World Child Cancer has opened 8 twinning projects linking LMIC with high income countries and fundamental to each one has been progression from a paper based data register to Excel spreadsheets to an online database most frequently POND with training of a data manager with clinical input.

Results: We request centres to record each patient’s presentation pathway/any delays; tumour diagnosis and stage (as far as is possible), refusal or untimely cessation of treatment, toxic deaths and 1 year, 3yr and 5yr survival, plus cause of any death. This data, clearly anonymised, forms the basis of an annual progress report to enable the centre to assess progress, put in place potential remedial action and plan future activity. Most developing centres have started to plan either satellite or shared care centres nearer to population centres in their catchment area linked by the registry.

Conclusion: The development of high ascertainment hospital based databases with fully trained data managers working closely with the medical team are critical for all start up centres in Low-Middle income countries to monitor changes in incidence, morbidity and mortality.

PP002

EVALUATION OF PATIENTS WITH INTRACRANIAL TUMORS PRESENTING WITH CENTRAL DIABETES INSIPIDUS

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Purpose: To evaluate the etiologic and clinical characteristics, treatment regimens and outcome of the patients with intracranial tumors presenting with central diabetes insipidus (DI).

Methods: 69 patients with intracranial tumors presenting with central DI between 1972 and 2012 were retrospectively evaluated. Surgery, chemotherapy, radiotherapy and steroids were used in treatment.

Results: 53 out of 69 patients were included in the analysis. 13 cases with missing information and follow-up problems were excluded. Male/female ratio was 1.52, median age was 7.6 years. Of 53 patients, 37 patients (69.8%) were diagnosed with Langerhans cell histiocytosis, 14 patients (26.4%) with germinoma, one (1.9%), with astrocystoma, one (1.9%) with optic glioma. Chemotherapy group consisted of vincristine-prednisolone in 22 patients (31.5%), bleomycin-etoyside-cisplatin in 14 (26.4%), etoposide in 2 (3.8%), DAL-X 83 protocol in one (1.9%), cyclophosphamide-prednisolone-vincristine in 2 (3.8%), prednisolone alone in one (1.9%), cyclophosphamide-vinblastine in one (1.9%), cyclophosphamide- mercaptopurine-vinblastine-prednisolone protocols in one patient (1.9%). 10-year overall survival rate and disease-free survival rate for all patients were 91.7% and 52%. 10-year overall survival rate according to diagnostic criteria was 91% for LCH cases, 79% for intracranial germinoma and 0% for astrocytoma and optic glioma which was statistically significant (p = 0.0001). 10-year overall survival rate according to the treatments was 89% for chemotherapy alone, 74% for radiotherapy alone, 66% for radiotherapy after chemotherapy (p = 0.237). There was no statistically significant difference according to chemotherapy protocols (p = 0.446).

Conclusion: Central DI may be very important clinical presentation of serious underlying disease in children. Intracranial tumors are the most frequent cause of DI. Most frequent diagnosis were LCH, and germ cell tumors in our series. Most important prognostic factor was histopathology. Intracranial tumors must be considered in patients with DI.

PP003

TRENDS IN SURVIVAL AFTER DIAGNOSIS OF MALIGNANCY OF EGYPTIAN ADOLESCENT PATIENTS (10 YEARS SINGLE CENTER EXPERIENCE)

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Purpose: Adolescents with malignancy represent a unique population in oncology that traditionally has received care in pediatric or adult oncology institutions. Aim of the work: to study the clinic-epidemiological aspects of adolescent cancer diagnosed in a Pediatric Oncology Unit over 10 years period, and to identify the associated risk factors, and the survival rate.

Methods: Retrospective data analysis of patients aged 10 years–18 years diagnosed and treated in the Pediatric Oncology Unit, Children's Hospital Ain Shams University, Cairo, Egypt during the period from January 1 2000 to December 31 2010.

Results: They were 159 patients (20% of total number of patients diagnosed during this period), 85 males (53%), and 74 females (47%). Hematological malignancies represented 90.5% the total number of patients (46.5% ALL, 12.5% NHL, 14.5% HD, 3% CML, 23.5% AML), and solid tumors represented 9.5% the total number of patients (26.5% bone tumors, 30% neuroblastoma, 20% germ cell tumor, 23.5% others). Male: Female ratio was 1.2:1 in hematological malignancies and 1.5:1 in solid tumours. The overall remission rate was 84% with hematological malignancies having the highest remission rate (89.5%). The overall survival rate was 60%. Infection was the main cause of death (50%). The 2-years and 5-years event free survival for the whole group were 43% and 30% respectively. The 2-years overall survival was 59.5% in ALL, 45.5% in AML, 25% in CML, 59% in lymphomas, 25% in neuroblastoma, 50% in Ewing, PNET and osteosarcoma, and 33% in germ cell tumours.

Conclusion: Age-related survival gap remains for adolescent cancer patients compared to children. Greater participation of adolescents and young adults in clinical trials and more detailed data collection are needed to provide evidence about optimal treatment regimens in these age groups.
ANALYSIS OF CHILDHOOD CANCER DEATHS - EXPERIENCE OF HOSPITAL AC CAMARGO  
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Purpose: To determine the frequency and causes of death in children and adolescents with cancer at a specialized Brazilian hospital (Hospital AC Camargo).  
Methods: Retrospective exploratory study, including patients under 21 years old who were diagnosed with cancer and died in the period from 2000 to 2010.  
Results: Among the causes of death, 82.4% died from disease progression and 17.6% died due to treatment toxicity, including infections. There was a predominance of deaths during the relapse treatment (44.1%), followed by deaths during the first treatment (36.2%) and deaths during palliative treatment (19.7%). Among patients with solid tumors, 94% died due to progression of the disease and 6% due to toxicity, whereas, among non-solid tumors 54% died due to progression disease and 46% due to toxicity (p < 0.005). 57 patients died during the palliative treatment, of whom 95% had solid tumors and only 5% had non-solid malignancies (p < 0.005).  
Conclusion: Despite the development of new therapies as well as multimodal treatments, patients with non-solid tumors still need special attention because the high risk of treatment-related toxicity. Lymphoma and leukemia often have faster evolution when compared to solid tumors, which may explain why many patients with non-solid tumors have died before the beginning of palliative treatment.
time to diagnosis negatively influences overall survival and survivorship through advanced disease. We conducted a systematic review to assess existing research in children and young adults (CYA) and to identify if a consensus exists within the literature for the definitions and methods used to investigate the time to diagnosis.

**Methods:** Medline, Embase, Centre for Reviews and Dissemination database and Cochrane library were searched for papers on CYA (0–30 years), published between 1960 and present day. The search strategy included the following filters: “Cancer”, “Child & Young Adult”, “Delay” and “Time to diagnosis”.

**Results:** Of the 1665 potential citations 31 papers met the inclusion criteria. The majority of papers undertaken in European (n = 15) or North American (n = 8) populations. Most work involved the brain tumour populations (n = 12), retinoblastomas (n = 6) and bone and soft tissue sarcoma (n = 4) with 10 papers containing multiple diagnostic groups within the study population. The majority of studies were in hospital-based setting (n = 25), only 6 papers adopted a population-based setting. “Time to diagnosis”, “lag-time”, “delay” and “symptom-interval” were used to describe the time between symptom onset and diagnosis. Summary statistics presented were mostly the median time to diagnosis, however the skewed distribution of the data meant comparisons between medians were difficult and combining studies within a meta-analysis was not appropriate.

**Conclusion:** No clear consensus in the CYA population exists relating to the methods or terminology used in the study of time to diagnosis of cancer. A population based study using agreed terminology is required to improve our understanding of the relationship between time to diagnosis and outcomes for cancer within CYA patients.

**PP009**

THE INFLUENCE OF BIRTH WEIGHT AND CONGENITAL MALFORMATIONS ON SURVIVAL FROM CHILDHOOD LYMPHOID LEUKAEMIA IN GREAT BRITAIN, 1980–2007

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**Purpose:** To evaluate the influence of birth weight and congenital malformations on five-year survival, as possible predictors of co-morbidity, in children who were diagnosed with lymphoid leukaemia.

**Methods:** Records for children who were diagnosed with lymphoid leukaemia aged 0–14 years while resident in Great Britain during 1980–2007 were identified in the National Registry of Childhood Tumours. The registrations were linked to birth records for birth weight data. Children’s and Leukaemia Group records and Hospital Episode Statistics (HES) data for information on congenital malformations (including Down syndrome) and MRC Clinical Trials records. Relative survival was estimated by birth weight (<2500g, 2500–4000g, >4000g), presence of Down syndrome or another congenital malformation, clinical trial entry and other demographic and prognostic factors. Multivariable analysis was used to model the influence of demographic, prognostic and potential co-morbid factors on survival.

**Results:** Children with a low birth weight tended to have slightly poorer five-year survival than other children, but the difference was of borderline significance. Children with Down syndrome had three times the excess mortality of children without a malformation. Children with other malformations had a similar outcome to children with no malformations. Children aged less than one year at diagnosis and those with a high white blood cell count at diagnosis consistently had poorer survival than other children. Children who were entered into clinical trials had higher survival than other children throughout the study.

**Conclusion:** Birth weight and malformations not including Down syndrome are not strong, independent prognostic factors for childhood lymphoid leukaemia survival. Down syndrome, age less than one year and a high white blood cell count at diagnosis, and non-entry to clinical trials are all predictors of a poorer outcome in children with lymphoid leukaemia.

**PP010**

SEASONALITY OF DIAGNOSIS IN CANCER AMONGST 15–24 YEAR OLDS IN ENGLAND, 1996–2005

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**Purpose:** There is increasing evidence that environmental factors, such as infections, which vary seasonally, and occur around the time of cancer diagnosis, may affect subsequent development of childhood cancer; however, few studies have examined whether this is true for teenagers and young adults (TYA). We aimed to examine evidence for an infectious aetiology among teenagers and young adults by analysing monthly seasonality of diagnosis amongst 15–24 year olds diagnosed with cancer in England.

**Methods:** Cases of cancer derived from the national TYA Cancer register, covering diagnoses of leukaemia, lymphoma and central nervous system (CNS) tumours between 1996 and 2005. Incidence rates and trends were assessed using Poisson regression. Seasonality of diagnosis was assessed using Poisson regression with cosine functions of varying periods whilst adjusting for sex.

**Results:** There were 6251 cases diagnosed with leukaemia (n = 1299), lymphoma (n = 3070) and CNS tumours (n = 1882), the overall incidence was 92 (95% CI 89–96) per 1,000,000 population (15–24 year olds) per year. We observed significant evidence of a seasonal effect around the time of diagnosis for Hodgkin’s lymphoma (P < 0.001) with peaks in February, and a significant seasonal effect at time of diagnosis for the ‘other CNS tumours’ group (P = 0.010) with peaks in December and June.

**Conclusion:** Our findings support an infectious aetiological hypothesis for certain subgroups of TYA cancer in England. Further work will examine correlation with specific infections occurring around the time of birth and diagnosis within certain diagnostic groups.

**PP011**

A RECORD-BASED CASE-CONTROL STUDY OF NATURAL BACKGROUND RADIATION AND THE INCIDENCE OF CHILDHOOD CANCER IN GREAT BRITAIN

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**Purpose:** Many epidemiological studies have attempted to detect associations between exposure to natural background radiation and childhood cancer. If such a link could be established it would provide evidence that radiation risks continue to be a region of low doses and dose rates. However, nearly all previous studies have suffered from insufficient power and/or other design deficiencies. The aim of this work is to test the association between childhood cancer and natural background radiation in a record-based case-control study. This study design offers two important advantages: freedom from participation bias and the potential for much larger studies than those which depend on individual interviews.

**Methods:** Cases of childhood cancer in children born and diagnosed in Great Britain during 1980–2006 were taken from the UK’s National Registry of Childhood Tumours (NRCT). The NRCT also has controls for each case, matched using birth registers. Radiation exposures were estimated for mother’s residence at the child’s birth. For natural gamma rays, County-District means based on a National Survey were used. Analogous County District means were available for radon but more precise estimates were derived from a predictive map based on domestic measurements grouped by geographical boundaries.

**Results:** A total of 27,447 cancer cases and 36,793 controls were included in the study population. Gamma ray exposures (including the directly ionising component of cosmic rays) were close to 95 nGy per hour. The mean radon exposure was about 22 Bq m⁻³.

**Conclusion:** Very much larger populations can be studied in such a record-based case-control study than in conventional interview based studies. Power calculations indicate that a study of this size has a power of ~50% to detect an association between gamma rays and childhood leukaemia.

**PP012**

NEONATAL CANCER IN GREAT BRITAIN. INCIDENCE AND SURVIVAL, 1988–2007

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**Purpose:** Little population-based information has been published on the descriptive epidemiology of cancer diagnosed in the first 4 weeks of life. The purpose of this study was to describe incidence and survival for neonatal cancer from a large population-based registry.

**Methods:** Neonates who were born during 1988–2007 and had cancer diagnosed before the age of 4 weeks were identified from the National Registry of Childhood Tumours, which is population-based for the whole of Great Britain. Diagnoses were classified according to the International Classification of Childhood Cancer, Third Edition. Incidence rates per million live births were calculated. Follow-up was through linkage to death certificates of children dying from cancer and flagging of survivors in the National Health Service Central Registers. Actuarial survival was calculated by the Kaplan-Meier method.

**Results:** There were 394 registered neonatal cancers in the 20-year study period, giving a total risk of 27.6 per million live births or 360 per million person years. The most frequent diagnoses were germ-cell tumours (24%), neuroblastoma (23%), leukaemia (18%), CNS tumours (13%), soft-tissue sarcomas (10%) and retinoblastoma (8%). Survival was 64% at 1 year and 62% at 3 years. Three-year-old survival was higher for retinoblastoma (100%), non-CNS extraneal germ-cell tumours (83%) and neuroblastoma (79%) but low for soft-tissue sarcomas (37%), leukaemia (36%) and embryonal CNS tumours (0%).

**Conclusion:** Neonates have a distinctive pattern of cancer occurrence which contrasts even with that among older infants (28–364 days). Most notably, germ cell tumours are more frequent in neonates than older infants (23% vs. 4%) whereas malignant renal tumours are less frequent (1% vs. 9%). Neonates with cancer have a poorer prognosis than older children with cancer because of their much lower one-year survival rate. The probability of survival conditional on surviving one year from diagnosis is much higher in than older children.

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Purpose: Classification of childhood solid tumours differs greatly from tumours diagnosed in adults. The purpose of establishment of childhood cancer registers is to monitor changes and progress in cancer care. Methods: All individuals born in the Nordic countries are allocated a unique ID number and have access to comprehensive health care services. Further, it is required by law that all new cases of cancer are reported to cancer registries. This makes it possible to achieve an almost complete registration of all childhood cancer cases with their classification and treatment. Status registrations were made partly from national population registries and partly from death registries only, as conditions differ between countries. Crude 5-year survival was modelled using the Kaplan-Meier method stratified by selected diagnostic groups, age groups and diagnostic period. The crude estimates were compared with log-rank tests. Results: In total, 12343 children < 15 yrs of age were diagnosed with cancer during 1986–2010 in the Nordic countries and classified according to Birch & Marsden classification. The overall incidence for the whole period was 11.2 per 100 000 children per year. Overall 5-year survival for all solid tumours reached 80.6%, 95% CI [79.3 to 81.7%]. Children diagnosed when older than 10 years reached higher survival than those diagnosed < 5 yrs, 82.4% and 78.3%, respectively. The highest survival was seen for retinoblastoma (97.0%), germ cell neoplasm (90.8%), renal tumours (88.3%) and lymphomas (88.2%). The lowest survival was observed for sympathetic nervous system (65.4%). There was a statistically significant and clinically relevant increase in survival for those diagnosed after 1991, compared to those diagnosed 1986–1990, p < 0.001. Conclusion: There has been some improvement in 5-year survival in recent time periods, especially for some diagnoses. However, there were no changes in overall survival with respect to sex and very limited changes in overall survival by age groups.

INCIDENCE OF SKELETAL-RELATED EVENTS AMONG CHILDREN WITH CANCER AND BONE METASTASES IN DENMARK

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Purpose: Bone metastases (BM) can lead to skeletal-related events (SREs), including fracture, spinal cord compression, radiation, and surgery to bone. As there are no published reports on the risk of SREs among children with BM, the burden of SREs in the pediatric population is unknown. Methods: Between 1-Jan-1999 and 31-Dec-2009, we identified children < 18 years old with BM diagnosis to first SRE (captured using ICD-10 and procedure codes in DNRP). Bone metastases (BM) can lead to skeletal-related events (SREs), including fracture, spinal cord compression, radiation, and surgery to bone. As there are no published reports on the risk of SREs among children with BM, the burden of SREs in the pediatric population is unknown. Results: Of 1234 children identified with cancer, 30 were diagnosed with BM and 20 (67%) developed an SRE during follow-up, yielding an IR of 590 per 1000 person-years (95% CI: 381–915). Seven of ten patients with osteosarcoma developed SREs (IR 812 per 1000 person-years (95% CI: 387–1704)), one patient with leukemia developed SRE, and of 16 patients diagnosed with other tumor types (details to be presented), 12 developed SREs (IR 857 per 1000 person-years (95% CI: 443–1497)). We observed a median of 18 days between BM diagnosis and first SRE, which could be due in part to SREs leading to BM identification. Of the 20 children with SREs, 15 (75%) died during follow-up, with a median of 261 days elapsing between SRE and death. Conclusion: This is the first population-based study to examine SREs in the pediatric setting. Although SREs are a common consequence of BM, few patients with SREs were identified during our 12-year study period because BM are rare among children. Survival tends to be less than one year after diagnosis of BM and SRE.
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low accrual to clinical trials related to the type of institutional care. This study aimed to determine the incidence of cancer in the 15–29 age group in Ontario, Canada and the 5 year survival of these cases by disease class, age at diagnosis group and highest level of institutional complexity of care.

Methods: The primary data source was Cancer Care Ontario (CCO). Diseases were classified according to an AYA-specific system (1). Age at diagnosis was grouped as 15–19, 20–24 and 25–29 years; and institutional complexity of care was categorized as Pediatric Oncology Group of Ontario (POGO) centres, regional cancer centres (RCC - tertiary care institutions associated with CCO), RCC affiliate and satellite institutions, and other institutions having no specialised cancer services.

Results: More than 10,000 incident cases were identified during 1990–2001. Carcinomas and lymphomas each accounted for > 20% of the total. Overall 5 year survival rate was 83%; this was significantly higher for lymphomas at POGO centres and RCC than elsewhere. About 40% of eligible AYA cases were treated at a POGO centre and 15% of these were accrued to clinical trials.

Conclusion: The low proportion of adolescents referred to pediatric cancer centres may result in a survival disadvantage for this group. All AYA with lymphomas should be referred to specialised centres. Accrual of AYA to clinical trials should be improved substantially.

References

PP018

TRENDS IN INCIDENCE OF PRIMARY CUTANEOUS MALIGNANCIES IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS: A POPULATION-BASED STUDY

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Purpose: Current studies have shown that skin cancer incidence among young adults is rising. However, the descriptive epidemiology of primary cutaneous lymphomas and cutaneous soft tissue sarcomas (CSTS) in individuals less than 30 years old has not been well investigated. We have analyzed the descriptive epidemiology and time-trends in the incidence of primary cutaneous malignancies in children and adolescents and young adults (AYA).

Methods: SEER-17 and -13 data were used to assess the descriptive epidemiology and time-trends in incidence of primary cutaneous malignancies in children and AYA. SEERstat and Jointpoint softwares were utilized to estimate annual percent changes (APC) in incidence.

Results: In total, 7,814 cases (ASR = 25.66/100,000 inhabitants) of primary cancers of skin in < 30 years old were diagnosed in the period 2000–2008. Females presented a significantly higher incidence of melanoma compared to males (risk ratio (RR) = 1.95, p < 0.001). Women have a lower risk of developing CSTS than men (RR = 0.64, p < 0.001). Compared to whites, blacks have a significantly lower incidence of melanoma (RR = 0.03, p < 0.001), whereas the risk of developing CSTS is increased (RR = 2.28, p < 0.001). Melanoma increased in females over a 15-year time period (1992–2006) (APC = 2.5, 95% CI 1.8; 3.2), and the overall incidence of cutaneous T-cell lymphomas increased over the period 1992–2008 (APC = 9.5, 95% CI 6.7; 12.4). Conversely, CSTS incidence decreased among males over the period 1992–1999 (APC = −21.5, 95% CI -27.2; -15.2, particularly due to decrease in Kaposi sarcoma incidence (APAC 1992–2008 = −12.7, 95% CI -20.2; -4.6), although with a notable racial disparity (whites, APC = −14.4, 95% CI -21.9; 6.2; blacks, APC = −8.8, 95% CI -11.4; 6.1).

Conclusion: Non-melanoma skin cancer is very rare in children and AYA. In this study we have shown variation in time-trends in incidence as well as in incidence patterns by race, sex, age, and histologic type, highlighting the importance of descriptive epidemiology to better understand the incidence and clinical characteristics of these rare malignancies.

PP019

CANCER INCIDENCE AND SURVIVAL AMONG CHILDREN AND ADOLESCENTS IN ISRAEL DURING THE YEARS 1998–2007

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Purpose: Our goal was to describe childhood cancer incidence and survival in Israel and identify demographic and epidemiologic variation among children and adolescents with cancer.

Methods: We have conducted a wide retrospective epidemiological study using data from the Israeli National Cancer Registry to examine the incidence and survival of pediatric cancer of Israeli children aged 0 to 19 diagnosed between the years 1998 and 2007. Cases were grouped by the international classification of childhood cancer and analyzed according to gender, age, origin and geographic region. Comparison age-standardized incidence rates various patient’s group was performed by Pearson chi-square test. Survival probabilities were estimated by Kaplan-Meier method.

Results: Among the 4255 cases of childhood cancer, there was a total age-adjusted incidence rate of 172.4 per million for children aged 0–19 and 153.4 per million for children aged 0–14. The incidence rate for boys was higher than for girls (192.5 and 153.3 respectively). The incidence cancer rate for Jewish children was higher than for Arabs (177.6 and 156.8 respectively). The largest diagnosed groups were Leukemias (22%), Lymphomas (20.2%) and CNS tumors (17.4%). The overall survival at 5 years was 80.8%, with 72.8% for the Arabic population and 83.2% for the Jewish. The 5-year survival depended upon the diagnosis, leukemia: 77.3%; lymphoma: 89.6%; CNS tumors: 70.4%; neuroblastoma: 77.2%; retinoblastoma: 92%; renal tumors: 85.2%; hepatic tumors: 39.1%; bone sarcoma: 70.8%; soft tissue sarcoma: 80.1%; germ-cell neoplasms: 95% and other epithelial neoplasms: 93.1%.

Conclusion: Incidence and survival in childhood cancer in Israel is in the same medium level compared to other parts of the world and the relative frequencies of various cancers is comparable. This study may set the basis for investigating the genetic and environmental factors which cause pediatric cancer in Israel delineating the genetic basis for the origin disparities in survival.

PP020


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Purpose: Since the mid-1970s there has been little progress in improving cancer survival for adolescents and young adults (AYAs, defined by the National Cancer Institute as individuals 15 to 39 years of age) in the United States, in contrast to the substantial improvements for children and older adults. The association between insurance status and cancer disparities (stage at diagnosis, survival, and treatment) in AYA patients has not been examined in a national sample.

Methods: The National Cancer Data Base, a US national hospital-based cancer registry, was used to examine insurance status and cancer disparities in 177,359 AYA cancer patients. We examined the association between insurance status and stage at diagnosis, stage-specific survival, and receipt of stage-specific treatments for common AYA sites (thyroid, female breast, non-Hodgkin lymphoma, and acute myeloid leukemia).

Results: Insurance status was strongly related to cancer disparities in AYA patients. For example, compared to patients with private insurance, uninsured patients were 1.71 times more likely to be diagnosed at stage IV (95% confidence interval [CI]: 1.63–1.79), had higher risk of death within every stage (stage I, hazard ratio (HR) (95% CI): 2.43 (2.13–2.76); stage II, 1.87 (1.70–2.06); stage III, 1.55 (1.43–1.68); stage IV, 1.39 (1.31–1.48); and unstaged (leukemias, CNS tumors, etc.), 1.67 (1.58–1.76), and for the four sites listed above, were less likely to receive the most frequently used stage-specific treatments. Insurance status remained a strong independent predictor for each of these outcomes in multivariate models adjusting for patient, hospital, and tumor factors.

Conclusion: In a large national sample, insurance status was a strong independent predictor of cancer disparities in AYA patients. The Affordable Care Act of 2010 should facilitate acquisition of adequate health insurance by AYA, who are the most under- and uninsured age group in the US population, and should contribute to remediation of such disparities.

PP021

RELATIVE SURVIVAL PROFILE OF PAEDIATRIC AND NON-PAEDIATRIC LOW GRADE GLIOMAS

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Purpose: To assess the population-based estimates of survival for children, young adult and elderly (0–15, 16–39, 40–65 & > 65) years with low-grade gliomas (LGG) and determine the impact of age and time on relative survival (RS).

Methods: Data from the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute from 1973 to 2006 was analysed to assess survivorship of 5,037. Cumulative relative survival (RS) was computed SEER expected mortality data and the Ederer II method for expected survival estimation, and modelled using Dickman’s piecewise constant hazards RS model.

Results: Overall, the 2- and 10-year OS and RS (OS/RS) was 72/73% and 45/48% respectively. When analysed by age group, the 10-year OS and RS for children, young adults, and elderly was 86/86, 61/62, 40/43, and 10/14. The observed difference in metrics with OS and RS was larger for elderly patients (4%) and was smallest for children (< 1%).

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Elderly patients were 30.53 times (eHR, 95%CI 20.26, 44.99) as likely to die in the first year as young adults. Differences were reduced at 5 years, where the difference in survival are much reduced, and the presence of an age-by-follow-up interaction is demonstrated.

Conclusion: The survivalship of elderly patients with LGG is substantially different from the one computed for young adults and children, and the trends across age groups are highly not proportional. Relative survival does not provide additional information that would have been provided by overall survival in populations with LGGs.

PP024
COMPARISON OF ANTICIPATED AND ACTUAL CONTROL GROUP OUTCOME IN RANDOMISED TRIALS IN PAEDIATRIC ONCOLOGY
PROVIDES EVIDENCE THAT NON-RANDOMISED STUDIES ARE BIASED IN FAVOUR OF THE NOVEL TREATMENT

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Purpose: Historically controlled studies (HCS) compare outcome data from independently conducted interventional studies to derive a relative comparison about treatment efficacy. This type of studies is common in pediatric oncology (PO) despite the potential biases being well known, e.g. factors change over time meaning that the groups may not be comparable. To compare the outcome in control group of RCTs in PO with that anticipated in sample size calculation, the rationale being that had a HCS been designed instead, the HCS outcome used would have been that used for the control group in the RCT’s sample size calculation.

Methods: A search for published PO RCTs was conducted using the Cochrane Central database. Only papers reporting sample size parameters and observed estimates were included. Data were extracted and compared on anticipated and observed outcomes in the control arms (and experimental arms).

Results: To date 48 randomised questions (RQs) included: 37 superiority trials, 11 equivalence/inferiority, 6 with dichotomous primary endpoints, 42 time-to-event; median recruited number of patients was 221 (range: 36–2618). In 34% the control group did better than anticipated (12 cases >10% absolute difference), in 12 the control group did worse (by >10% in six); outcome was the same as anticipated in one trial. The median absolute difference between control groups’ observed outcome and anticipated outcome was 5.0% (range: -23%–+34%); mean 3.8%. The median observed difference between the experimental and control groups was 2.0% (range: -16%–+21%); the median difference between the observed experimental and anticipated control group outcome was 6.5% (range: -20%–+34%).

Conclusion: Since the control group in RCTs did better than anticipated, HSCs that use similar assumptions for outcome with standard treatment can overestimate benefit of new treatments. This could lead to children with cancer being given inappropriate therapy.

PP025
INTRODUCING RELIABILITY INTO PRESCRIBING PRACTICE: REDUCING THE RISK AND IMPACT OF MEDICATION PRESCRIBING ERRORS ON HAEMATOLOGY/ONCOLOGY PATIENTS – THE GREAT ORMOND STREET EXPERIENCE

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Purpose: To achieve highly reliable prescribing on haematology and oncology wards by employing the principles of ‘High Reliability Organisations’. Reducing prescribing errors on Haematology and Oncology wards by 50% within 12 months from November 2010 to November 2011.

Methods: Two full time pharmacists were employed, providing permanent presence and ward based pharmacy service to Haematology/Oncology wards. Five principles of highly reliable organisation were employed:

1) Pre-occupation with failure. a) Each day pharmacist monitored prescribing for errors; b) Medication history checked for every child within 24 hours of admission. (2) Reluctance to simplify interpretations. a) Errors picked up are highlighted to prescriber and where necessary highlighted to larger group. (3) Sensitivity to operations. (4) Commitment to resilience. a) Errors are contained, prescriber that made the error rectifies it; b) Intervention and proactive prescribing support before prescribing. (5) Under specification of structures/Deference to expertise. a) All prescribers get one week 1:1 supervision when starting. Multiple measure used to show sustained change, were sub-divided into outcome, process and balancing measures.

Results: Outcome measures were instances of harm and prescribing errors/100 items prescribed.

Conclusion: Outcome measures were instances of harm and prescribing errors/100 items prescribed. Since November 2010, 0 instances of harm were seen and process mean of 7.47 improved to 4.68 errors/100 drugs prescribed. For new admissions, 49% to 62% improvement was seen of drugs prescribed on admission correctly. Process measures were interventions by pharmacist and % of doctors given one week of 1:1 prescribing supervision. Since November 2010, number of pharmacist interventions decreased from 4.65 to 2.09/100 drugs prescribed. 100% of doctors received one week 1:1 supervised prescribing. Balancing measures, number of prescribing error incidents reported, 9 were reported from November 2010 to July 2011 reduced from 20 incidents from November 2009 to 2010.

Conclusion: Presence and intervention of a permanent ward based pharmacists helped introduce improved reliability in prescribing practice and reduction in errors and risk.

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FIVE YEARS OF ONCOPEDIA. AN INTERACTIVE EDUCATIONAL WEBSITE FOR PEDIATRIC ONCOLOGY

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Purpose: To evaluate the contents and usage of Oncopedia (www.oncopedia.org) 5 years after its launching.

Methods: Oncopedia, an interactive educational website in the Cure4kids.org network is totally composed of user-submitted, peer-reviewed educational material including cases, images, videos and chapters dealing with pediatric oncology. Once posted, all the material is open for moderated discussion among all users and chapters can be also edited. Links to full text articles in Pediatric Blood and Cancer are available and nursing contents have been recently released. Other interactive features include polls about controversial topics in the specialty and image challenges. All the material is freely downloadable and offered at no cost to registered users, targeting colleagues in developing countries.

Results: Since its launching in May 2007 to February 2012, a total of 133 cases, 158 images, 72 videos and 50 chapters were posted. Oncopedia users are located in Latin America in 29%, North America in 28%, Europe in 16%, Africa in 13% and Asia in 9%. The site has been visited 203,789 times by a mean of 494.27 single users each month from May 2007, and a total of 784 comments have been posted by our users. Chapters have been accessed a total of 52, 159 times by over 5,000 users. Cases, images and videos have been visited on a mean of 27,538 times. Twenty-five percent of the content was submitted by users in developing countries. Contents are available in 5 languages.

Conclusion: Oncopedia has demonstrated the feasibility of a global online discussion forum for pediatric oncology and a valuable open-access publication opportunity for developing countries.

References
http://www.cure4kids.org/umns/oncopedia/

PATTERN OF REFUSAL TO TREAT AND ABANDONMENT IN A NEW PEDIATRIC ONCOLOGY UNIT IN SOUTHERN INDIA

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Purpose: Refusal to treat (RTT) and abandonment of therapy (AOT) are the major causes for the poor overall outcome of children with cancer in the developing world. Socioeconomic constraints, religious beliefs, fatalistic attitude and belief in alternative therapies all contribute to these. We report on the pattern of RTT and AOT for the first three years of a new Pediatric Oncology Unit from a university hospital in southern India.

Methods: We conducted a retrospective review of all pediatric oncology patients seen in the Pediatric Oncology unit of our hospital from June 2009 to date.

Results: Of 137 patients referred to the Pediatric Oncology unit, 115 were newly diagnosed and 22 patients were referred either for a second opinion, for palliative care or for follow up as survivors. Malignancy was ruled out in 4 patients. Of the 111 patients with newly diagnosed cancer, 93 opted for treatment whereas 18 refused treatment. Seven of the 93 patients who started therapy abandoned it before completion. Of these 25 patients (22.5%) (RTT + AOT), 8 had leukemia (ALL, AML 2). Of the 17 patients with solid tumours, 7 had early stage disease and 12 had advanced stage disease. The median age was 4 years (range 1–18 years) and the male to female ratio was 1.7:1. The reasons for abandonment included financial constraints, distance from residence to the hospital, the belief that cancer is incurable and belief in alternative and complementary therapy.

Conclusion: This review has provided an insight into the magnitude of the problem of abandonment of therapy and its impact on overall survival. The possible interventions that can help reduce this high rate of RTT and AOT include a robust financial support programme, patient accommodation facility near the hospital and increasing pediatrician and physician awareness about the curability of childhood cancers.

SIOP PEDIATRIC ONCOLOGY IN DEVELOPING COUNTRIES (PODC) ABANDONMENT OF TREATMENT WORKING GROUP: AN EVALUATION OF PROGRESS

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Purpose: Evaluation has emerged as a priority in global health; however, evaluations of global health partnerships in pediatric oncology are not widely reported. An interdisciplinary SIOP PODC Abandonment of Treatment Working Group was established at SIOP Congress 2010 to promote efforts to study and reduce pediatric cancer treatment abandonment. An evaluation tool was developed to assess group functioning and progress and to guide strategic planning.

Methods: A self-evaluation tool was iteratively created to assess group function (including personnel, organization, and activity), projects, and member involvement.

Results: Membership grew since inauguration from 16 to 35 participants from 30 institutions in 14 countries, including trainees, mid-career participants, and global leaders, who provide multidisciplinary pediatric oncology care, conduct clinical and epidemiology research, or

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engage as parent and community advocates. Collaborations in research, education, and advocacy have progressed through emails and online meetings (including five group-wide and multiple sub-group sessions), using the freely accessible Cure4Kids website (www.Cure4Kids.org). Initial achievements include publication of consensus clarifications of abandonment’s definition and measurement[1], establishment of an online repository (including 64 keyword-tagged resources), and mobilization of international members in developing and implementing abandonment projects. Activities underway include 1a) a global health provider survey on abandonment magnitude, associated factors, and prevention strategies; 2a) a systematic review of abandonment in low- and middle-income settings; 3a) a multi-site protocol to assess families’ cancer treatment-related costs; and 4a) a tracking and early intervention proposal for children at risk of abandonment. The evaluation served to communicate partnership activities, highlighted site-specific needs, members’ expertise and interests, and identified opportunities for next steps.

Conclusion: Through open partnerships, interdisciplinary online collaboration of volunteer members, the establishment of a research, education and advocacy efforts towards addressing needs in global pediatric oncology. Structured self-evaluation can help groups to promote cohesive decision-making; mobilize resources, expertise, and interests; monitor and stimulate new ideas.

References

PP030
P-MEDICINE: A SOLUTION FOR TRANSLATIONAL RESEARCH?

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Purpose: The nature of healthcare is changing from reactive to preventive. These changes are catalysed by a new approach to disease, which focuses on integrated diagnosis, treatment and prevention in individuals. Molecular biology and information technology are the main drivers in this process. The question is how such a translational approach can be implemented in daily clinical care of patients.

Methods: Multi-level data collection within clinico-genomic trials and interdisciplinary analysis by clinicians, molecular biologists and others involved in life science is mandatory in this process. The question is how such a translational approach can be implemented in daily clinical care of patients. These tools are intended to facilitate the run of clinical trials, to support physicians in their decisions toward patient treatment, to empower patients, to run system biology driven cancer models in the computer (in silico oncology) and to mine data from literature for knowledge discovery. Scenarios and examples of such tools will be demonstrated.

Conclusion: The p-medicine infrastructure is able to address demanding needs in translational research. To sustain a self-supporting infrastructure realistic use cases and requirements. These tools are intended to facilitate the run of clinical trials, to support physicians in their decisions toward patient treatment, to empower patients, to run system biology driven cancer models in the computer (in silico oncology) and to mine data from literature for knowledge discovery. Scenarios and examples of such tools will be demonstrated.

References
http://p-medicine.eu

PP031
RECENT MELANOMA INCIDENCE ACROSS ENGLAND AND AMONG WHITE RESIDENTS IN YOUNG PEOPLE RELATIVE TO ADULTS

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Pediatric Cancer DOI 10.1016/j.ypedi.2012.05.021

PP031
RECENT MELANOMA INCIDENCE ACROSS ENGLAND AND AMONG WHITE RESIDENTS IN YOUNG PEOPLE RELATIVE TO ADULTS

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Pediatric Blood Cancer DOI 10.1002/pbc

PP031
RECENT MELANOMA INCIDENCE ACROSS ENGLAND AND AMONG WHITE RESIDENTS IN YOUNG PEOPLE RELATIVE TO ADULTS

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Pediatric Blood Cancer DOI 10.1002/pbc

Purpose: Melanoma incidence continues to rise in England, particularly among white populations. Previous studies have described trends of increasing melanoma incidence with decreasing latitude; however, they have not accounted for the uneven distribution of low-risk non-white populations country-wide. We compared recent incidence rates of melanoma across regions of England in youth (< 25 years) and adults, accounting for regional distribution of non-white populations.

Methods: All incident primary invasive cutaneous melanomas in England, 1996–2006, were identified from national cancer registration. Region of residence at time of diagnosis was assigned as one of nine Government Office Regions (GOR) in England. Population estimates by ethnicity were obtained from national census data. Age-standardized, region-specific incidence rates (per million person-years) were calculated by sex and age group (< 25, 25–54, 55–89 years) for the entire population, and for white residents.

Results: During the study period, 69819 cases of melanoma were diagnosed, 1607 (2.3%) of which occurred among < 25 year olds. Melanoma incidence did not follow an increasing trend from north to south latitude, most strikingly among young people. Among white residents, rates in young males varied less across the country (5–10 per million) than in young females (10–20 per million). Under age 25, young women in the North West had the highest rates of all. Among older adults, highest incidence occurred in the South West and South East but the latitude gradient was disrupted by high rates in the North West and Yorkshire and the Humber GOR in north eastern England.

Conclusion: The former inverse relation of latitude of residence to melanoma incidence in England has much more remarkably changed in youth under age 25. Notably, young females in the north appear to be at particularly high risk for their age group. Prevalent sun use and holidays abroad likely underlie these changing patterns.

LATE EFFECTS

PP001
GENETIC RISK FACTORS OF ANTHRACYCLINE CARDIOTOXICITY – RELEVANT POLYMORPHISMS IDENTIFIED IN ENZYMES AND TRANSPORTERS OF ANTHRACYCLINE PHARMACOKINETICS

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Purpose: One of the main dose limiting side-effects of anthracyclines is late cardiotoxicity. Survivors of anticancer therapy have increased risk for cardiovascular problems and have higher such mortality. Subclinical changes may become crucial in case of later accompanying diseases affecting the heart or the circulation, or these changes can precede severe symptoms. Identifying patients with altered tolerance to anthracyclines would provide great clinical benefit.

Methods: We studied 164 paediatric acute lymphoblastic leukaemia (ALL) patients who had been treated with ALL BFM protocols. They had cardiac ultrasound scans with a mean follow up of 6.4 years after anthracycline therapy. Left ventricular function was assessed as fractional shortening (LVSF). A total of 19 single nucleotide polymorphisms (SNPs) were genotyped in the ABC1, CBR1, CBR3 and AKR1A1 genes. General linear model statistics were performed to test for associations.

Results: Patients with ABC CI rs246221CT/TT genotype had reduced LVFS at the time of the latest echocardiography compared to CC patients (38.4% and 40.7% respectively, p = 0.027). Those with AKR1A1 rs2088102CC genotype had lower LVSF than those harbouring at least one T allele (36.9% and 39.3% respectively, p = 0.013). Further SNPs showed no association with left ventricular function. Conclusion: Our results suggest that the ABC CI rs246221 and the AKR1A1 rs2088102 variations are associated with altered left ventricular function in late survivors of childhood acute lymphoblastic leukaemia. The identified early subclinical changes may contribute to a polygenic disorder that evolves over a longer time and manifests in congestive heart disease later. A concise overview of the literature will be presented on gene polymorphisms found in association with anthracycline-induced cardiotoxicity.

PP002
MYOCARDIAL 2D STRAIN ECHOCARDIOGRAPHY AND CARDIAC BIOMARKERS IN CHILDREN DURING AND SHORTLY AFTER ANTHRACYCLINE THERAPY FOR ACUTE LYMPHOBlastic LEUKAEMIA (ALL): A PROSPECTIVE STUDY

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Conclusion: myocardial 2D strain echocardiography and cardiac biomarkers are useful in survivors were associated with more fatigue and poorer QoL.

Methods: Cardiac function of 60 children with ALL was prospectively studied with measurements of cardiac Troponin T (cTnT) and N-Terminal-pro-brain natriuretic peptide (NT-pro-BNP) and conventional and myocardial 2D strain echocardiography before start (T = 0), after three months (T = 1) and after one year (T = 2), and were compared to 60 healthy age-matched controls.

Results: None of the patients showed clinical signs of cardiac failure. The fractional shortening (FS) remained normal. Cardiac function decreased significantly during treatment and was significantly decreased compared to normal controls. cTnT levels were abnormal in 11% of the patients at T = 1 and were significantly related to increased time to global peak systolic longitudinal strain at T = 2 (p = 0.003). NT-pro-BNP levels were abnormal in 13% of patients at T = 1 and in 20% at T = 2. Absolute values of NT-pro-BNP increased throughout treatment in 59% of the patients. Predictors for abnormal cardiac biomarkers and myocardial 2D strain parameters at T = 2 were cumulative anthracycline dose, z-score of the diastolic left ventricular internal diameter and FS at baseline, abnormal NT-pro-BNP at T = 0 and T = 1, and global longitudinal strain and strain rate at T = 1.

Conclusion: Myocardial 2D strain echocardiography and cardiac biomarkers are useful in the detection of early anthracycline-induced cardiotoxicity.
sibling controls. The assessments included components of the metabolic syndrome, cardiovascular late effects and several relevant biomarkers.

Results: The metabolic syndrome is more common in CCS than in sibling controls (respect. 10.4% and 4.0%; p = 0.035). Among survivors the metabolic syndrome is associated with high leptin levels (21.1 ng/ml versus 8.3 ng/ml, p = 0.007) and low adiponectin levels (4361.5 ng/ml versus 7625.9 ng/ml, p < 0.001). CCS with the metabolic syndrome has an abnormal cardiovascular profile with increased endothelial markers and increased intima media thickness of the carotid- and femoral-arteries.

Conclusion: The risk of the metabolic syndrome is increased in CCS.Survivors with the metabolic syndrome have a worse cardiovascular risk factor profile and more signs of cardiovascular late effects. These findings underscore the importance of follow up for these patients with the focus on early developing components of the metabolic syndrome and subclinical cardiac dysfunction and vascular abnormalities. Further investigation is required to estimate how soon during/after cancer treatment these abnormalities develop and how they can be prevented.

PQ007
LONG-TERM NEUROCOGNITIVE DEFICITS IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA SURVIVORS: STUDYING THE POTENTIAL ROLE OF CELLULAR SENESCENCE
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Purpose: Childhood cancer survivors have increased risks of developing neurocognitive deficits. Underlying biological mechanisms have not been fully deciphered. Cellular senescence is a permanent growth arrest state correlated with aging in humans. Anti-cancer treatments induce cellular senescence in mice. Assuming that senescence can be associated with tissues and organs impairment, anti-cancer treatments may trigger exacerbated senescence, translating into young-onset diseases and deficits in childhood cancer survivors.

Methods: Childhood acute lymphoblastic leukemia long-term survivors (patients) (n = 9, average years post-diagnosis = 13.5) participated in this pilot study. All patients received CRT. For each patient, one of their sibling (controls) (n = 9) also participated. The full Weschler IQ test battery and a specific visuo-spatial memory test were used to assess neurocognitive performance of all participants. p16INK4A expression, a cellular senescence marker, was measured by RT-PCR from skin biopsies originating from an irradiated region (patients) and a non-irradiated region (patients and controls).

Results: Average global IQ score was lower for patients compared to controls (p = 0.05). A similar trend was observed specifically for the working memory performance scale (p = 0.12) of the IQ test battery. The specific visuo-spatial memory test validated this finding (1 stimulus or 2 stimuli; p < 0.05). p16INK4A expression was also more expressed in the irradiated skin region (biopsy from patients) compared to the non-irradiated skin region (biopsy from patients) (p = 0.02). p16INK4A expression was also more elevated in irradiated skin region (biopsy from patients) compared to controls’ skin biopsies (p = 0.02). Finally, a positive association was observed between p16INK4A expression fold increase (ratio patient/control) and the performance gap between patients and controls at the visuo-spatial memory task (Pearson’s correlation, R² = 0.52, p < 0.05).

Conclusion: Cellular senescence as a potential player in explaining individual differences regarding anti-cancer agents-related side-effects should be further investigated.

PQ008
LONG-TERM INTELLECTUAL DECLINE IN ADULT SURVIVORS OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA TREATED WITH CRANIAL RADIATION
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Purpose: To evaluate long-term (20 year) change in intellectual function associated with cranial radiation therapy for adult survivors of childhood acute lymphoblastic leukemia (ALL). It is unknown whether function continues to decline in the two decades following the immediate post-therapy period.

Methods: Estimates of Full Scale (FSIQ), Verbal (VIQ) and Performance (PIQ) intelligence were obtained in 103 adult survivors of childhood ALL (54.4% female; mean age = 38.2 years [range = 26.2–54.7]). Adult outcomes were compared to an initial evaluation conducted at least one-year following completion of therapy (mean SD; 14.1 ± 2.8 years) to initial evaluation (mean ± SD; 6.6 ± 3.5; time between initial evaluation and adult evaluation = 26.6 ± 9.0 years). Multivariable regression models examined degree of intellectual decline in reference to radiation dose (18 Gy vs. 24 Gy), gender, age at radiation exposure, time between diagnosis and initial evaluation, and time between initial and adult evaluations.

Results: Compared to age-adjusted national norms, on the initial evaluation survivors demonstrated lower PIQ (mean SD; 95.8 ± 15.98; p = 0.009) and FSIQ (96.6 ± 15.21; p = 0.03), but not VIQ (97.7 ± 14.86; p = 0.12). However, VIQ demonstrated a significant decline at adult follow-up (mean SD; change = 10.0 ± 11.68; p < 0.0001), while no change in PIQ over time was apparent (change = 0.05 ± 14.13; p = 0.97). Multiple regression analyses revealed no statistically significant associations for decline in VIQ with gender (β = 0.68, p = 0.78), radiation dose (β = 0.30, p = 0.42), age at radiation exposure (β = 0.51, p = 0.14), or time between diagnosis and initial evaluation (β = −0.28, p = 0.42).

Conclusion: Cranial radiation therapy for childhood ALL is associated with an initial decline in performance abilities, followed by a late decline in verbal intelligence. Traditional variables associated with early decline do not predict change in IQ over subsequent decades. Since total IQ being is heavily dependent upon learning new information over time, the integrity of encoding and long-term memory functions should be explored.

PQ009
PULMONARY FUNCTION FOLLOWING ALLOGENIC STEM CELL TRANSPLANT IN PEDIATRIC CANCER PATIENTS IN FINLAND: A RETROSPECTIVE COHORT STUDY OF 51 PATIENTS
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Purpose: Haematopoietic stem cell transplant (HSCT) has over the past 30 years become the curative treatment for children diagnosed with a wide range of malignant and benign conditions. In this setting, intensive preconditioning treatments, including alkylating agents and total body irradiation place these patients at high risk of developing various late morbidities. Respiratory complications are expected to occur in every other patient receiving a stem cell transplant. The aim of the study was to evaluate the timeframe and occurrence of pulmonary dysfunction following stem cell transplant for childhood haematological malignancies as well as potential risk factors for pulmonary dysfunction.

Methods: A retrospective evaluation of medical records of 51 patients aged over 6 years treated with HSCT in a single centre were evaluated. Patients had taken part in spirometry measurements prior to HSCT (baseline) as well as 6–12 (spirol1), 18–24mos (spirol2) and 3–5ys (spirol3) post HSCT. Main outcome measures were changes observed in FVC and FEV1 over time. The Wilcoxon signed rank test was used to analyse changes in pulmonary function tests over time. Mann-Whitney statistics were used to analyse potential explanatory factors.

Results: Significant reductions of 15.6% (p = 0.05) in FVC could be seen when comparing baseline spirometry and spirometry conducted at first post HSCT follow-up visit. FVC reduction was progressive as a significant reduction of 11.4% (p = 0.05) was also seen between baseline and the spirometry performed on the last follow-up. Some improvement was seen between the spirol1 and spirol2 as the FVC changed 6.6% (p < 0.05). Similar decline profiles over time were observed for FEV1. Acute- and chronic graft-versus-host-disease were separately significantly associated with FVC decline.

Conclusion: Patients who have undergone HSCT are at elevated risk of restrictive lung disease and should be followed-up with spirometry. Acute- and chronic graft-versus-host-disease are significant risk factors for these pulmonary complications.

PQ010
LATE CARDIAC DYSFUNCTION, ESPECIALLY DIASTOLIC, IS COMMON AFTER ANTHRACYCLINE USAGE AND MAY OCCUR EVEN AT LOWER “SAFE” DOSES
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Purpose: We present our data regarding the incidence of late anthracycline-cardiotoxicity in childhood with cancer.

Methods: Retrospective study; Children having cancer, age < 15 years at diagnosis, treated with doxorubicin/daunorubicin, were screened after completion of therapy for cardiac dysfunction. Study period June 2003–January 2012. Cardiac evaluation was done by echocardiography. Systolic ventricular function was assessed by M mode-Fractional shortening (FS). Global ventricular function was assessed by myocardial performance index (MPI). From 2008 all measurements also included tissue doppler imaging (TDI) of mitral annular velocities and E/e’ ratios of the lateral mitral annulus. Results were considered abnormal if FS < 29%, MPI > 0.32, Mitral E/e’ > 8 and spectral Doppler (SD) mitral inflow velocity ratios of < 1 or > 1.5. Both anthracyclines were considered equivalent while computing cumulative doses. Patients having multiple assessments were evaluated for deterioration/improvement in cardiac parameters.

Results: 88 echocardiographic assessments were available in 65 patients. No patient had clinical evidence of cardiac failure at the time of assessment. 17 patients had repeat assessments at 1–7 year intervals; Median cumulative anthracycline dose = 325mg/m² (25–370); Median duration since last anthracycline = 1297days (196–4346). 2 patients had received mediastinal RT 3265 (49) patients showed evidence of cardiac dysfunction on
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echocardiography. Abnormalities in FS, MPI, TDI and SD were seen in 4/86 (6%), 18/55 (33%), 12/40 (30%) and 20/31 (64%) patients tested, respectively. Abnormalities in 2 or more parameters were seen in 14/31 patients who had all 4 parameters available. Those receiving cumulative doses < 200mg/m², 200–350mg/m² and > 350mg/m² showed abnormalities in 4/17 (23%), 10/46 (22%) and 27/28 (96%) patients respectively (p = 0.91). On follow-up, systolic function improved in 5/17 patients, while 2/17 showed worsening. All 3 patients having follow-up of diastolic parameters showed worsening function.

Conclusion: Late cardiac dysfunction, especially diastolic, is common after anthracycline usage and may occur even at lower “safe” doses. Screening for systolic dysfunction alone (M-mode, MUGA) may underestimate cardiotoxicity.

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Dr Atul Mulay and KRNST for assistance in statistical analysis.

PO011
SECOND MALIGNANCIES IN SURVIVORS OF A MALIGNANT BONE TUMOR: TWENTY FIVE YEARS POST TREATMENT

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Purpose: Second Malignant Neoplasms (SMN) are one the threatening late effects in cancer survivors. In the literature the 10 years cumulative incidences of second malignancies after osteosarcoma ranges from 2% to 4.6%. The average follow up after diagnosis ranges from 2.7 to 10.6 years [1–4]. Purpose To assess SMNs in survivors of a malignant bone tumor.

Methods: Our cohort consisted of 31 patients (23 men/8 women), treated for a bone tumor at a single institution between 1977 and 1990, with a mean age at diagnosis of 20.2 (9–45 years). Twenty-six were treated for osteosarcoma and 5 for malignant fibrous histiocytoma. They were treated with chemotherapy, according to Rosen protocols (T5 before 1979 and T10 after 1979) and with surgery. None of the patients received radiotherapy. Mean duration of follow up was 25.6 (14–34) years.

Results: 33.8% of the survivors had a second malignancy (2/31 skin cancer, 5/31 gastrointestinal tumor, 3/31 mammary carcinoma and 1/31 not classifiable). Mean time of SMN after diagnosis 20.6 (7–30) years. Twenty-six patients are still alive. Five survivors died, mean 22.4 years (17–29) after the diagnosis of a malignant bone tumor. The cause of death in three survivors was the second malignancy, in one a cerebrovascular accident and in one an unknown sudden death.

Conclusion: The rate of second malignant neoplasms was significantly higher compared to the literature. Almost half of these patients had a gastro intestinal tumor and almost a third a mammary carcinoma. There were no hematological malignancies. The length of our follow up is much longer than described in the other reports (mean 25 versus 10.6 years). This might be a reason for the enormous increase compared to the literature.

References
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PO013
EPIDEMIOLOGY OF LATE ONSET ANTHRACYLINE INDUCED MYOCARDIAL DYSFUNCTION IN CHILDHOOD CANCER SURVIVORS

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Purpose: To characterize anthracyline induced myocardial dysfunction in childhood cancer survivors.

Methods: Records of all children attending the Pediatric Cancer Survivor Clinic (PCSC) were screened. Children treated with anthracyline based chemotherapeutic regimes were eligible. Myocardial function was assessed by conventional echocardiography at baseline, at completion of chemotherapy and at 6 months interval subsequently.

Results: 483 records from PCSC were screened and 319 children were treated with anthracyline based regimes. Details of echocardiography were available in 203 patients. Mean age was 7.8 yrs. All patients were asymptomatic on completion of chemotherapy. The cumulative dose of anthracycline received was calculated (ALL (230mg/m²), AML (450mg/m²) HL (250mg/m²), Neuroblastoma 170mg/m²). Baseline myocardial function was normal in all. 27 survivors (13.3%) had myocardial dysfunction. Of this 3 occurred during chemotherapy and after completion of chemotherapy in 24 cases. Highest prevalence of myocardial dysfunction was seen in children with AML (31.25% of patients with LV dysfunction) who also received the highest cumulative dose of anthracycline. This was followed by ALL (15.6%) and then HL (8.7%). There was wide variation in the onset of myocardial dysfunction with earliest onset in AML patients who also got the maximum cumulative dose.

Conclusion: With improved survival focus is now on long term effects of cancer therapy. Myocardial dysfunction can be a late effect of cancer therapy and can manifest even after chemotherapy is over. There is a need for continued follow up of children after completion of chemotherapy even if they are asymptomatic.

PO014
CHEST HEALTH SURVEILLANCE UTILITY IN EARLY DETECTION OF BRONCHIOLITIS OBLITERANS SYNDROME IN CHILDREN POST HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Purpose: Bronchiolitis obliterans syndrome (BOS) is a progressive lung disease affecting allogeneic SCT recipients. Early detection is key for stabilization. To prospectively assess if periodic chest surveillance is beneficial for early detection of BOS in children post SCT.

Methods: Children up to 18 years receiving allogeneic SCT from Sept 2009 to Sept 2011 were prospectively studied. Chest surveillance was initiated pre SCT, and post SCT at 1, 3, 6, 9, 12, 18 and 24 months. A 13-item respiratory system questionnaire was administered at each time point along with a respiratory examination, oxygen saturation monitoring and full pulmonary function tests (PFT’s). Diagnosis of BOS was according to NIH criteria.

Results: Thirty-nine patients were enrolled in the study (26 malignant and 13 non-malignant). Seven patients died from transplant related mortality (one BOS patient) and 2 died from disease relapse. Five children developed BOS at a median time of 192 days (range 94–282). The chest questionnaire and examination were not beneficial to early differentiation between BOS from non-BOS patients. Upon diagnosis with BOS, the history and clinical chest examination was abnormal with cough, crackles and wheezes in BOS patients. However, PFT’s were useful for early detection of lung volume changes in the asymptomatic phase. Patients with BOS in the asymptomatic phase have shown an average of 32% reduction in their forced expiratory volume at first second (FEV1_) just prior to BOS diagnosis compared to 6% reduction in those without BOS taking into accounts all PFT’s points time post SCT (p = 0.005).

Conclusion: Periodic detailed history and chest examination is not useful for early detection of BOS in children post SCT. Positive history and positive chest findings only occur after treatments.
significant damage has occurred and a diagnosis of BOS is made. Periodic PFT’s were useful in early detection of BOS prior to appearance of signs and symptoms.

**PQ015**

**GONADAL FUNCTION RECOVERY IN VERY LONG-TERM MALE SURVIVORS OF CHILDHOOD CANCER**

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**Purpose:** To study recovery of gonadal function in very long-term male survivors of childhood cancer using paired serum Inhibin B levels.

**Methods:** A cross-sectional retrospective single-center study was performed in our adult late-effects outpatient clinic for long-term childhood cancer survivors. Male survivors diagnosed between 1944 and 2005 who visited our late-effects outpatient clinic twice or more were included. Serum Inhibin B levels were measured during the two visits. We analyzed our data with non-parametric tests and used a logistic regression model to predict the probability of achieving normal Inhibin B levels.

**Results:** 203 male survivors were included. Median age at diagnosis was 5.9 years (range 0.0–17.5) and cessation of treatment was reached at a median age of 5.2 years (range 0.0–20.8). Inhibin B levels were first measured after a median follow-up time of 15.7 years (range 3.0–37.0). Median interval between the first and second measurement was 3.3 years (range 0.7–13.3). Median Inhibin B level was 127 ng/L (range 5–366) at first assessment and 155 ng/L (range 10–507) at second assessment. The prediction model suggests that Inhibin B levels do not normalize in survivors with a very low Inhibin B level at the first follow-up time point. This group included mainly survivors of Hodgkin lymphoma treated with MOPP and adriamycin or survivors treated with pelvic irradiation or with an Alkylating Agent Dose score >3, which is an important threshold for alkylating agent dose.

**Conclusion:** In general, Inhibin B levels increase over time, which is suggestive for recovery of gonadal function long after discontinuation of treatment. However, this increase does not seem to occur in survivors who already reached critically low Inhibin B levels at first assessment.

**PQ016**

**LIFE CHALLENGES EXPERIENCED BY LONG-TERM PEDIATRIC BRAIN TUMOR SURVIVORS: PARENTS’ PERSPECTIVES**

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**Purpose:** Pediatric brain tumour survivors (PBTS) are at high risk for psychosocial late effects. Parents witness the difficulties their children face as they transition to adulthood and usually play a substantial role supporting and advocating well into their child’s adult years. Our purpose is to document Canadian parents’ perspectives of challenges such as discrimination and financial difficulties experienced by PBTS.

**Methods:** Parents of PBTS were recruited consecutively through the British Columbia Cancer Agency Late Effects Clinic to complete an anonymous online survey.

**Results:** Preliminary analysis of 26 parents’ responses detail discrimination and unfair treatment experienced by their children at school and later at work. Although 92% graduated from high school, 46% of parents did not think their child received adequate support. The majority were bullied by peers (58%) and school staff (38%). Following high school, PBTS had difficulty getting or keeping a job (65%) and once employed, experienced significant problems, such as barriers to, or denial of, assistance to accommodate special needs (27%). Most PBTS were unable to cover daily living expenses without parental support (77%). Despite the Canadian public health system, most parents pay for their child’s medical expenses out of pocket (69%) and 30% experienced financial hardship as a result. PBTS were also the victim of theft, assault or fraud (19%). The qualitative descriptions provide vivid examples of these difficulties.

**Conclusion:** Long-term PBTS are very likely to experience psychosocial and economic challenges, many of which are previously undocumented and are poorly addressed by health and social programs.

**PQ017**

**EVALUATION OF CISPLATINUM OTOTOXICITY AND ITS EFFECT ON QUALITY OF LIFE IN LONG-TERM SURVIVORS**

Pediatr Blood Cancer DOI 10.1002/pbc

**PQ018**

**LONGITUDINAL CHANGES IN BODY MASS INDEX AND BODY COMPOSITION AMONG 417 ADULT SURVIVORS OF CHILDHOOD CANCER**

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**Purpose:** Obesity, represented by high body mass index (BMI), is a major complication after treatment for childhood cancer. High amount of total fat and low lean body mass are described as more reliable determinants, predicting the development of cardiovascular disease. In this study longitudinal changes of BMI and body composition in adult childhood cancer survivors were evaluated.

**Methods:** Data of 417 adult childhood cancer survivors, who had visited the late effects clinic twice, were analyzed retrospectively. Median follow up time was 16 years (interquartile range 11–21) and time between visits 3.2 years (2.9–3.6). At both time points BMI was measured and body composition was assessed by dual X-ray absorptiometry (Lunar Prodigy). BMI and body composition measures were compared with those of healthy Dutch references and calculated as standard deviation scores (SDS).

**Results:** BMI was significantly higher in female survivors, without significant change over time, with the highest SDS after CRT treatment (SDS T1 = 0.41 P = 0.021, T2 0.51 P = 0.031). Male survivors had a significantly lower BMI at T1 (SDS = −0.17, P = 0.022) and showed a significant change over time (SDSS = 0.19, P < 0.003). Percentage fat was significantly higher than controls in both men (SDS 1.37, P < 0.001) and women (SDS 1.05, P < 0.001), with the highest SDS after CRT (mean SDS 1.73 in men, 1.48 in women, P < 0.001). Only in men, increase in total fat percentage was significantly higher as compared with controls (SDSS = 0.22, P < 0.001). Lean body mass did not significantly change over time.

**Conclusion:** At 16 year of follow up after treatment for childhood cancer, we found significantly higher increase of BMI and total fat percentage as compared with controls, especially in men and after CRT treatment.

**PQ019**

**GLOMERULAR FILTRATION RATES IN LONG-TERM SURVIVORS OF WILMS TUMOUR**

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**Purpose:** Wilms tumour (WT) is an embryonal tumour of the kidney that is diagnosed in approximately 80 children in the UK each year with a 5 year survival of over 80%. Surgery, chemotherapy and radiotherapy are utilised to treat WT. Renal function can be affected by all treatment modalities. This study aims to describe the glomerular filtration rates (GFR) of long-term WT survivors at a single UK centre.
Methods: Long-term WT survivors (> 5 years) were identified from the Royal Marsden database. GFR data for these patients were obtained from laboratory records in addition to information on staging and treatment received.

Results: 56 WT patients were identified from the database with a mean age at diagnosis of 5.2 years (range 0.3–15.9), median follow-up time was 22.0 years (range 7.4–40.0). LTSs and controls did not differ in full-scale IQ, age or gender. However, LTSs scored significantly lower in a range of neurocognitive domains, specifically speed of information processing, verbal learning/memory, executive functions, and working memory. Standardized T-scores based on control group performance were calculated. The LTSs completed questionnaires on mental health, sleep, fatigue, and quality of life. In bivariate regression analyses, female gender, anxiety and, surprisingly, lower cumulative steroid doses were significantly associated with reduced executive functioning. Depression and fatigue were significantly associated with reduced working memory. No associations were found between reduced neurocognitive function and cumulative doses of other cytotoxic drugs (high-dose or intrathecal methotrexate, vincristine), age at diagnosis or follow-up time.

Conclusion: LTSs of childhood ALL treated exclusively with chemotherapy showed no condition associated with future clinically significant disease in aging populations. The purpose of this investigation was to characterize frailty among CCS and evaluate associations between frailty and treatment and frailty.

Methods: Participants were St. Jude Lifetime Cohort members (10 + year survivors) who completed risk based medical and physical function assessments. Pre-frailty and frailty were defined as: 2 + or 3 + of: low resting energy expenditure, self-reported exhaustion, low physical activity, reduced walking speed, and weakness. Demographic and treatment variables were abstracted from medical records, and evaluated for association with frailty in regression models.

Results: Among 1667 CCS (49% male, median age 32, range 18–59 years, median diagnosis age 6, range 0.1–21 years), 34.1% had no, 28.1% had two, and 6.6% had three or more components of frailty. Frailty increased with age (5.4%, 5.8%, 11.4% for 18–29, 30–39 and 40–59 years), was more common among females (10.8% vs. 2.8% males) and highest among leukemia (7.9%), CNS tumor (7.4%), non-Hodgkin lymphoma (7.9%) and bone tumor (7.1%) survivors. In adjusted models, cranial (OR 2.5, 95% CI 1.6–3.5) or abdominal/pelvic radiation (OR 1.8, 95% CI 1.2–2.8) were associated with frailty. Cranial (OR 2.2, 95% CI 1.8–2.9) or abdominal/pelvic radiation (OR 1.6, 95% CI 1.3–2.1) and anticholinergic dose > 350 mg/m²/OR 1.6, 95% CI 1.1–2.4) were associated with pre-frailty.

Conclusion: Percentages of pre-frailty and frailty in this young adult CCS cohort are comparable to the Cardiovascular Health Study (28.1 vs. 22.2% and 6.9 vs. 7.2%), the cohort of older adults (65–101 years) where this phenotype was first described.

PQ022

HOSPITALIZATION OF CHILDHOOD CANCER SURVIVORS: LINKAGE OF A COHORT TO A NATIONAL REGISTRY OF HOSPITALIZATION DATA

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Purpose: Childhood cancer survivors (CCS) are at risk of late adverse effects due to previous cancer treatment. It is not well known to what extent these late effects cause an increase in health care use and what the characteristics of hospitalization are in childhood cancer survivors. We aimed to define the burden of clinical late effects in CCS by determining hospitalization characteristics in comparison to a representative reference population.

Methods: We performed a cohort study using record linkage. We linked a complete cohort of five-year CCS who were treated in the Emma Children’s Hospital from 1966 to 1999 and survived up to January 1995, with data from Statistics Netherlands (Dutch acronym: CBS). We retrieved hospitalization characteristics for the CCS cohort longitudinally from 1995 until 2005 and compared these with a random sample from the general Dutch population matched on age, gender and calendar period.

Results: Of the 1564 eligible childhood cancer survivors, 1477 (94%) could be linked to CBS and 1382 (88%) had potential hospitalization events. CCS had an increased risk of a first hospitalization (RR 1.74, 95% CI 1.40–2.16) and a higher risk of hospitalization than the reference population was 2.76 (2.13–3.57). CCS had an increased risk of a first hospitalization for malignancies (RR 7.19, 95% CI 5.48–9.42) and endocrine disorders (RR 5.51, 95% CI 3.56–9.02). CCS were on average two years younger at first hospitalization and were hospitalized almost a day longer than controls. Further results of this study will be presented at the conference.

PQ023

CHANGE IN IQ OVER TIME AMONG PEDIATRIC BRAIN TUMOR PATIENTS TREATED WITH PROTON BEAM RADIATION THERAPY VERSUS CONVENTIONAL RADIATION THERAPY

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Purpose: Cranial radiation therapy (RT) remains an essential treatment for pediatric brain tumors, yet increases the risk of cognitive impairment following therapy. Advanced RT techniques offer increased sparing of normal tissues with the potential for improved cognitive outcomes. Proton beam radiation therapy (PBRT) minimizes low-dose irradiation to surrounding healthy brain tissue, which may spare cognitive functioning better than...
conventional RT (CRT) techniques (i.e., photon irradiation). We examined change in IQ over time between patients treated for pediatric brain tumors with PBRT versus CRT.

Methods: IQ scores were abstracted for pediatric brain tumor patients previously treated with PBRT or CRT (mean inter-evaluation interval = 13 years).

Results: Baseline and follow-up IQ scores were available for 42 survivors (21 PBRT, 21 CRT). 43% male, baseline age mean = 9.5 years (range 4–18), RT dose median = 54.0 Gy. No differences by treatment group were identified on age-at-RT, time-since-RT, or age-at-testing. A linear regression model predicted follow-up IQ scores controlling for baseline IQ, age-at-RT, and time-since-RT, F(6,35) = 24.0, p < .001. IQ scores at baseline predicted follow-up IQ scores with a significantly stronger effect in the PBRT group (p < .05), suggesting that the CRT group experienced greater loss of IQ points at follow-up than the same level of baseline IQ. The CRT group lost 7.7 IQ points on average with each additional year post-RT (p < .001), while the PBRT group lost only 0.8 IQ points per year. The difference between groups, though clinically notable, was not statistically significant in this small sample (p = 0.121). Age-at-RT was not associated with IQ for either group (p = 0.336).

Conclusion: Findings suggest significant cognitive risk is associated with CRT, with IQ scores declining by half a standard deviation with each additional year post-RT. In contrast, IQ remained generally intact for the PBRT group. Preliminary findings support the theoretical supposition that PBRT may spare cognitive functioning, although further study is needed.

POQ24 SURVIVOR HEALTHCARE PASSPORT: A TOOL TO EDUCATE AND ENHANCE THE CARE OF SURVIVORS OF CHILDHOOD CANCER

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Purpose: Despite efforts to educate survivors of childhood cancer, gaps still exist in the dissemination of both individual treatment histories and recommended long-term follow-up care. The Survivors of Childhood Cancer Program at UCSF has developed the “Survivor Healthcare Passport” (Passport), a portable, plastic card containing printed information on an individual’s treatment history, late effect risks and recommended follow-up care. A randomized study was conducted to evaluate the efficacy of the Passport.

Methods: Subjects were randomized to one of two arms (Arm A and Arm B). Subjects in both arms complete a baseline questionnaire (Q0) regarding their treatment history, late effect risks and recommended follow-up care before their clinic visit. They receive verbal education and written information during a standardized clinic visit. Arm A subjects receive the Passport at the time of the clinic visit whereas Arm B subjects do not. Subjects in both arms complete the identical questionnaire again at 1 month (Q1) and at 4 months (Q2) after the clinic visit.

Results: Preliminary data shows that a higher percentage of patients who received the Passport display knowledge improvement when compared to patients who did not receive the Passport. In the first 14 months of data collection, 17 patients were enrolled on Arm A and 20 on Arm B. Results from Q1 revealed that 56% of the subjects who received the Passport displayed knowledge improvement compared to 30% of the subjects who did not receive their Passport. The results from Q2 showed a more dramatic difference in knowledge; 72% of the subjects with the Passport showed knowledge improvement as opposed to 17% of the patients without the Passport.

Conclusion: The Survivor Healthcare Passport can be an effective way to disseminate information to survivors and their providers to ensure optimal health and quality of life for survivors of childhood cancers.

POQ25 VERY LONG-TERM EFFECTS OF CRANIAL IRRADIATION COMPARED WITH INTRATHECAL CHEMOTHERAPY IN TREATMENT OF CHILDHOOD LEUKEMIA: MEG POWER SPECTRUM DEVIATIONS AND CORRELATED COGNITIVE DYSFUNCTION

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Purpose: Cranial irradiation (CRT) and/or intrathecal chemotherapy (CT) are essential parts of acute lymphoblastic leukemia (ALL) treatment and have been described to cause late effects associated with neurotoxicity. This study evaluates oscillatory neuronal activity in long-term survivors, to study the underlying mechanisms of late neurocognitive deficiencies. We hypothesized that MMG power spectrum deviations from controls and correlates with cognitive dysfunction. In this study, late effects are investigated 25 years after diagnosis.

Methods: Resting state eyes-closed magnetoencephalography (MEG) recordings were obtained from 14 ALL survivors treated with CT + CRT, 18 treated with CT alone and 35 controls. Relative spectral power was calculated in the 0, 6, 21, 25, β and γ frequency bands.

Results: In the 0 power was slightly decreased and 2 power was significantly decreased; a pattern resembling normal aging, but also Alzheimer’s Disease. The CT + CRT group performed worse on various cognitive tests. A deficiency in visuomotor accuracy could be clearly associated with the deviating regional 0 and 2 powers. Patients treated with CT alone did not deviate much from controls.

Conclusion: The MEG data showing a tendency towards slow aging of brain oscillatory activity, together with the fact that dementia has been reported as a late effect of whole brain irradiation and the neuropsychological deficiencies currently present, suggest that the irradiated brain might be aging faster and could be at risk for early onset dementia. The CT group showed no signs of early aging.

POQ26 TASTE AND SMELL FUNCTION IN CHILDHOOD CANCER SURVIVORS AND THEIR AFFECTS ON QOL AND FOOD PREFERENCES

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Purpose: Childhood cancer survivors (CCS) have been shown to have poor dietary habits but it is not known if their poor dietary habits are related to their cancer therapy. Taste and smell dysfunction is implicated in preventing adequate dietary intake during cancer treatment. This study aimed to determine if taste and smell dysfunction is present in CCS and whether this affects their food preferences and quality of life (QoL).

Methods: Fifty-one childhood cancer survivors, greater than 5 years off treatment (mean age: 19.69 (±7.09) years), were recruited through the long-term follow-up clinics of two children’s hospitals in Sydney, Australia. Taste function was assessed using a 25 sample taste identification test comprised of five concentrations each of sweet, salty, sour and bitter tastes and water. Smell function was assessed by determining the ability of participants to identify 16 common odors. The participants’ QoL was assessed using the Functional Assessment of Anorexia Cachexia scale and food preferences were assessed using a 94-item food liking tool.

Results: Taste dysfunction was found in 27.5% of participants (n = 14) and smell dysfunction was found in 17% (n = 6) of participants. The data showed that the most liked foods were non-dairy liquids, followed by takeaway foods and snacks. There was significantly lower food liking scores for those with a smell dysfunction compared with those without for dairy foods (p = 0.027), fruit (p = 0.001) and salad/greens (p = 0.0001). Results from the additional concerns section of the QoL tool indicated that the participants had no significant food related concerns.

Conclusion: Significant levels of taste and smell dysfunction was found in CCS and there is some suggestion that smell dysfunction may influence food likes. Larger prospective longitudinal studies are needed to ascertain when CCS acquire these dietary habits.

POQ27 RECORD LINKAGE OF A COHORT OF CHILDHOOD CANCER SURVIVORS WITH POPULATION REGISTRIES TO STUDY CLINICAL EVENTS

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Purpose: Childhood cancer survivors (CCS) have a high risk of chronic health conditions. Due to relatively low patient numbers and long duration of follow-up that is needed, it is time-consuming and costly to study clinical events in CCS. Also it is difficult to find appropriate controls. Linkage of a cohort with population registries could efficiently overcome these issues. In the Netherlands record linkage with population registries is possible based on a combination of date of birth, gender and postal code (DGP). This study reports the feasibility of studying clinical events in CCS using record linkage.

Methods: We linked a complete cohort of five-year CCS (treated in Emma Children’s Hospital from 1966–1999; survived up to 1995) with population registries of Statistics Netherlands using DGP. We randomly sampled a reference population, matched on year of birth, gender and calendar period. We retrieved sociodemographic and hospitalization characteristics from 1995 until 2005 during the time a person was eligible and unique based on DGP.

Results: Of the 1564 CCS, 1477 (94%) could be linked by Statistics Netherlands. Of these, 1382 (94%) were unique between 1995 and 2005 as a five-year survivor. There were no
GENETIC VARIATION MAY MODIFY OVARIAN RESERVE IN FEMALE CHILDHOOD CANCER SURVIVORS

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Purpose: Gonadotoxicity is a well known late side effect of chemotherapy and radiotherapy in adult childhood cancer survivors. In the healthy population, several genetic polymorphisms were associated with the age at natural menopause. The aim of this study was to evaluate whether previously identified genetic polymorphisms associated with the natural age at menopause were associated with ovarian reserve in female adult long-term childhood cancer survivors.

Methods: We determined serum AMH levels in a single center cohort of female adult childhood cancer survivors and studied single nucleotide polymorphisms (SNPs) previously reported to be associated with the age at natural menopause: BRSK1 (rs1172822), ARHGEF7 (rs7333181), MCM8 (rs261114), PCSK1 (rs271924), IGFR2 (rs4957827) and TNF (rs909253). Association analysis was performed using the additive genetic model. Linear regression was conducted to assess the effect of significant polymorphisms in two previously published menopause prediction models.

Results: The heterozygous BRSK1 polymorphism was associated with decreased serum AMH levels in our cohort (CT: OR = 3.146, 95% CI 1.353–7.317, p = 0.008) and was significantly associated with the predicted age at menopause (p = 0.04). The other SNPs were not associated with serum AMH levels or with the predicted age at menopause.

Conclusion: BRSK1 (rs1172822) is negatively associated with serum AMH levels and predicted age at menopause in female survivors of childhood cancer.

RISK OF CONGENITAL MALFORMATIONS IN CHILDREN OF CHILDHOOD CANCER SURVIVORS

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Purpose: Previous investigations did not show an increase in the risk of health impairment (congenital malformation, genetic abnormalities, cancer) among offspring of childhood cancer survivors1. Despite these findings, in a recent large Scandinavian register study it has been reported of an increased risk of congenital malformations among the offspring of male cancer survivors, with offspring of fathers with hematological diseases having the highest risk.2 We examined the occurrence of reported malformations among offspring of German childhood cancer survivors.

Methods: In 2008 we conducted a nationwide survey on fertility among 2754 German childhood cancer survivors treated between 1980 and 2004. Participants reported a total of 590 offspring.

Results: Among the offspring of our participants, five had had a cleft lip and palate and one a spina bifida. The occurrence of 0.8% (5/590) of the event of cleft lip and palate was significantly higher compared to 0.14% (1/700) in the general population (p < 0.05). One of the children had a father, five of them a mother with a history of childhood cancer. In five out of the six cases the underlying disease of the parent was a hematological malignancy.

Conclusion: Our study results show a significant increase of malformations among offspring of childhood cancer survivors, with the majority of these parents having had a hematological disease. Nevertheless, some large studies that included patients who have been treated up to the 1980’s have shown no increase in the risk of malformations. It remains to be examined, if the risk for congenital malformations among offspring of cancer patients is increased among patients that were treated according to a more recent therapy approach and which therapy is to be held accountable for this. Until then survivors of childhood cancer should be reassured concerning the health of their offspring.
MORBIDITY AMONG SWEDISH SURVIVORS OF ACUTE LYMPHOBLASTIC LEUKAEMIA IN CHILDHOOD

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Purpose: We studied morbidity after acute lymphoblastic leukaemia (ALL) in childhood by investigating whether 5-year survivors of ALL had an increased hospitalization rate compared with the general population and what the risk factors for increased hospitalization were.

Methods: From the Swedish cancer registry, we identified all individuals diagnosed with cancer before the age of 18 from 1970 to 1999 in the southern region of Sweden. Of these 1,617 individuals, 213 were 5-year survivors of ALL and thus constituted the study population. A population comparison group of 10,650 individuals (50:1 ratio) was randomly selected from the central population registry and matched by sex, age, and county of residence.

Information on in-patient care was obtained from the Swedish hospital registry. Detailed information on cancer treatment was collected from medical records.

Results: Ninety-five percent (125/213) of the 5-year survivors of ALL had had at least one hospital admission by the end of the study period (71.3% women and 64.6% men). The corresponding number for the controls was 46% (4,909/10,650), which was significantly lower than that of the ALL survivors (p < 0.001). Moreover, survivors also had an increased number of admissions to hospital and were admitted for longer periods than controls. Among those who were admitted to hospital at least once, a diagnosis of infectious disease, benign tumour or disorder of the nervous system was more frequently seen in survivors compared with controls. In contrast, diagnoses of psychiatric or pulmonary disorder, intoxication or injury were more frequent among controls. Further details will be given.

Conclusion: This population-based study shows that survivors of ALL in childhood have an increased frequency of hospitalization and longer hospital stays than population controls. This knowledge is important both for the planning of future treatment protocols minimizing late complications and for optimal patient counselling and follow-up care.

CHILDHOOD CANCER SURVIVORS’ PERSPECTIVES AND PREFERENCES FOR LONG-TERM MEDICAL FOLLOW-UP

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Purpose: Childhood cancer survivors (CCS) face numerous long-term health risks. Leading North American organizations recommend long-term follow-up (LTFU) care for CCS that includes second malignancy screening, surveillance and management of physical and psychosocial late effects and promotion of healthy lifestyle behaviours. No comprehensive LTFU program currently exists in British Columbia (BC). The perspectives and preferences of CCS themselves are essential for developing patient-centered health services. The purpose is to describe CCS perspectives and preferences for LTFU medical care.

Methods: 111 CCS were recruited prospectively through the BC Cancer Agency Late Effects Clinic to complete an anonymous survey (consecutive CCS, 03/2009 to 03/2010, Response rate: 99%).

Results: The median age of respondents was 7 years at diagnosis and 31 years at survey completion. CNS tumors were the most common prior malignancy (32.4%). Most CCS had a family doctor (92.8%), whom they saw on average 4.8 times per year. Over half (54%) thought the responsibility to organize appropriate LTFU for CCS and to be aware of new knowledge regarding long-term health risks ought to be shared between family doctors, physicians at an adult cancer centre and paediatric oncologists. 29.8% were of the opinion that this ought to be the sole responsibility of physicians at an adult cancer centre. The majority of CCS preferred to receive LTFU care from physicians at an adult cancer centre in combination with their family doctor (90.1%). 79.3% thought it was appropriate that they be given written details of their original treatment.

Conclusion: The majority of CCS surveyed preferred LTFU care with their family doctor in conjunction with physicians at an adult cancer centre, wanted written details of their previous therapy and felt that the responsibility for organizing follow-up rested with family doctors and both pediatric and adult oncology services.

References


SUICIDAL RISK AMONG CHILDHOOD CANCER SURVIVORS IN SLOVENIA

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Purpose: Suicide as a cause of death in the general population in Slovenia is on the fourth place. Suicide is one among causes for late mortality in childhood cancer survivors. The aim of our study was to analyse suicidal risk among childhood cancer survivors in comparison with that of the general population of Slovenia.

Methods: We included children with cancer registered at the Cancer Registry of Slovenia between 1978 and 2008, at the start of observation at least 5 years old. The observation period was from 1978 to 2010. Information on patient status (alive/suicide/other cause of death) was obtained from Cancer Registry or Clinic for Late Effects at the Institute of Oncology.

Childhood cancer patients and subjects from the general population of Slovenia were compared with the expected number of suicides. Results: A total of 1,647 persons with cancer in childhood (713 women and 934 men) were included in the analysis. Among these, 3 patients committed suicide. All were men. Their age at diagnosis of cancer was 2, 12 or 17 years, their age at suicide was 28, 19 or 32 years. Two of them committed suicide by strangulation and the third by asphyxiation. The calculation of the expected number of suicides in the group of individuals with childhood cancer from the general Slovene population revealed the number of 3,155 persons.

Conclusion: The comparison of observed and expected probability showed that there was no statistically significant difference in the suicide rate between childhood cancer survivors and the general population of Slovenia (p = 1).

EXPLORE CHILDHOOD CANCER SURVIVORS’ UNDERSTANDING OF THE EFFECTS OF THERAPY ON THEIR FERTILITY

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Purpose: Although the impact of childhood cancer treatment is usually discussed with patients and their families at diagnosis, childhood cancer survivors may have questions regarding their fertility years after completing treatment. In the long-term follow-up clinic at our health centre childhood cancer survivors have often expressed uncertainty about whether or not their cancer treatment has had an impact on their fertility. The purpose of this study was to explore what adolescent and young adult (AYA) survivors of childhood cancer understand about the impact of their cancer and its treatment on their fertility. Results may be used to inform clinicians when educating childhood cancer survivors about their treatment late-effects.

Methods: A qualitative approach guided by a grounded theory framework and analysis was employed. A purposive sample of volunteer participants were recruited through personal and treatment follow-up clinics at the IWK Health Centre in Halifax, Nova Scotia, Canada. As well, volunteer participants were identified from an existing list of cancer survivors who have transitioned from the pediatric healthcare centre. Data were collected through semi-structured telephone and in-person interviews. Audio-taped interviews were transcribed, entered into qualitative analysis software and then analyzed using grounded theory’s constant comparative technique.

Results: Preliminary results indicate that childhood cancer survivors may not have a complete understanding of the impact of their cancer therapy on their fertility. Major themes found in the interview transcripts will be reviewed and implications for clinical practice will be discussed.

Conclusion: This study should inform practice by providing insight into AYA cancer survivors understanding of the impact of their treatment on their fertility. Results of this study may be used to improve the treatment related fertility education for this population and may guide further research in this area.

RISK STRATIFICATION: A MODEL FOR THE FUTURE

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Purpose: It is recognised that a proportion of childhood cancer survivors, at low risk of late effects, could be seen out of traditional consultant led clinics in an environment more appropriate to their needs.

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Methods: The aim of the project, which was part of the National Cancer Survivorship Initiative (NCSI), was to develop a three-tier model of care according to clinical risk stratiﬁcation: discharge from active follow-up with GP questionnaire (level 1), nurse-led follow-up (level 2) and consultant-led clinics for those with more complex health needs (level 3).

Results: Postal Follow-up. Of 63 GPs surveyed, 94% were happy to complete a questionnaire (95% annually) and 77% were happy to perform routine toxicity monitoring. 28 patients have been actively transferred to postal follow-up since 2009. All reported that they were fully aware of the reason, and 75% were conﬁdent that they knew how to re-access the service in the future. Nurse led Follow Up. In a baseline survey of patient/carers’ views (n = 89) 81% felt it was necessary to see the consultant although 43% expressed a preference to be seen outside of the treatment clinic setting. 48% (oncology) and 71% (haematology) of patients indicated they would not be happy to see a specialist nurse. Despite this, the Nurse-led clinic was launched in September 2009 and 65 new patients have been referred to the service since then. Feedback has indicated that it is acceptable and preferable to their previous style of follow-up and attendance rates have been consistently high giving additional conﬁdence in the acceptability of this practice.

Conclusion: As the population of cancers survivors increases, these results indicate that services can be safely adapted and tailored to meet individual patient need. Different models of care, based upon risk stratiﬁcation, can be appropriate, acceptable, reliable and cost effective.

PQ037
AN UPDATE FROM SINGAPORE CHILDHOOD CANCER SURVIVOR STUDY (SINGAPORE-CCSS)
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Purpose: With the advent of aggressive multi-disciplinary treatment modalities, survival rates among childhood cancer patients are increasing in the East. Thus assessing risk of late effects and complications are becoming ever more important.

Methods: Our study included patients who were diagnosed with cancer before age of 21 years and survived for at least 2 years after completion of all treatments at KK women’s and Children’s Hospital and National University Hospital, Singapore. Data abstraction and self-administered questionnaire adapted from the CCS was completed.

Results: A total of 1068 out of 1518 children diagnosed with cancer in Singapore from January 1980 to December 2005 are long-term survivors. Hematological malignancies represented 54.3% (n = 590) of survivors whilst 45.6% (n = 495) were diagnosed with solid tumors. Currently, 266 patients are enrolled onto the study with 151 (56.8%) males and 115 (43.2%) females. Mean age of study cohort is 14.9 (range, 4.9–31.8 years) with a median age at diagnosis was 5.1 years (range, 1.0–16.7) and median age at completion of treatment was 8.2 years (range, 4.0–19.6). Evaluation time-points were set at 1 Diagnosis; 2 End of treatment, 3 One year later; 4 More than three years following treatment cessation. Patients who underwent transplantation were censored at that time-point. Commercially available assays for serum hormone detection and thyroid gland ultrasonography were applied.

Results: Out of the 168 eligible patients (93 males), 141 had ≥1 TF evaluation following treatment. At ALL diagnosis 19/27 patients (70.4%) had results within normal limits (wnl), 6/27 euthyroid sick syndrome and 2/27 compensated hypothyroidism. At cessation of chemotherapy 26/38 patients (68.4%) had results wnl, 2/38 compensated hypothyroidism and 10/38 evidence of hidden hypothyroidism. One-year two following chemotherapy cessation 31/38 (81.6%) had results wnl, 3/38 with compensated and 4/38 evidence of hidden central hypothyroidism. At 3 or more years following chemotherapy cessation 80/87 patients (88.3%) had results wnl, 6/77 central hypothyroidism, 2/77 Hashimoto’s thyroiditis and 1/77 patients had elevated TSH due to IFN-γ treatment for hepatitis-C. Among the group of patients with long-term follow-up 12% is found to have thyroid dysfunction of variable etiology. Ultrasound showed compatible ﬁndings. No TF abnormality was identiﬁed in 25 high risk patients who received 12Gy of cranial irradiation. No case of thyroid cancer was reported.

Conclusion: We have identiﬁed TF abnormalities in ≥10% of ALL survivors. This is higher than that reported in other ALL cohorts, like the Finnish (Madanat et al, 2007). ALL patients should be screened for TF throughout treatment and for long-term sequelae following treatment cessation.

PQ039
THYROID FUNCTION EVALUATION IN CHILDREN DIAGNOSED AND TREATED FOR CHILDOOD ACUTE LYMPHOPROLIFERATIVE LEUKEMIA
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Purpose: To identify the short and long-term effects of childhood acute lymphoblastic leukemia (ALL) and its treatment on thyroid function (TF).

Methods: We analyzed retrospectively a pediatric ALL patient population, treated according to the BFM-90/95 Protocols (period 1994–2010, MR = 149HR = 19 patients). Median age at diagnosis was 5.1 years (range, 1.0–16.7) and median age at completion of treatment was 8.2 years (range, 4.0–19.6). Evaluation time-points were set at 1 Diagnosis; 2 End of treatment, 3 One year later; 4 More than three years following treatment cessation. Patients who underwent transplantation were censored at that time-point. Commercially available assays for serum hormone detection and thyroid gland ultrasonography were applied.

Results: Out of the 168 eligible patients (93 males), 141 had ≥1 TF evaluation following treatment. At ALL diagnosis 19/27 patients (70.4%) had results within normal limits (wnl), 6/27 euthyroid sick syndrome and 2/27 compensated hypothyroidism. At cessation of chemotherapy 26/38 patients (68.4%) had results wnl, 2/38 compensated hypothyroidism and 10/38 evidence of hidden hypothyroidism. One-year two following chemotherapy cessation 31/38 (81.6%) had results wnl, 3/38 with compensated and 4/38 evidence of hidden central hypothyroidism. At 3 or more years following chemotherapy cessation 80/87 patients (88.3%) had results wnl, 6/77 central hypothyroidism, 2/77 Hashimoto’s thyroiditis and 1/77 patients had elevated TSH due to IFN-γ treatment for hepatitis-C. Among the group of patients with long-term follow-up 12% is found to have thyroid dysfunction of variable etiology. Ultrasound showed compatible findings. No TF abnormality was identified in 25 high risk patients who received 12Gy of cranial irradiation. No case of thyroid cancer was reported.

Conclusion: We have identiﬁed TF abnormalities in ≥10% of ALL survivors. This is higher than that reported in other ALL cohorts, like the Finnish (Madanat et al, 2007). ALL patients should be screened for TF throughout treatment and for long-term sequelae following treatment cessation.

PQ040
FERTILITY AND SPERM CRYOPRESERVATION IN YOUNG MALE ADOLESCENT PATIENTS FOLLOWING CANCER DIAGNOSIS
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Purpose: To establish practices in preserving future fertility for young adolescent males diagnosed with cancer.

Methods: Since 1997, sperm cryopreservation has been proposed to male patients newly diagnosed with malignancy. According to regulations, we are allowed to admit patients < 16 years old (< 14 years old until 2007). Thus, our patient pool was limited. Male patients in good general condition (excluding leukemias) demonstrating Tanner stage ≥ III and adequate testicular volume (≥12ml) were eligible, provided that a few days delay in initiating treatment was not felt to jeopardize their care perspective. The procedure was performed in one stage: spermogram and cryopreservation were done simultaneously, without previous screening.

Results: Sperm cryopreservation was proposed to a total of 17 boys, with median age of 14.7 years (range, 12.2–17.1) diagnosed with: Hodgkin’s Lymphoma (8), Non-Hodgkin’s Lymphoma (2), Sarcomas (7). Four families refused due to religious beliefs and one patient did not produce sperm. Twelve patients completed successful sperm collection for 1 to 3 times. One Hodgkin Lymphoma patient was azoospermic and 11 patients had normal spermogram or oligospermia and all samples were cryopreserved. None of the patients has
been requested for fertilization so far. The young patients understood and complied with the procedure readily. Furthermore, dealing with fertility preservation strengthened their expectation for long-term survival.

Conclusion: With appropriate approach, explanation and guidance, usually with support from older siblings, our young patients proved mature and competent in handling such complex issues, like the concept of future fertility preservation, while at the same time they were being prepared with the diagnosis of malignancy. The procedure was fast and effective. Our proposal also indicated to them our expectation for long-term survival, while being an integral part of our manifold approach to cancer treatment.

**PQ041**

**NEUROPSYCHOLOGICAL FUNCTIONING OF CHILDREN TREATED WITH INTENSIVE CHEMOTHERAPY FOLLOWED BY MYELOABLATIVE CONSOLIDATION CHEMOTHERAPY AND AUTOLOGOUS HEMATOPOIETIC CELL REUSE FOR NEWLY DIAGNOSED CNS TUMORS: LONG-TERM FOLLOW-UP ANALYSIS OF THE “HEAD START II” SURVIVORS**

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**Purpose:** To evaluate the neuropsychological late effects among survivors treated on the “Head Start II” protocol between 1997–2003.

**Methods:** Forty-nine of 51 patients (mean age 2.9 years) diagnosed with a malignant brain tumor underwent baseline neuropsychological assessment prior to autologous hematopoietic cell transplantation (AutoHCT). Fourteen survivors (mean age 11.35 years) were re-tested after a median 7.9 years post-treatment while 21 patients did not survive.

**Results:** Craniospinal irradiation was avoided in two-thirds of survivors and delayed in the balance. At baseline, Full Scale IQ (89.56, sd = 18.2) and Visual-Motor Integration-VMI (87.69, sd = 9.4) were in low average range. Verbal IQ (97.22, sd = 17.3), Performance IQ (95.43, sd = 16.7), Reading (108.86, sd = 22.9), Spelling (102.17, sd = 15.1), Math (99.33, sd = 13.9), and Overall Memory (90.00, sd = 21.2), as well as Social-Emotional and Behavioral functioning (Internalizing T = 50.65, sd = 11.3, Externalizing T = 45.80, sd = 9.4), were all within the average range. Follow-up testing approximately eight years post-AutoHCT revealed generally stable Full Scale IQ (88.83, sd = 14.64) and Verbal IQ (91.42, sd = 12.29), while Performance IQ (85.85, sd = 23.72) declined to the low average range. Reading (93.45, sd = 15.38), Spelling (96.70, sd = 13.97) and Math (90.08, sd = 13.97) skills remained average. In contrast, VMI (91.50, sd = 15.67) improved to the average range, while Overall Memory (95.63, sd = 24.33) as well as Social-Emotional and Behavioral functioning (Internalizing T = 55.29, sd = 14.10; Externalizing T = 51.86, sd = 6.18) remained average. Age at diagnosis and time since diagnosis were not correlated with outcomes; and those who received intrathecal methotrexate (MTX) did not significantly differ on any outcome measures.

**Conclusion:** Long-term survivors assessed on the Head Start II regimen displayed generally stable neuropsychological with the exception of Non-Verbal IQ. These follow-up data provide support for a regimen of induction, with or without intensification using intravenous MTX, followed by myeloablative consolidation chemotherapy with AutoHCT. Continued follow-up of the remaining survivors is essential to determine the preservation of neuropsychological, academic, memory, and social-emotional/behavioral functioning.

**PQ042**

**N-TERMINAL PRO BRAIN NARIETRIC PEPTIDE FOR PREDICTION OF CYCLOPHOSPHAMIDE-INDUCED CARDIOTOXICITY IN PATIENTS UNDERGOING HIGH-DOSE CHEMOTHERAPY**

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**Purpose:** Cyclophosphamide-related cardiotoxicity in patients treated with high-dose chemotherapy and autologous stem cell rescue (HDCT/ASCR) is an uncommon but fatal complication. Therefore, this study was conducted to prospectively investigate indicators of cyclophosphamide-induced heart failure in patients undergoing HDCT.

**Methods:** From 2007 to 2009, eighty-one patients with high-risk solid tumors were treated with HDCT/ASCR. Cyclophosphamide was used in all patients at a cumulative dose of 4800–6000 mg/m2 during HDCT. Biochemical markers, such as N-terminal pro brain natriuretic peptide (NT-proBNP), troponin I (TnI), and creatine kinase MB (CK-MB) were measured before, during, and after the administration of cyclophosphamide.

**Results:** Seven of 81 patients developed heart failure at median 3 days (range, 0–36 days) after the first dose of cyclophosphamide. One of them died due to congestive heart failure despite the extracorporeal membrane oxygenation treatment. ICU care was required in 4 of 7 patients. There was no significant difference between the patients developing heart failure and the patients without heart failure in variables such as median age, previous anthracycline exposure, cumulative dose of anthracycline, ejection fraction on echocardiography prior to HDCT, and cumulative dose of cyclophosphamide during HDCT. The median levels of NT-proBNP, TnI, and CK-MB were not different before and after the administration of cyclophosphamide in patients developing heart failure or not. However, the median value of NT-proBNP after the first dose of cyclophosphamide was 498.0 ng/mL (range, 108.7–2580.0) in patients developing heart failure and 143.0 ng/mL (range, 13.1–2613.0) in patients without heart failure, respectively (P < 0.02). A NT-proBNP concentration > 362.6 ng/mL after first dose of cyclophosphamide, there was a sensitivity of 83.3% and specificity of 78.4% for identification of cyclophosphamide-induced heart failure.

**Conclusion:** The concentration of NT-proBNP after the first dose of cyclophosphamide may be an early marker for predicting cyclophosphamide-induced cardiotoxicity.

**SUPPORTIVE CARE – FEVER/NEUTROPENIA/INFECTIOUS**

**PR001**

**FUNGAL INFECTIONS IN PAEDIATRIC ONCOLOGY PATIENTS, AN 11 YEAR STUDY**

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**Purpose:** Invasive fungal disease (IFD) is a significant cause of morbidity and mortality during cancer therapy. Data on the incidence in children with malignancy are limited. We undertook a retrospective audit of paediatric IFD at the Royal Marsden Hospital (RM) to determine the number of cases seen and to characterise patient groups affected, spectrum of disease, outcome, and risk factors.

**Methods:** Patients were identified using pharmacy records for children prescribed treatment dose antifungal agents over an 11 year period from January 2000 to December 2010. Predetermined data were extracted from case records using a standard questionnaire. EORTC guidelines were used to classify episodes as definite, probable or possible IFD and to classify outcome.

**Results:** Sixty three patients with proven, possible or probable IFD were identified (mean 5.7/year). The commonest underlying diagnoses were acute lymphoblastic leukaemia (ALL) (14/22%), relapsed ALL (17/27%), and acute myeloid leukaemia (9/14%). IFD was commonest during induction phase of leukaemia treatment at first diagnosis (n = 14). Of the cases of IFD, 19 (30%) were classified as proven IFD, 12 (19%) as probable and 23 (37%) as possible. Denominator data were not available to allow incidence calculations during standard chemotherapy. The incidence of IFD in patients receiving hematopoietic stem cell transplant was 5.4% and was greater in allogenic (8.8%) than in autologous (2.2%) transplants. Proven infections included candida (18), Aspergillus (6), Mucormycosis (2), Trichosporon (1) and Scedosporum (1). Three month mortality was greater in culture positive Aspergillus infection (83%) than candida infection (28%). Overall, complete response rate was 48% and mortality 33% at 3 months.

**Conclusion:** These data describe the profile of IFD in children at the RM and confirm haematological malignancies as the highest risk group. IFD was commonest in the induction period for ALL and AML, highlighting the need to consider fungal prophylaxis during ALL induction therapy.

**PR002**

**PREDICTORS OF ADVERSE OUTCOME IN CHEMOTHERAPY INDUCED FEBRILE NEUTROPENIA IN CHILDREN**

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**Purpose:** Febrile neutropenia/infections contribute significantly to the mortality and morbidity in pediatric oncology patients. Several scoring systems have been developed to predict the risk of severe infection/adverse outcome in children with febrile neutropenia. However, only a few of these have been found to be reproducible. Aim: To identify clinical or laboratory parameters which may predict adverse outcomes in chemotherapy induced febrile neutropenia patients.

**Methods:** This is a prospective study and data were collected from all children who were admitted with chemotherapy induced febrile neutropenia to the pediatric oncology ward at Tata Memorial Hospital, Mumbai from November 2011 to March 2012. Various clinical and laboratory parameters were analysed to identify predictors of adverse outcome. An adverse outcome was defined as any of the following: 1. Serious complications like septic shock, intensive care admission, other life threatening complications or death, 2. Microbiologically defined infection or 3. Radiologically defined pneumonia.

**Results:** 177 episodes of chemotherapy induced febrile neutropenia were studied during this period. On univariate analysis, patient characteristics which were associated with an adverse outcome were female sex (p = 0.045), hematological malignancy (p = 0.05), use of high dose Cytarabine (p = 0.01), clinical focus of infection at presentation (p < 0.01), and protein energy malnutrition (p < 0.01). Laboratory parameters which were associated with an adverse outcome were absolute phagocyte count (p < 0.10) at presentation (p = 0.03), High C-Reactive
EVALUATION OF SERUM GALACTOMANNAN ASSAY FOR THE DIAGNOSIS OF INVASIVE ASPERGILLOSIS IN CHILDREN WITH HEMATOLOGICAL MALIGNANCIES

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Purpose: Diagnostic efficacy of galactomannan assay (GMA) for invasive aspergillosis (IA) is variable. The diagnostic cut-off values are debated. Methods: Children ≤14-years with hematological malignancies and fever were enrolled prospectively. Blood sample for GMA was drawn on day of admission; levels were measured using latex reagent test (Platellia Aspergillus enzyme immunoassay). Diagnostic criteria were adapted from EORTC-MSG. GMA was evaluated at various cut-offs, with proven, probable and possible episodes being considered as disease group. Results: 100 febrile episodes in 78 patients were included. Mean-age was 6.1 years. Majority (75%) episodes were in patients with ALL, followed by AML (17%). CT-scan-lung was performed in 23 episodes. BAL, bronchial-lung-biopsy and functional-endoscopic-sinus-surgery were performed in 2 episodes, each. Post-mortem investigations included autopsy in 11 and single tissue biopsy (6) Diagnosis of IA was proven and probable in one case each. A possible diagnosis was made in 23 episodes; remaining 75 were categorized as “No IA”. Other fungal infections diagnosed included mucormycosis (3), candidiasis (1) and fusariosis (1). Best results were obtained with a cut-off value of 1.0, with sensitivity, specificity, positive and negative predictive value of 60%, 93%, 75 and 87, respectively. With GMA > 1.0 as cut-off, the probability of a positive test to be true or false positive was 0.71 (95% CI: 0.48–0.88) and 0.28 (95% CI: 0.12–0.52), respectively. For a negative test, the probability of true negative was 0.87 (95% CI: 0.78–0.95) and false negative was 0.13 (95% CI: 0.16–0.22). The sensitivity dropped to 40%, at cut-off value of 1.5 and specificity was 38%, at a cut-off of 0.5. Significant correlation of a higher GMA was observed with pulmonary nodules (p = 0.037), duration of Amphotericin >10-days (p = 0.043) and mortality (p = 0.001).

Conclusion: Confirming the diagnosis of aspergillosis is a challenge; this renders assessment of efficacy of GMA difficult. At a cut-off value of 1.0, the sensitivity and specificity were 60% and 93%, respectively.

References

RESULTS: In 521 pediatric patients with cancer, 783 episodes of FN were recorded during a cumulative chemotherapy exposure time of 6009 months (rate, 0.13/month [95% CI, 0.12–0.14]). 124 of them were associated with bacteremia (16% of FN; 0.022/month [0.017–0.025]). In univariate analysis, the definition 39°C versus 38.5°C was associated with a lower rate of FN diagnosed (0.10/month [0.08–0.11] versus 0.15/month [0.13–0.16]; rate ratio, 0.66 [0.45–0.97]; p = 0.036), while the definition 38.5/39.0°C was intermediate (0.13/month [0.11–0.15]). However, this difference was not confirmed in multivariate analysis (rate ratio, 1.00 [0.70–1.44]; p = 1.00). Finally, the definition 39.0°C versus 38.5°C was not associated with an increased rate of FN with bacteremia in univariate analysis (0.01/month [0.011–0.024] versus 0.02/month [0.017–0.028]; rate ratio, 0.77 [0.25–2.37]; p = 0.65), and multivariate analysis (rate ratio, 1.48 [0.58–3.75]; p = 0.41).

Conclusion: Unexpectedly, a higher fever definition was not associated with a lower rate of FN diagnosis. Moreover, it was not associated with an increased rate of FN with bacteremia neither. Due to the methodological limitations of this retrospective study, these findings need verification in prospective studies.
Results: 311 FN episodes occurring in 138 patients were analyzed. Hemoglobin was >90 g/L in 141 (45%) episodes, specifically in 59 (59%) of 103 episodes with AE, and in 82 (39%) of 208 episodes without AE (OR: 2.20; 95% CI: 1.34–3.60; p = 0.002). Information on transfusion was available in 311 (100%) episodes, and information on dehydration in 219 (70%). In FN with AE, hemoglobin was bimodally distributed, with a dip around 85 g/L (moderate anemia) between peaks at severe anemia and mild/moderate anemia. Center, age and sex were relevant confounders. In multivariate analysis, AE was significantly and independently associated with leukocenia < 0.3 G/L (OR: 3.11; 95% CI: 1.62–5.94; p = 0.001), with dehydration (29.0; 3.10–27.1; p = 0.004) and with non-moderate anemia (1.59 per 10 g/L difference from 85 g/L; 1.20–2.10; p = 0.002), but not with recent RBC transfusion.

Conclusion: In children and adolescents with FN, the association of mild/moderate anemia with AE was partially due to dehydration and partially to non-moderate anemia, but not to recent transfusion. Further research on the association of non-moderate anemia with AE is ongoing.

PR007
RISK FACTORS FOR BACTEREMIA IN PEDIATRIC PATIENTS WITH CANCER AND NON-NEUTROPENIC FEVER
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Purpose: The management of fever in non-neutropenic children with cancer is not well defined. We investigated the incidence of bacteremia, clinical outcome and characteristics of well-appearing patients treated with outpatient parenteral antibiotics to understand risk factors that may guide management.

Methods: We reviewed the records of children treated between January 2009 and December 2011 in the outpatient settings. All children had a complete blood count and blood culture (BC) drawn from the central venous catheter, received at least one dose of ceftriaxone and had a follow-up visit 24 hours later.

Results: 164 febrile episodes occurred in 85 patients. Mean age was 7.8 years (range 11 months–22 years): 42% females, 58% males. Underlying diagnoses: leukemia (53%), brain tumor (9%), solid tumor (38%). No patients had received a bone marrow transplant. Mean absolute neutrophil count (ANC) was 4.1 cells x 10^9/L (range 0.576–19). 7 (4.3%) bacteremias were identified in 7 children. Isolated microorganisms were: Staphylococcus epidermidis (2), Staphylococcus hominis (1), Staphylococcus aureus (1), Candida (1), Escherichia coli (2). All children were well at follow up and 4/7 BC became sterile. Notably, 6/7 bacteremias occurred in children at higher risk for infection due to relapsed disease, Down syndrome, and post-transplant lymphoproliferative disease. 12 additional episodes of fever in well-appearing patients, but with ANC < 500 and absolute phagocyte counts (APC) > 500, were managed with outpatient parenteral antibiotics. 1/2 BC grew Staphylococcus epidermidis in one child with relapsed neumacma.

Conclusion: We report a very low incidence of bacteremia in non-neutropenic febrile patients. Febrile, well-appearing children with ANC < 500 but APC > 500 may be safely treated with outpatient parenteral antibiotics. Patients with advanced disease or other conditions associated with increased immunosuppression may be at higher risk of bacteremia. Further analysis is needed to identify patients at risk for bacteremia who may benefit from empiric outpatient antibiotic therapy.

PR008
INFECTION AND OTHER COMPLICATIONS OF CENTRAL VENOUS CATHETERS IN PAEDIATRIC ONCOLOGY PATIENTS: THE EXPERIENCE OF TWENTY-ONE THOUSAND LINE-DAYS IN A UK REGIONAL CENTRE IN 2010
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Purpose: Most paediatric oncology patients require central venous access but continue to be at risk from infections and other complications of catheter use. We aimed to assess the rates of complications requiring catheter removal and rates of catheter-associated bloodstream infection in our regional paediatric oncology centre and compare these with previous studies.

Methods: Patients with central lines during 2010 were identified from our departmental database. A retrospective case note review identified removal dates and cause of removal. Microbiology records locally and at the relevant ‘shared care’ unit were interrogated for positive blood cultures during 2010. Patient notes for each culture were reviewed against internationally-agreed criteria for ‘Catheter Associated Bloodstream Infection’ (CABSI1): confirmed infections were categorised by infecting organism and severity.

Results: 141 lines (22 ports, 115 tunneled lines, 4 PICCs) in 124 patients (21,877 line-days) were analysed. 24 lines (17%) were removed for complications: 16 (66.7%) required replacement. Mechanical causes included line blockage (5, 0.23/1000 line-days) and line migration (9, 0.41/1000 line-days). 10 (7.1%, 0.46/1000 line-days) were removed for infection, 3 affecting the exit-site and 7 bloodstream infections. Of the 7 presumed bloodstream infections, 6 (85.7%) were confirmed as CABSI. 54 (2.47/1000 line-days) discrete episodes of positive blood cultures affected 37 patients. 23 (1.05/1000 line-days) episodes (18 patients) were confirmed as CABSI. 9 (0.41/1000 line-days) caused by gram-positive organisms, 6 (0.27/1000 line-days) gram-negative, 1 (0.05/1000 line-days) fungal and 7 (0.32/1000 line-days) by multiple organisms.

Conclusion: Complications requiring removal continue to affect 1 in 6 central lines, similar to rates in previous studies. Infection is the most common cause of removal, although mechanical failures also contribute significantly. A minority of patients suffer recurrent line infection. The most common causative organisms for CABSI were coagulase-negative staphylococci and pseudomonads: this information can be used to shape empirical treatment policies.

References

PR009
VARICELLA ZOSTER IMMUNE STATUS IN CHILDREN TREATED FOR ACUTE LEUKAEMIA
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Purpose: Patients between 1 and 16 years of age receiving treatment for acute myeloid leukaemia (AML) or acute lymphoblastic leukaemia (ALL) as per national protocols between October 2002 and October 2004 at The Royal Marsden Hospital were enrolled in this study. All children had their VZV serostatus checked using time resolved fluorescence immunosassay (TRFIA) before starting treatment, and then at least 6 months after completion of leukaemia treatment.

Results: Pre-treatment and post-treatment VZV serology results were available for 52 and 26 cases, respectively. Paired sera were available for 26 cases (20 ALL, 6 AML). Blood samples were obtained at a median time of 0.67 years (quartile: 0.5–0.96) after completion of treatment. Median age of patients at this point was 7.96 years (range 2.75–18). There was no significant difference in age between ALL and AML patients. The serology pre- and post-treatment were as follows (26 cases): 11 remained positive (3 AML, 8 ALL), 2 remained negative (1 AML, 1 ALL), 1 changed from positive to negative (ALL), 5 from positive to equivocal (2 AML, 3 ALL), 3 from negative to positive (ALL) and 4 from equivocal to positive or negative.

Conclusion: On completion of treatment for acute leukaemia most patients maintained protective VZV immunity. However, six patients changed from positive VZV serology pre-treatment to negative/equivocal after completion of treatment; this highlights the importance of checking VZV serostatus on exposure to VZV irrespective of serostatus prior to starting treatment.

PR010
RISK-BASED THERAPY FOR FEBRILE PATIENTS WITH NEUTROPENIA: A ROLE FOR EARLY HOSPITAL DISCHARGE
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Purpose: Our objective is to test a low-risk febrile-neutropenia (LRFN) predictive model in our children population in order to provide a less intensive antibiotic therapy and combined treatment (inpatient, outpatient) for patients considered of having a low-risk of invasive bacterial infection (IBI).

Methods: We have prospectively enrolled all children with chemotherapy-induced febrile neutropenia (FN) from may 2010. On admission clinical and laboratory factors were collected along with physical examination. Children identified as having a LRFN episode were discharged on oral treatment after 48 hours of observation and intravenous antibiotherapy and instructed to return every 48 hours for clinical examination and blood sampling until episode resolution.

Results: From May 2010 to November 2011 46 children with FN were enrolled. 5 patients (10.8%) were eligible for a LRFN treatment while the other 39 (89.2%) were assigned to the high-risk FN (HRFN) protocol and treated as usual. Median age (115 months), sex and state of disease were similar in both groups. Reasons for being assigned to HRFN were (order of frequency) ≤7 days from last chemotherapy cycle, Platelets at onset< 50,000/mm3, PCR >2mg/dl or at least 3 times.

Conclusion: In children with FN, the LRFN protocol resulted in short stays in hospital and low rates of antibiotic use.
NHL or non-remission leukemia, and ≥2 of the next: NToR MT < 100, mucositis (grade 2-3), PTCA > 2 mg/dL, HB < 7, TP < 39, LMA, age < 1 year, pathological lung auscultation. There were significant differences between LRNF/IRFN (median, p < 0.05); Leukocytes,1,300 ± 600; No. of days with iv antibiotic therapy: 2 vs 5, No. days hospitalized: 2 vs 6; lymphocytes 600 vs 400, No. days platelets ≤ 50,000/mm³, 0 vs 3.5, No. days monocytes < 100/mm³. Final diagnosis was in the LRFN group: 4 fever without source (FWS) and 1 viral infection (rhinovirus) and in the IRFN group 9 severe infections, 3 FWS. All LRFN patients did well without readmission and without complications.

Conclusion: Our risk prediction model has to be validated with a big sample but apparently could be a good way to support less aggressive management for FN patients with low-risk of IBI.

PR011
AN INITIAL ATTEMPT TO STRATIFY CHILDREN WITH CHEMOTHERAPY-INDUCED FEBRILE NEUTROPHILIA

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Purpose: Our objective was to evaluate risk factors of severe infection in children admitted to the hospital because of chemotherapy-induced febrile neutropenia (FN) in order to stratify cancer patients according to risk of infectious complications.

Methods: From May 2010 to November 2011 all children with therapy-induced FN were prospectively enrolled in the study. We evaluated physical signs, clinical and laboratory parameters on admission and during the episode as well as development and outcome. We analyzed the differences between the patients that were finally diagnosed as having a fever without source (FWS) episode and the ones that had a severe infection, mostly invasive infection (IBI).

Results: 45 episodes were enrolled: 36 (80%) were finally diagnosed as FWS and 9 (20%) of IBI: 1 central venous catheter (CVC) infection, 2 CVC-related bacteremias, 2 sepsis, 2 typhilitis, 1 pseudomembranous colitis and 1 pneumonia. Bacteremia incidence was 11.1% similar to the reviewed literature. Comparing both groups (FWS/IBI) there were no significant differences in sex distribution, PCR at onset (0) and at 48 hrs (48), Hb0, N T 0, nor sex distribution of IBI. Our risk prediction model has to be validated with a big sample but apparently could be a good way to support less aggressive management for FN patients with low-risk of IBI.

PR014
HUMAN SERUM-DERIVED IMMUNOGLOBULINS REDUCE BACTERIAL VIRULENCE IN AN IN VITRO MODEL FOR ORAL MUCOSITIS

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Purpose: Mucositis is one of the most frequent severe adverse events induced by cancer therapy. Mucositis severely affects the patients’ wellbeing, causes treatment delays and excessive expenditures, and is associated with an increased risk for invasive infections during febrile neutropenia. Oral bacteria are co-factors in the pathogenesis of mucositis, and saliva immunoglobulin levels are altered in patients receiving anti-cancer treatments. No effective therapy is available. The aim of this in vitro study is to assess the potential usefulness of pooled, purified human type specific immunoglobulins in the prevention and/or treatment of mucositis.

Methods: Purified serum-derived human IgG, IgA and IgM were produced according to standard chromatographic procedures (provided by CSL Behring, Bern, Switzerland). A previously described model consisting of standard bacterial adherence and invasion assays using Detroit 562 pharyngeal cells and Monoctys catarrhalis ATCC 25238 was used. Standard immunoblotting and FACS analyses were performed.

Results: Standard bacterial adherence assays demonstrated statistically significant, dose dependent inhibition of bacterial adherence induced by a 30-minute exposure of Detroit cell monolayers to bacteria (MOI 30) and purified human IgA (adherence rate, MEM-PHS 60.6 ± 6.9% vs. IgA 5 mg/ml 28.1 ± 8.7%, p < 0.05), IgG (at 10 mg/ml only), and IgM (at 0.5 - 5.0 mg/ml). Similarly, in a gentamicin protection assay, IgA (10 mg/ml; 0.09 ± 0.03% vs. 0.03 ± 0.006%), IgG (10 mg/ml) and IgM (5 mg/ml) reduced epithelial cell invasion by bacteria. There was no evidence both by immunoblotting using whole cell lysates and by FACS that Detroit cells express CD89 (FcγRII).

Conclusion: The in vitro model suggests that pooled human immunoglobulins are capable of inhibiting the interaction between a pharyngeal bacterial species and a pharyngeal epithelial cell line. The anti-inflammatory IgA isotype is of particular interest, because it may also downregulate intracellular proinflammatory cascades by way of immune exclusion.

PR013
ANTIBIOTIC AND OTHER LOCK TREATMENTS FOR TUNNELED CENTRAL VENOUS CATHETER RELATED INFECTIONS IN CHILDREN WITH CANCER: A SYSTEMATIC COCHRANE REVIEW

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Purpose: The risk of developing a tunneled central venous catheter (CVC)-related infection ranges between 0.1 and 2.3 per 1000 catheter days for paediatric oncology patients. These infections are difficult to treat with systemic antibiotics (salvage rate 24-66%) due to biofilm formation in the CVC. Lock treatments can achieve 100–1000 times higher concentrations locally without exposure to high concentrations systemically. Our objective was to investigate the efficacy of antibiotic and other lock treatments in the treatment of CVC-related infections in paediatric oncology patients.

Methods: An extensive literature search was performed (until August 2011) for eligible randomised controlled trials (RCT’s) and controlled clinical trials (CCT’s). Two authors independently selected studies, extracted data and performed quality assessment of included studies.

Results: Two RCT’s and one CCT (including 132 children with CVC-related infections) evaluated lock treatments (n = 36 monotherapy, 15 ethanol) and concomitant systemic antibiotics versus systemic antibiotics only (n = 61). Preliminary results show that in 50/71 (70%) children in the experimental group and in 42/61 (69%) in the control group the CVC-related infection was cured (relative risk (RR) 1.03 [95% CI 0.82–1.29]). In the experimental group 18 (25%) CVC were removed prematurely and 16 (26%) in the control group (RR 0.96 [95% CI 0.55–1.69]).

Conclusion: Preliminary results show no significant effect of urokinase or ethanol lock in addition to systemic antibiotics. However, this could be due to low power. Final results will be available at the conference. No RCT’s or CCT’s were published on antibiotic lock treatment only. More well-designed RCT’s are needed to further explore the effect of antibiotic or other lock treatments.

PR002
HOMOGENEITY INTERVAL IN CHILDREN WITH FEBRILE NEUTROPHILIA IN ALL

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Purpose: Febrile neutropenia [FN] is an oncological emergency to be assessed urgently and treated within an hour. In a developing country patients are often unable to reach hospital speedily. Our study was to determine the home to hospital interval (HHI) in children on treatment for acute lymphoblastic leukaemia (ALL) & to identify factors resulting in delay.

Methods: This was a prospective study of children with ALL (< 14 years) presenting with FN in one year. Data for demographics, clinicopathological details, therapy, profile of caregivers, distance from hospital, travelling time & HHH were recorded.

Results: Among 320 FN episodes, median duration of HHI was 24 hours (IQR 8, 36). Seventy six (72.8%) patients presented to hospital within 24 hours of symptoms, 20 (19.7%) between 24 and 48 hours and 7.5% after 48 hours. The median travel time to hospital was 30 minutes (IQR 15-207.5) Univariate analysis was done taking age, sex, education, socio-economic status, time from last chemotherapy, phase of chemotherapy, travelling time & degree of fever. Travelling time had a significant association with HHI (Pearson’s r = 0.03, p < 0.01). However, travelling time could explain only 31% variability in HHI (coefficient of determination R² = 0.31) with regards to distance from hospital. Less HHI was seen during the intensive phases of therapy in comparison to the maintenance phase (p < 0.01). On multivariate analysis, travelling time and maintenance therapy were found to be independent predictors of delay. However, no association with HHI was seen in rates of complications.

Conclusion: Onset of symptoms to reaching hospital is prolonged in our set up. Association of HHI with phase of therapy can be partially explained by patients living near hospital during the intensive phases. This calls for the need of shared care to circumvent long distance travel and education of the family for FN.
**SIOP ABSTRACTS**

**PR015**

**VARIATIONS IN COMPLETE BLOOD COUNTS AND SPECIFIC INFLAMMATORY PARAMETERS AS PREDICTORS FOR INVASIVE INFECTION IN PEDIATRIC ONCOLOGY PATIENTS WITH FEVER AND NEUTROPENIA**

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**Purpose:** To determine if complete blood tests and specific inflammatory parameters can predict bacteremia in pediatric oncology patients with F&N.

**Methods:** Prospective study from Jan. 2007 to Nov. 2010, based on collected details from the “Soroka” university medical center. Including criteria: 1. Fever ≥38.3°C or fever ≥38°C, lasted ≥1 hour. 2. Children ≤18 years of age with neutrophils count <500 cells/mm³.

**Results:** 73 children with 195 episodes of F&N were examined. Bacteria or fungi were isolated in (Cx [+]) 38 episodes (19%) and in 157 (81%) episodes no pathogen was isolated (Cx [−]). The average duration of fever was significantly longer in the Cx [+] than in Cx [−] group - 5 days vs. 2 days, respectively (p = 0.01). Of all blood cultures, 47% were gram positive bacteria, 43% gram negative bacteria and 10% fungi. The average monocyte count in the first day of fever was higher in the Cx [−] group (0.13 ± 0.33 cells/mm³), vs. Cx [+] group (0.06 ± 0.1 cells/mm³) (p < 0.05). The average CRP at days 5th-8th was significantly higher in the Cx [+] group vs. Cx [−] group (p < 0.01). Duration of zero neutrophils counts was longer in the Cx [+] group vs. Cx [−] group (p = 0.05).

**Conclusion:** The following factors were found significantly different in F&N pediatric oncology patients with Cx[+] compared with Cx[−]: a) Duration of fever. b) Duration of zero neutrophils count. c) Average number of monocytes at the first day of hospitalization. d) Average level of CRP at days 5th-8th. These factors may serve predictors of bacteremia in oncologic pediatric patients with F&N at the initial clinical evaluation as well as in the first days of treatment.

**PR016**

**CLINICO-LABORATORY PROFILE OF HEPATITIS C VIRUS INFECTION AND EFFECT OF RIBAVIRIN MONOTHERAPY IN CHILDREN ON CANCER CHEMOTHERAPY – A PILOT STUDY**

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**Purpose:** Hepatitis C (HCV) infection is an important problem in multiply transfused children especially in those with cancer due to its immunocompromised state. Acute HCV infection is considered to be predominantly subclinical and an earlier observation of clinically overt and prolonged HCV hepatitis in our patients causing interruption in chemotherapy, prompted us to study the role of ribavirin monotherapy in reducing the severity of hepatitis and consequent reduction in duration of chemotherapy protocol interruption.

**Methods:** Routine screening for HCV and HBV infection (by anti-HCV, HBsAg) is done in all our cancer patients at registration and every 3 months thereafter apart from when clinically indicated. Ribavirin monotherapy was given to all children developing HCV hepatitis during chemotherapy (evidenced by deranged LFT and seroconversion to anti-HCV positivity and/or detection of HCV-RNA) whenever afforded by them. The demographic, clinical and laboratory data were retrieved from the case sheets of children with HCV infection.

**Results:** HCV infection was detected in 47 of 799 (5.8%) children registered between 2009and 2011, of which eight were off chemotherapy at detection. Clinically overt hepatitis was seen in 26 (55.4%). Of 39 patients on chemotherapy 12 took Ribavirin. Duration (Mean ± SD) of derangement of liver function was 78.91 ± 66.17 days versus 110.22 ± 102.4 days (p = 0.34) and mean number of days of interruption in scheduled chemotherapy was 11.63 versus 23.29 days (p = 0.18) respectively in children who took Ribavirin versus who did not. HBV co-infection detected in 21 (44.6%) did not cause any difference in derangement in LFT.

**Conclusion:** Clinical hepatitis was seen in more than half of HCV infected children during chemotherapy. Ribavirin monotherapy helped in reducing the duration of altered LFT and that of chemotherapy interruption. HBV co-infection seen in nearly half of HCV infected patients did not alter the severity of hepatitis.

**SUPPORTIVE CARE - MISCELLANEOUS**

**PR017**

**THE UTILITY OF CYSTATIN C FOR EVALUATION OF RENAL FUNCTION IN PEDIATRIC CANCER PATIENTS**

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**Purpose:** Accurate assessment of renal function is essential for pediatric cancer patients treated with anti-cancer drugs. Serum creatinine (Cr) concentration and creatinine clearance (CCr) have been standard methods for measuring glomerular filtration rate (GFR), although their accuracy may be decreased when muscle volume is low or when Cr is excreted from the renal tubule to compensate for low GFR. In addition, collection of urine, which is needed to calculate CCr, is often difficult for younger children. Recently, serum Cystatin C (CysC) concentration has been found to be a more accurate endogenous marker of GFR. However, it has been hypothesized that the synthesis and secretion of CysC is increased in malignant cells, making it unclear whether the CysC method can be used in cancer patients.

**Methods:** We measured CCr and serum Cr and CysC levels (a total of 111 measurements) in 26 patients with malignancy between 1 and 20 years of age that were treated with anti-cancer drugs.

**Results:** In all patients, CCr was found to be significantly and negatively correlated with both CysC and Cr, with the former correlation being stronger. Both correlations were also found in patients who had protein in the urine, who were administered steroids, and who had cancers that were not in complete remission, but not in the patients whose CCr was less than 70mL/minute/1.73m². Estimated GFR (eGFR) based on CysC (eGFR CysC) was more strongly correlated with CCr than eGFR based on Cr (eGFR Cr). Also, the regression equation between eGFR Cr/CC (Cr/Cr) and age was closer to 1 than the regression equation between eGFR CysC and age.

**Conclusion:** Thus, CysC may be a more accurate marker than Cr and a more convenient marker than CCr for assessing GFR in pediatric patients with malignancy although careful evaluation of CysC is needed in patients with reduced renal function.

**PR018**

**RAPID HYDRATION: SMALL CHANGE WITH BIG GAINS**

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**Purpose:** Many of the chemotherapy protocols commonly used in Pediatric Oncology require the patient to receive pre-chemotherapy intravenous hydration to optimize renal excretion, and prevent complications related to the toxicity of these drugs. Historically, the duration of this pre-hydration can be up to 12 hours, and may result in administration of chemotherapy very late in the day or overnight. We have identified that the administration of chemotherapy for newly admitted patients during the night time as a patient safety issue. As a Quality Improvement project, we wanted to answer the question “Can we reduce the hours of hydration prior to chemotherapy?” and “Will this help facilitate the number of patients who receive chemotherapy prior to 6 pm?”

**Methods:** We collected data on 50 patients who received either Cyclophosphamide, Ifosfamide, High Dose Methotrexate or Cisplatin over a 4 week period and found on average it was requiring 6 hours and 24 minutes to hydrate children prior to the start of their chemotherapy and of our patients receiving chemotherapy as an in-patient, only one of 39 patients received their chemotherapy prior to 6 pm. A Rapid Hydration protocol was developed based on published literature and disseminated throughout the Oncology Department.

**Results:** Data were then collected on 31 patients who received rapid hydration prior to the administration of High Dose Methotrexate, Cisplatin, Cyclophosphamide or Ifosfamide. We were able to reduce the number of hours of hydration prior to chemotherapy from 6 hours and 24 minutes to 2 hours and 13 minutes, which was statistically significant. With regards to the number of in-patients who received chemotherapy prior to 6 pm, we were able to accomplish this in 7 of 26 patients.

**Conclusion:** Despite the introduction of a Rapid Hydration Protocol, significant obstacles to starting chemotherapy prior to 6 pm included the late hour of admission to the hospital.

**References:**


**PR019**

**USE OF TRADITIONAL COMPLEMENTARY/ALTERNATIVE MEDICINE (TCAM) AMONG CHILDREN WITH CANCER IN BUENOS AIRES, ARGENTINA**

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**Purpose:** International surveys demonstrate children with cancer are significant consumers of traditional and complementary/alternative medicine (TCAM). Prevalence of TCAM use
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among Mexican and Guatemalan children with cancer are 70% and 92% respectively. Utilization of TCAM among children with cancer in Argentina has yet to be explored.

Methods: Institutional review board approval was obtained for a survey of TCAM use and its associations in children with cancer at the Hospital de Pediatria Samic ‘J P Garrahan.’ Buenos Aires, Argentina. A random, cross-sectional sample of 199 parents was interviewed in person from 2/2011 to 11/2011 after obtaining consent. Demographic data, health-seeking behaviors, TCAM therapies used, and referral and communication about use were collected.

Results: Median age 8 years (6mos–19y). Gender: 56 male/43 female. Diagnoses: leukemia/lymphoma (23%), solid tumors (60%), brain tumors (12%) and other (5%). Presenting symptoms at diagnosis were frequently believed related to trauma (golpe) (26%); evil eye, suso, and chicxumab were reported by 3% of respondents, respectively. Overall, 34 patients reported TCAM use. Among TCAM users, 74% reported using prayer, 41% bioenergetic treatments, 27% dietary supplements, 24% manual healing, and 15% herbal supplements; 56% reported using juicing, other treatments by a mouth, topical therapies, water treatments, yoga/movement therapies, aromatherapy, mind/body programs, and whole medical systems. TCAM was primarily used for overall strengthening/well-being (41%), faith (21%), and cure/tumor reduction (9%). The majority of TCAM therapies used was referred by family/friends (42%), described as somewhat or very effective (78%), and not disclosed to the physician (60%).

Conclusion: Children treated for cancer in Argentina are less frequent TCAM users than those treated in Guatemala and Mexico. Spirituality and energy-healing practices are embedded into conventional care but are often not discussed with the physician. Information collected will aid in the development of TCAM communication guidelines and education materials for the medical personnel working with this population.

PR020

PHYSICAL ACTIVITY (PA) AND SLEEP AMONG CHILDREN AND ADOLESCENTS WITH CANCER

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Purpose: To investigate the relationship between physical activity (PA) and sleep in pediatric patients receiving chemotherapy and/or radiation therapy for cancer.

Methods: Between 11/12/09 and 02/08/12, 36 pediatric oncology patients between 8 and 18 years of age completed the study. Participants were receiving chemotherapy and/or radiation therapy for cancer and were evaluated over 7 days without hospitalizations. PA was assessed by actigraphy as daily total activity counts, average activity counts, maximum activity count and immobile time. Sleep was assessed objectively by actigraphy as sleep time, wake after sleep onset (WASO), number of wake bouts and sleep efficiency. Sleep was assessed subjectively by sleep diaries completed by participants and their parents to determine sleep time, sleep quality and morning mood.

Results: The study participants consisted of 36 pediatric patients receiving chemotherapy and/or radiation therapy for cancer (26 males, 10 females, mean age 11.9 years). The objective and subjective sleep data demonstrated that these pediatric oncology patients had impaired sleep compared to historic, normal controls. They have decreased total sleep time (mean 6.6 hours, SD = 1.3 hours), increased WASO (mean 2 hours, SD = 1.4 hours), increased awakenings during sleep period (mean 28.3 wake bouts, SD = 7.8 bouts), and decreased sleep efficiency (mean 74.2%, SD = 13.3%). In longitudinal models that controlled for age, diagnostic group, sex, race, and steroid use, actigraphy measures of higher PA were associated with improved sleep quantity and quality.

Conclusion: Greater PA was significantly associated with improved sleep quantity and quality in pediatric oncology patients receiving chemotherapy and/or radiation therapy. As a potentially modifiable factor, PA may offer a mechanism to improve sleep in pediatric oncology patients. Future randomized studies are needed to evaluate the impact of an exercise intervention on PA and sleep in children with cancer.

References

PR021

VACCINATION STATUS OF CHILDREN WITH CANCER AFTER COMPLETION OF STANDARD-DOSE CHEMOTHERAPY AND AFTER HAEMATOPOIETIC STEM CELL TRANSPLANT

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Conclusion: Greater PA was significantly associated with improved sleep quantity and quality in pediatric oncology patients receiving chemotherapy and/or radiation therapy. As a potentially modifiable factor, PA may offer a mechanism to improve sleep in pediatric oncology patients. Future randomized studies are needed to evaluate the impact of an exercise intervention on PA and sleep in children with cancer.

References

PR022

SHOULD THERE BE GUIDELINES ON HORMONAL THERAPY IN THE PREVENTION OF MENSTRUATION IN TEENAGE GIRLS RECEIVING CHEMOTHERAPY FOR CANCER?

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Purpose: The use of hormonal therapy, particularly progestogens, has become widespread in teenage girls receiving cancer chemotherapy. However, clinical indications, formulations and dose are widely variable and often based on historical practice rather than evidence. Hormonal therapies, however, are not without hazards and are associated with a risk of thrombo-embolic events. This abstract aims to explore the rationale for hormonal therapy and initiate guidance on its use in adolescent girls receiving chemotherapy.

Methods: To capture varying methods of practice a questionnaire survey was sent to TYAC members in February 2012. The questionnaire included assessment of the unit’s clinical indications for hormonal therapy, preparations in use, and availability of local guidelines.

Results: Twenty-five members responded from 16 centres. Paediatric oncology (PO) centres (age 0–16 yrs) included Bristol, Liverpool, Sheffield, Dublin, and Cambridge (5). Teenage and Young adult units (TYA) (age14–25 yrs) included Royal Marsden Hospital, University College Hospital London, Manchester, Glasgow, Cardiff, Southampton, Leeds, Birmingham, (8). Adult oncology (AO) centres (> 16 yrs) included Nottingham, St. Georges Hospital (London) and Belfast (3). The main clinical indication was stopping problematic bleeding during myelosuppressive phases (PO,5/5, TYA,7/8, AO,2/3). For 2 centres (1,TYA, 1, AO) the main indication was ovarian preservation and reduction of long-term fertility toxicity. Written guidelines were available in very few centres (1,PO, 2, TYA). In most units hormonal therapy was used in selected patients only with input from gynaecology teams (6/8,TYA, 3/3,AO). For all other units it was routinely prescribed in all patients (5/5,PO, 3/3,TYA). In a very small proportion of centres Gonadotrophin releasing hormone analogues were used (3/8,TYA). Most other units used Progestogen-only preparations (5/5, PO, 6/8, TYA, 3/3 AO).

Conclusion: There is varied practice around the UK on role of hormonal therapy in the prevention of menstruation or influence on ovarian cycling in teenage girls. Guidelines are needed and are in development.

PR023

CURCUMIN AGAINST CANCER THERAPY INDUCED MUCOSITIS: COMPARISON OF PURE SYNTHETIC VERSUS NATURAL PURIFIED CURCUMIN IN AN IN VITRO MUCOSITIS MODEL

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Purpose: Curcumin (CC) is a promising topical agent against cancer therapy induced mucositis because of its strong anti-inflammatory and antibacterial properties. Natural curcumin (nCC), an extract from yellow root, consists of several curcuminoids, whereas synthetically manufactured curcumin (sCC) is pure. The goal of this study was to compare the two products for the first time with respect to their potential anti-mucositis effects.
bacterial activity, inhibition of bacterial adherence and invasion, anti-inflammatory effects).

**Methods:** sCC, which fulfills GRAS criteria as a functional food product, was obtained from Monascus purpureus. In vitro studies were performed using *M. catarrhalis* ATCC 25238 as previously described (Lu¨er S et al. Support Care Cancer 2011;19:799).

**Results:** In contrast to sCC, nCC is both odorless and tasteless and did not stain teeth after 72 hours of exposure. 200μM sCC and nCC were equally bactericidal for 2 different strains of *M. catarrhalis* after 180 minutes of exposure. Both sCC and nCC reduced effectively adherence of *M. catarrhalis* to Detroit cells by > 50%, and similarly inhibited cellular invasion. Precipubication of Detroit cells for 60 minutes with 200μM sCC or nCC prior to infection with *M. catarrhalis* (MOI 100) completely abolished IL-8 secretion. Equally suppressed were MCP-1, GM-CSF, IL-6, VEGF and TNFα.

**Conclusion:** Both sCC and nCC appear equally effective in an in vitro model for mucositis. sCC, in addition to being synthetically manufactured and thus free from any products/ contamination in the natural grown yellow root extract nCC, is tasteless and odorless and may therefore be the preferred active ingredient in a topical oral composition intended to prevent or treat cancer therapy induced mucositis.

**PR026**

**NITROUS OXIDE IS AS EFFECTIVE AS KETAMINE-MIDAZOLAM SEDATION FOR PROCEDURE RELATED PAIN IN CHILDREN WITH CANCER**

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**Purpose:** Nitrous oxide (NO) seems a good choice to relieve procedure-related pain in children with cancer, but it is still not used universally. We compared the efficacy and safety of NO with Ketamine-Midazolam (KM) for procedures in children.

**Methods:** This was a prospective study conducted at Sri Ganga Ram Hospital from 2006 to 2009. 100 children with cancer were enrolled in the study; first 50 were randomized in NO group and next 50 in KM group. In KM group 38 children aged more than 6 years and in NO group it was 37. The pain assessment during procedure was recorded by VAS or CHEOPS score as per age of the child. The side effects and recovery time were also recorded.

**Results:** Mean CHEOPS score in NO group was in 17 ± 2.25 (range 6–12) whilst in KM group was 9.46 ± 2.67 (range 6–13) (p value 0.204). Mean VAS score on scale of 0–10 in KM group was 2.87 ± 0.66 (range 2–4) and in NO group was 2.73 ± 1.22 (range 1–6) (p 0.544). Mean satisfaction level on a scale of 1–0 by the nurse regarding sedation was 7.26 in KM group and 7.10 in NO group. The mean satisfaction score by the physician was 7.20 in KM group and 6.98 in NO group. Desaturation (SPO2 < 92%) was seen in 6% in NO group and in 14% in KM group. Other minor side effects were seen in 44% in NO group and 52% in KM group. The most frequent side effect seen in NO group was restlessness (12%) and in KM group it was nausea (16%). The mean recovery time from sedation was 17.2±8.16 sec in NO group and 60.2±18 sec in KM sedation (p value less than 0.05).

**Conclusion:** Nitrous oxide sedation is as effective as Ketamine-midazolam in pain relief. Recovery is quicker with nitrous oxide.

**PR027**

**THE EFFECTS OF EXERCISE TRAINING ON CARDIORESPIRATORY FITNESS AND MUSCLE STRENGTH IN CHILDREN WITH HEMATOLOGICAL MALIGNANCIES: OBSERVATIONS IN CLINICAL PRACTICE**

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**Purpose:** To investigate the effects of a supervised exercise training program on cardiorespiratory fitness and muscle strength in children with hematological malignancies, both during and after medical treatment. Furthermore a subgroup analyses in patients diagnosed with ALL with other hematological cancer types was performed.

**Methods:** The supervised training program was patient-tailored, and consisted of one or two training sessions per week. Every session consisted of running, jumping, playing and performing various exercises in order to strengthen muscles, and to improve cardiorespiratory fitness. At the start and the end of the training intervention peak oxygen uptake (VO2peak and VO2peak/kg), and peak work rate (Wpeak) were determined. Muscle strength was measured with Hand-Held Dynamometry.

**Results:** Data were available in 18 children. Children in the training group had a 4% increased VO2peak and 4% increased Wpeak as a result of the exercise training program. The children who trained during medical treatment increased significantly in VO2peak and Wpeak (68% and 76% respectively). After treatment, a 16% increase in VO2peak, and 11% increase in Wpeak was observed, this increase was 8%, 7% and 15% in children with other hematological malignancies, respectively. In general, children significantly increased muscle strength in the shoulder adductors (49%) and elbow flexors (46%).

**Conclusion:** Exercise training improved cardiorespiratory fitness and muscle strength in children during and after cancer therapy. Improvements were observed mainly during medical treatment, not depending on cancer diagnosis. Cancer care providers should be encouraged to start exercise training interventions during the medical treatment, and motivate...
patients to remain active after cessation of their treatment. This could contribute in better functional outcome of the cancer therapy and a lower level of fatigue.

P0238

CAN WE OMIT PLAIN CT SCAN WHILE PERFORMING AN ABDOMINAL SCAN AND THEREFORE REDUCE THE RADIATION BURDEN IN CHILDREN? IMAGE GUIDANCE: A RATIONAL APPROACH

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Purpose: To determine whether omission of plain CT done while performing an abdominal scan deters diagnosis of abdominal masses in children.

Method: We retrospectively evaluated 86-scan performed at our hospital for children with solid abdominal tumors. The first observer was supplied with the complete scan: plain and contrast enhanced CT (CECT) and the second observer was provided with CECT scans only. Both the radiologists were blinded to the histological diagnosis which was considered as Gold Standard. The two observers reviewed the scans separately and were asked to formulate the most likely diagnosis and to comment on the presence or absence of tumor calcification and/or fat. The agreement between the two observers was measured using kappa statistics.

Results: There was almost complete agreement (κ = 0.97 and 0.96) for the most likely diagnosis for the two observers. There was no statistically significant difference between the diagnosis made by the two observers and the histopathology results. Both the observers had similar sensitivity and specificity for the common abdominal tumors. Considering observer 1 as the gold standard for detection of calcification and fat, observer 2 showed a sensitivity and specificity of 83% & 100% and 60% & 100% respectively. Also noted was that diagnostically significant findings were rare in the pelvis.

Conclusion: Information obtained from only CECT scan is comparable to the complete scan and the plain scans can be omitted from CT protocols. The habitual inclusion of the pelvis on abdominal CT for primary abdominal tumor is also not justified. This can help in reducing the radiation burden by reducing the phases and the scan area.

P029

CHEMOTHERAPY PASSPORT: A TOOL TO IMPROVE SAFE DELIVERY OF CHEMOTHERAPY

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Purpose: The majority of medication errors have been attributed to systems related problems. Chemotherapy errors, especially in children, have a significant potential for adverse events due to its narrow therapeutic range and high toxicity levels. We introduced patient specific individualized “Chemotherapy Passports” with an overall goal to improve safety of chemotherapy delivery and to reduce medicinal errors.

Methods: A multidisciplinary group formed a Pediatric Chemotherapy Practice Committee to improve the process of chemotherapy ordering, verification, administration and documentation. An individualized patient specific “Chemotherapy Passport” was created that traveled with the patient from outpatient to inpatient visits. Chemotherapy checklist was created as a functional and convenient way for physicians, nurse practitioners, pharmacists and nurses to document their practice. The impact of practice change was assessed by pre- and post surveys completed by the health care providers (HCP) (n = 46) and comparison of number of violations on one commonly used chemotherapy study protocol.

Results: There was 85% increase in the use of treatment roadmaps by HCP when prescribing and/or delivering chemotherapy, a 40% increase in confidence regarding the safety of chemotherapy prescription/delivery and a 30% increase in the comfort level of HCP to answer patient and parent questions about medications and modifications. Also, HCP reported a 59% increase in the ease of access to the information required to make treatment decision. There was only 4% increase in the perception that the new process of chemotherapy pre-administration verification and documentation is extra work. The major therapy violations reduced from 10 during pre-treatment period (308-209) to none during post treatment period (309-121). The Chemotherapy Passport also became an important tool for source documentation for audit.

Conclusion: The practice change improved the access to information, safety and accountability of chemotherapy administration at our institution. This also resulted in reduction in major violations and provided reliable tool for source documentation.

P030

PREVALENCE OF VITAMIN C DEFICIENCY IN PEDIATRIC PATIENTS UNDERGOING HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Purpose: Vitamin C is an essential vitamin for maintenance of connective tissue, wound healing, has antioxidant properties and is a cofactor in metabolic reactions. Deficiency is more common in patients with cancer and undergoing hematopoietic stem cell transplant (HSCT) due to poor intake, nausea, vomiting, mucositis and other gastrointestinal complications. Deficiency may result in delayed healing, more infections and may lead to poorer outcome in patients undergoing HSCT. Monitoring was introduced in the unit after cases of floral scurry were diagnosed in this population.

Methods: Vitamin C blood levels were measured in patients undergoing HSCT pre transplant and monitored regularly post transplant. A level more than 40μmol/L was taken as normal and levels of 25–40μmol/L, 11–24μmol/L and < 11μmol/L were classified as mild, moderate and severe deficiency. Patients found to be deficient were supplemented with Vitamin C.

Results: 135 patients with age range 0.25–19 years (Mean: 7.1 yrs) (Males = 90, Females = 45) undergoing HSCT had Vitamin C levels monitored from 2003 to 2011. Of these 33 (24.4%) patients underwent autologous and 102 (75.6%) allogeneic HSCT respectively for malignant (n = 101) and non-malignant (n = 34) indications. 101 (74.8%) patients were found to have low Vitamin C levels at some time point (pre or post-HSCT), with 21 (15.5%), 44 (32.6%) and 36 (26.7%) patients having mild, moderate and severe deficiency. Pre-transplant levels were available in 94 patients (not tested in 41) and out of these, 59 (62.7%) had low levels (22% mild, 39% moderate and 9% with severe deficiency). Conclusion: Vitamin C deficiency is highly prevalent in children undergoing HSCT. With recognition of this deficiency in a population of predominantly enterally fed children, we have started to look for, and found this deficiency even before proceeding to HSCT. Early recognition and management, well before HSCT, and post-transplant period until adequate dietary intake is established is recommended.

P031

PARENT FEEDING INTERACTIONS AND PRACTICES DURING CHILDHOOD CANCER TREATMENT: A QUALITATIVE INVESTIGATION

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Purpose: Parents’ feeding practices and interactions with their child during mealtimes can directly shape a child’s life long food preferences. Negative experiences for the child can contribute to maladaptive feeding behaviors. Children treated for cancer can experience feeding difficulties due to the treatment regimens and toxicities experienced, often resulting in many errors. This study aimed to investigate parent-child feeding interactions and self-reported parent feeding practices during their child’s cancer treatment.

Methods: Parents of childhood cancer patients who had received treatment in the previous 3 years participated in semi-structured telephone interviews. Data were collected and analyzed using the qualitative framework of Miles and Huberman in QSR NVivo.

Results: Thirty eight parents participated in this study (child’s mean age: 7.65 years). All parents reported that eating and feeding during cancer treatment was a major concern and greatly impacted parent-child relationships. Sixty-one percent of parents (n = 23) reported high levels of distress during their child’s mealtimes. The impact of their child’s eating on weight loss was a clear cause of anxiety in 55.3% of parents (n = 21). Anxiety, coupled with feelings of helplessness surrounding the child’s eating, often led to conflict and/or tension between parents and the child at mealtimes (n = 22; 57.9%), as well as between parents (n = 5; 15.2%), resulting in a negative mealtime environment. Many parents described using negative feeding practices, such as pressuring their child to eat (n = 25; 65.7%), threatening the insertion of a nasogastric feeding tube (n = 4; 11.7%) and forcing their child to eat (n = 6; 18.8%) to increase their oral intake.

Conclusion: Parents are using negative feeding practices and interactions during their child’s cancer treatment creating a traumatic mealtime environment. This has the potential to influence their child’s future eating behavior and dietary intake. The long-term consequences of these feeding practices in childhood cancer survivors are understudied.

P032

NUTRITION OF CHILDREN RECEIVING HEMATOPOIETIC CELL TRANSPLANTATION

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Purpose: Hematopoietic cell transplantation (HCT) is a treatment of choice for numerous hematological disorders including relapsed leukemia and lymphoma, and many non-
malignant, yet equally lethal conditions, such as severe aplastic anemia, congenital hemoglobinopathies (e.g., sickle cell disease and thalassemia) and neutrophopic lysosomal and panlysosomal storage disorders (e.g., mucopolysaccharidosis type I and adrenoleukodystrophy). The purpose of this presentation is to present research supported recommendations for nutritional management of children undergoing HCT.

Methods: Many side effect of HCT affect the nutritional status of patient including nausea, vomiting, loss of appetite, alteration of taste, mucositis, pneumonia intestinalis, colitis, and graft versus host disease (GVHD). Malnutrition in children precludes optimal healing and recovery form HCT; therefore maximal effort should be focused on its prevention and treatment.

Results: We will review current guidelines for nutritional assessment and dietary intervention. Special attention will be paid to metabolic derangements of macronutrients and micronutrients affecting children undergoing HCT such as protein energy malnutrition, and deficiencies of vitamin D, vitamin K, Zinc, Copper and Selenium. We will discuss specific recommendations for micronutrients supplementation; we will review recommendations for improvement of nutritional status in HCT patients; and we will suggest dietary interventions based on current research including the use of dietary supplements, modular boosters, appetite stimulants, probiotics, enteral and parenteral nutrition. Lastly, we will review the basic science behind guidelines for specific diets used during HCT as is neutropenic diet and graft versus host disease diet.

Conclusion: HCT is standard of care for many diseases of childhood, however, evidence-based nutritional guidelines are missing and dietary management of pediatric HCT recipients varies among hospitals and among countries. In this presentation we will make specific recommendations based on current research.

**SUPPORTIVE CARE – PALLIATIVE/PsychoSociAL**

**PR033**

**PSYCHOLOGICAL HEALTH IN SIBLINGS WHO LOST A BROTHER OR SISTER TO CANCER TWO TO NINE YEARS EARLIER**

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**Purpose:** To assess long-term psychological distress in siblings who lost a brother or sister to cancer two to nine years earlier, as compared with a control group of non-bereaved siblings from the general population.

**Methods:** During 2009, we conducted a nationwide follow-up study in Sweden, using an anonymous study specific questionnaire. Siblings who had lost a brother or sister to cancer between the years 2000 and 2007 were invited to participate, and also a control group of non-bereaved siblings from the general population. The Hospital Anxiety and Depression scale (HADS) was used to measure psychological distress; and to test for differences in the ordinal outcome responses between the groups, we used Wilcoxon-Mann-Whitney rank-sum test.

**Results:** Among the bereaved siblings 174/240 (73%) participated and among the non-bereaved 219/293 (75%). Self-assessed low self-esteem (p = 0.002), difficulties falling asleep (p = 0.005) and low level of personal maturity (p = 0.007) at follow-up were more prevalent among bereaved siblings. However, anxiety (p = 0.298) and depression (p = 0.846), according to HADS, were similar.

**Conclusion:** Bereaved siblings are at increased risk of low self-esteem, low level of personal maturity and difficulties falling asleep as compared with non-bereaved peers. Yet, the bereaved were not more likely to report anxiety or depression.

**PR034**

**THE IMPACT OF COMMUNICATION PRIOR TO AND FOLLOWING THE LOSS OF A BROTHER OR SISTER TO CANCER – A NATIONWIDE LONG-TERM FOLLOW-UP**

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**Purpose:** To study siblings’ psychological health two to nine years following the loss of a brother or sister to cancer in relation to communication with health-care professionals, family, and others prior to and following the loss.

**Methods:** A Swedish nationwide follow-up study on siblings bereaved due to cancer two to nine years earlier were conducted during 2006 by using a study specific questionnaire. The Hospital Anxiety and Depression scale (HADS) was used to measure psychological distress.

**Results:** 174/240 (73%) sibling’s responded to the study specific questionnaire. Siblings who avoided the health-care professionals (not physicians) of fear of being in their way during their brother or sisters last month of life reported an increased risk of anxiety as compared with those who did not avoid them (HADS > 11), RR = 2.2 (1.1–4.6). Siblings who talked less often with others (not family) about their feelings regarding their brother or sisters illness as compared with those who talked more had an increased risk of anxiety RR = 2.8 (1.3 – 6.2). And so did siblings who avoided talking to their parents about their deceased brother or sister in respect of their parent’s feelings RR = 2.4 (1.1–5.4) as compared with those who did not avoid talking to their parents.

**Conclusion:** Avoidance of health-care professionals, of fear of being in their way, during the last month in the cancer ill brother or sisters’ life increases Swedish bereaved siblings’ risk of anxiety long-term. Avoidance to talk to others as well as their parents also increases the siblings’ risk of anxiety long-term.

**PR035**

**IDENTIFYING THE HEALTH AND SUPPORTIVE CARE NEEDS OF ADOLESCENT AND YOUNG ADULT CANCER PATIENTS AND SURVIVORS**

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**Purpose:** Current cancer programs in Canada manage adolescents (15–18 years) under a pediatric model of care, and young adults (19–25 years) under a patient-centered model of care. Key issues arise because of the inability of either model to meet the needs of adolescents and young adults (AYA). An initiative is underway in Hamilton to design an AYA program to address their specific needs. The aim of this study is to identify long-term and supportive care (HSC) needs of AYA’s, and to use the information to inform the development of a new AYA specific model of care.

**Methods:** A concurrent nested mixed-method design was employed. Qualitative description and a systematic review were used. A purposive sample of AYA patients and survivors of cancer, aged 15–25 years were recruited. Face-to-face qualitative interviews were digitally recorded and transcribed verbatim. Line-by-line coding was used to establish categories and themes. Medline, Cochrane Central, PubMed, PsychInfo CINAHL and EMBASE were searched from their date of inception to October 2011. A comprehensive search strategy was developed. The search was not limited to any languages.

**Results:** Recruitment and data collection were completed. Qualitative findings are based on 20 interviews. Ten diagnosed during adolescence and 10 in young adulthood. A range of cancers were included. Participants described several HSC needs that we categorized into 7 broad themes (e.g., social health). Within each theme, important sub themes have been identified (e.g., social support). Our systematic literature search retrieved 760 citations. Among them, 12 were relevant. By far, the most common need reported from the literature is information, followed by counseling, social and practical support.

**Conclusion:** Findings from our systematic literature review will be triangulated with findings from our qualitative interviews. This will ensure a comprehensive understanding of AYA specific needs, and inform the development of a state-of-the-art AYA healthcare program.

**PR036**

**CREATING A CHILD SELF-REPORT MEASURE OF ADVERSE EVENTS RELATED TO CANCER TREATMENT**

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**Purpose:** The National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE, v. 4) is the standard lexicon for grading adverse events (AEs) in oncology trials. Children with cancer experience significant numbers of subjective AEs such as fatigue, pain, or sadness. The current clinical trial standard is that AEs are reported only by clinicians even though 30% of the 790 CTCAE items are subjective. Children are not routinely asked about AEs experienced during treatment, resulting in subjective AEs being underreported and undermanaged, and the total impact of treatment not fully documented. Soliciting child reports on subjective AEs could help clinicians to better anticipate and manage AEs, and collecting both child and clinician AE reports would contribute to more accurate judgments about the relative benefits and burdens of treatments.

**Methods:** We completed a 3-step content validity study with 147 oncology clinicians (77.8% response rate) to identify the subjective AEs from the CTCAE that 7- to 20-year olds in cancer treatment could be expected to valid report.

**Results:** In step 1, a panel of pediatric clinicians and researchers removed 528 AEs that were laboratory or clinically measured. In step 2, the remaining 262 AEs were assessed by 147 oncologists, pediatric oncology clinicians (physicians (49%), nurses (48.3%), physician assistants (2.7%)) from across the US who rated which CTCAEs were subjective in nature. This step led to 40
items being removed as not subjective. In step 3, the study team members reviewed all remaining items for 4 characteristics (clinician survey ratings, clinically observable AEs, likely to be missed by the clinician, and priority for inclusion) and prepared the second survey for the same 147 clinicians for their final selection of AEs.

Conclusion: These AEs will now be translated into easy to understand terms for 7- to 20-year olds and evaluated through cognitive testing with children with cancer.

References


PR037

PAEDIATRIC ONCOLOGY REFERENCE TEAM (PORT) WORKS TO ENSURE THAT THE INFORMATION GIVEN TO PARENTS, CHILDREN AND YOUNG PEOPLE IN THE UK IS ACCESSIBLE, IN EASY TO UNDERSTAND LANGUAGE AND EXPLAINED WELL AND APPROPRIATE FOR EACH AGE GROUP

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Purpose: PORT works to ensure that information given to parents, children and young people in the UK is accessible, easily understood and explained properly. This helps ensure everyone understands what is happening, and can give truly informed consent. Our aims include: (1) Create an ongoing consultation process between parents, survivors and clinicians to establish better communication, in particular patient information sheets and consent forms. (2) Provide clinicians with access to parents to advise on any issues affecting families living with cancer. (3) Support an audit of information in the UK cancer centres and address inequalities in the information they disseminate. (4) Promote better use and take up of clinical trials. (5) Support overseas cancer centres by promoting literature for families. (6) Lobby government to fund further research into children’s cancers.

Methods: PORT consists of parents of children that had cancer, with different backgrounds covering medicine, nursing, journalism, marketing and writing. We assist in written material, usually produced by paediatric oncology research scientists and doctors. We work to enhance the documentation given to parents explaining their child’s cancer type, treatment protocols and possible clinical trials. We enjoy a close working relationship with Professor Saha (Manchester), and Dr Kears and the CRCTU team (Birmingham) but we are an independent body that has developed autonomously.

Results: Since forming in January 2012 we have reviewed documentation for two trials (InterR and IMPORT) and commented on other issues covering consent, treatment and documentation. We are looking forward to working on IntReALL, and other trials from CRCTU.

Conclusion: We hope that PORT will become well known and paediatric oncologists can contact us as parents, and to review documentation to ensure it is appropriate and high quality.

PR038

TRANSITION OR TRANSFER? AN EXPERIENTIAL PERSPECTIVE ON MOVING FROM PAEDIATRIC TO ADULT CANCER SERVICES

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Purpose: To explore the experiences of young adult survivors of childhood cancer, their parents, health care professionals and case note evidence of the process of transition from paediatric to adult cancer services.

Methods: A qualitative study, with 12 cases recruited. Audio recorded, individual, semi-structured interviews were conducted to explore experiences of transition with young people, parents and health care professionals. Young people: 7 males and 5 females aged between 17 and 25 and who were survivors of childhood cancer were interviewed; Parents: 11 mothers and 1 father were nominated and interviewed; Health care professionals: 11 health care professional interviews were conducted. Also, young people’s case notes from both the paediatric and adult sector, where available, were subjected to a case note review for further evidence relating to their transition experience. In total, 22 sets of case notes were reviewed.

Results: The findings from this study provide a detailed, triangulated multi-perspective and multi-layered depiction of the transition experience of young people, parents, and health care professionals, explained by an orienting theme, ‘The experience of readiness in the context of transition’. This readiness was considered multi-dimensional in nature and was supported by means of three main themes, as derived from the interview and case note data in this study.

These three main themes are: The childhood cancer experience; Planning and preparation: Transition or transfer? and A process of change.

Conclusion: Patient experience needs to be better incorporated into and reflected in transitional care service provision. Assessments of readiness for transition are based informally on young people’s age, but this study has highlighted the need to consider this readiness within the entire context of their illness experience and the relationships they have with professionals and their parents. Better planning and preparation is required to support the transition experience.

PS001

IMPORTANT FACTORS TO UNDERSTANDING QUALITY OF LIFE ACCORDING TO CHILDREN WITH CANCER AND CHILDHOOD CANCER SURVIVORS

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Purpose: There is growing interest in assessing quality of life (QoL) of children with cancer, especially now that more than 80 percent of children survive their initial disease. In pediatric cancer, treatments in general have become more intensive; intensification of therapy has caused considerable QoL implications. Research to understand implications of treatment on children with cancer that is guided by a theoretical framework and examines the complex interrelationships between important determinants of QoL is critical but lacking. This study aims to produce much needed theoretical forms of knowledge, thereby improving conceptual insight in the field of QoL research within pediatric oncology.

Methods: Building upon a systematic review and developed preliminary conceptual framework of determinants of QoL for children with cancer and childhood cancer survivors (1), a multi-site qualitative study is being conducted to elicit the experiences and perspectives of childhood cancer patients. Data obtained from interviews ensures that the framework is as comprehensive as possible, and provides a fuller understanding of determinants of QoL as well as QoL outcomes.

Results: To date a total of 20 patients (12 male, 60%) have participated (median age 13.5 years; range 8–18 years). Twelve of these patients were in-treatment. Preliminary results illuminate differing patterns of QoL in relation to important child, disease and family factors. Findings indicate that there may be an important subset of QoL outcomes of greater importance to pediatric cancer patients not captured in the literature, in particular dimensions of positive transformation experiences including an enhanced sense of self, more meaningful interpersonal relationships, altered priorities and an appreciation for life.

Conclusion: The conceptual framework emerging from this study will help guide and direct future research. Moreover, the framework offers direction to enhance the care provided to pediatric cancer patients and develop intervention strategies and protocols to improve outcomes.

References

PS002

EXPLORING RESPONSE SHIFT IN CHILDHOOD CANCER PATIENTS AND ITS EFFECT ON HRQL

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Purpose: Cancer patients often report good Health Related Quality of Life (HRQL) despite a deterioration in their health status. Apparently, cancer changes an individual’s perception of HRQL. This change in perception, called response shift, might affect the magnitude of change in HRQL over time. This study assessed the response shift phenomenon in childhood cancer patients.

Methods: Participants included children ≥8 years (n = 37), their parents, and parents of children ≥2 years (total number of parents: n = 80). The then-test method was used to determine response shift. HRQL was assessed within two weeks after diagnosis (pre-test) and three months later (post-test) using both child- and parent-report of PedsQL and Cantril’s ladder. The post-test and then-test were administered concurrently.

Results: HRQL improved between pre- and post-test. Cantril’s then-test was lower than the pre-test in both child- and parent-reports, indicating an overestimation of overall HRQL at
the pre-test. Children experienced a greater response shift than parents. No differences were found between the PedsQL, then- and pre-tests.

Conclusion: Brahms' and parent-report ratings of overall HRQL were affected by response shift, resulting in an underestimation of the improvement in overall HRQL between diagnosis and three months post-diagnosis. No response shift was demonstrated in the more specific domains of HRQL (PedsQL). Therefore, the use of the PedsQL instruments is recommended when aiming to demonstrate changes in HRQL. By explicitly measuring response shift, differences between HRQL ratings of childhood cancer patients can be interpreted more accurately.

PS003

HOSPITAL-BASED HOME CARE FOR CHILDREN WITH CANCER – HEALTH RELATED QUALITY OF LIFE AND THE PSYCHOSOCIAL IMPACT ON THE FAMILY

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Purpose: This non-randomised controlled intervention study aimed to evaluate hospital-based home care (HBHC) by comparing HBHC with standard hospital care in relation to the children’s general and cancer-specific health-related quality of life (HRQL), and the psychosocial impact on the family.

Methods: Children were included if they were below the age of 18, had been diagnosed with any type of cancer, were on intravenous anticancer therapy with a curative intent, and the parent was fluent in speaking and reading Danish. Children who lived within a radius of 50 kilometres from the hospital were included in the home care group and received part of their therapy, eg. intravenous chemotherapy, at home by a hospital-based home care nurse with paediatric oncology experience. The standard hospital care group consisted of a historical and a concurrent group, and these children received all their treatment at hospital. The children’s HRQOL were assessed at one time point by parent-reported and self-reported PedsQL-General Core Scale and PedsQL-Cancer Module, and the psychosocial impact on the family by PedsQL-Family Impact Module.

Results: 28 children and 43 parents were included in the home care group, and 47 children and 66 parents in the standard hospital care group. When adjusting for age, gender, diagnosis and time since diagnosis, we found significant differences between the groups in parent-reported physical health (p = 0.04; 95% confidence interval (CI): 0.2–19.5) and worry (p = 0.04; 95% CI: 0.4–20.6) in the home care group indicating better physical health and less worry for children in the home care group. No significant differences he groups were found in the Family Impact Module.

Conclusion: This study indicates that specific dimensions in children’s HRQOL may be improved with HBHC, and the psychosocial burden on the family seems to remain the same regardless of the place of treatment delivery.

PS004

A NEW QUESTIONNAIRE TO MEASURE TEEN-CENTRED CARE IN PEDIATRIC ONCOLOGY: GIVE YOUTH A VOICE

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Purpose: While parents provide valuable insights concerning their children’s healthcare, teenagers have their own views about the care received and how they feel they are treated. The 56-item Give Youth a Voice (GYV) questionnaire was developed to measure teen-centred care from the perspective of adolescents and young adults with a disability. Since teenagers have their own views about the care received and how they feel they are treated.

Methods: While parents provide valuable insights concerning their children’s healthcare, teenagers have their own views about the care received and how they feel they are treated.

Results: 28 children and 43 parents were included in the home care group, and 47 children and 66 parents in the standard hospital care group. When adjusting for age, gender, diagnosis and time since diagnosis, we found significant differences between the groups in parent-reported physical health (p = 0.04; 95% confidence interval (CI): 0.2–19.5) and worry (p = 0.04; 95% CI: 0.4–20.6) in the home care group indicating better physical health and less worry for children in the home care group. No significant differences he groups were found in the Family Impact Module.

Conclusion: This study indicates that specific dimensions in children’s HRQOL may be improved with HBHC, and the psychosocial burden on the family seems to remain the same regardless of the place of treatment delivery.

PS005

DO ADOLESCENTS WITH CANCER AND HEALTHY PEERS DIFFER WITH REGARD TO THE CONTENT AND ABSTRACTION LEVEL OF THEIR SELF-GENERATED PERSONAL GOALS?

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Purpose: Severe illnesses such as cancer may disturb the attainment of personal meaningful goals. Being able to adjust one’s goals to what is possible is an adaptive way to deal with goal disturbance. This study aims to investigate, (1) whether adolescents with cancer differ from healthy controls with regard to the content and abstraction level of their goals, and (2) whether the content and abstraction level of the goals of the adolescents with cancer change over a 9 months period.

Methods: 33 adolescents with cancer (age medium = 14 years, 55.9% girls, all types of cancer) and 66 matched controls completed Little’s Personal Project Analysis Inventory. Participants were asked to generate their personal goals for the upcoming year. All goals were coded by two independent raters on goal content and abstraction level (based on methodology Carver & Scheier 1990).

Results: (Aim 1) Patients reported more health (t(31) = 18.68, p < 0.001) and leisure goals (t(31) = 11.67, p = 0.001) and less material (t(31) = 5.63, p = 0.02) and psychological (t(31) = 5.50, p = 0.02) goals than controls. Their goals were also reported on a lower level of abstraction (t(31) = −2.28, p = 0.03) (Aim 2) Although adolescents with cancer reported less school goals at follow-up (p = 0.01), there were no significant differences between baseline and follow-up in the other content domains (all ps > 0.05). Similarly, the abstraction level of the goals did not change between baseline and follow-up (t(29) = −2.83, p = 0.05).

Conclusion: Group differences in goal-content and abstraction level indicate that adolescents with cancer use goal-restructuring (shift in goal-content) and hierarchy-restructuring (shift in abstraction level) as strategies to deal with changing life circumstances. The lack of change over time suggests that goal adaptation begins early in the disease trajectory and continues over time. More research with a longer follow-up is needed to determine whether these shifts in goal content and abstraction level are permanent or not.

References


PS006

SELF PERCEPTION AND QUALITY OF LIFE IN ADOLESCENTS DURING TREATMENT FOR A MALIGNANT BONE TUMOR

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Purpose: Adolescents, by definition, experience physical and psychosocial disturbances as part of their normal development. It can be hypothesized that they have lower scores on Quality of Life (QoL) and self perception when additional changes occur due to cancer treatment. Little, and conflicting data are available about this topic so far. The purpose of our study was to evaluate self perception and QoL of adolescents during adjuvant treatment for a malignant bone tumor.

Methods: Ten adolescents (median age of 15 years) were included, during or within three months after treatment with adjuvant chemotherapy, and after surgical tumor resection. Intensive psychosocial care was part of the multidisciplinary treatment. Every patient was matched with two healthy peers. Participants completed the Competention Behaviour Scale for Adolescents (CBSA) to measure self perception and the KIDSCREEN-52 questionnaire for QoL. For both instruments, norm data are available.

Results: Adolescents with a bone tumor had lower scores on QoL, as compared to healthy peers. Significantly lower QoL scores were seen on the domains: physical well-being (p = 0.001), psychological well-being (P = 0.02), autonomy (P = 0.02), social support (P = 0.02) and school environment (P = 0.009). Scores on self perception in adolescents with a malignant bone tumor were similar to those in healthy controls.

Conclusion: Adolescents with a malignant bone tumor during adjuvant treatment had lower scores on QoL (KIDSCREEN-52), significantly on the domains of mental and social
functioning. Unlike most other quality of life instruments, the KIDSCREEN-52 contains different areas of social functioning and has shown to be a useful instrument in our patient group. The lower QoL scores had, remarkably, no influence on the adolescents’ self-perception during treatment. It is not known what the role of intensive psychosocial support was on the patients’ self perception. Follow-up study will show whether the unaffected self perception sustains after cessation of treatment.

**Conclusion:** Time alone as part of the psychosocial review was highly valued by the adolescent survivors and their parents. Implementing such a model can create organisational challenges, which need to be anticipated and addressed in order to facilitate this opportunity for adolescent patients and their families.

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**PS007**

**ONLINE GROUP-BASED COGNITIVE-BEHAVIOURAL THERAPY FOR ADOLESCENTS AND YOUNG ADULTS AFTER CANCER TREATMENT: THE RECAPTURE LIFE-AYA PILOT STUDY**

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**Purpose:** Adolescents and young adults (AYAs) with cancer face a unique set of challenges, and may not always have the coping skills to adapt well to this event. Recent research by our team indicates that AYAs with cancer respond positively to a multi-session, peer-group intervention, and rate online sources of support highly. Here we report on a pilot study of a new, online, cognitive-behavioural intervention for AYAs in the critical post-treatment period, called ‘ReCapTure LiFe’. This one-hour group intervention, which takes place weekly for 6 weeks, aims to reduce distress and build adaptive coping skills. Sessions involve 3–5 AYAs, and are facilitated by a psychologist using online video-conferencing technology.

**Methods:** AYAs aged 15–25 years who finished cancer treatment in the last 3 years were recruited. Two weeks following participation, AYAs completed a questionnaire evaluating the program, as well as a semi-structured telephone interview.

**Results:** Six AYAs have been enrolled to ReCapTure LiFe, with one full treatment program completed as at March 2012. Attendance has been excellent (all sessions fully attended) with few technical difficulties reported. All AYAs found the program’s coping skills elements to be the most beneficial, followed by peer discussion. The findings of this study led to several changes to the program content, to reflect a greater emphasis on skills to manage fear of cancer recurrence, as well as integrating positive changes into their life.

**Conclusion:** ReCapTure LiFe is a promising model of support for young people at the cusp of survivorship. A phase II randomized-controlled trial has been planned as a result of this pilot, for which the primary outcome will be quality of life. This trial will commence in 2012, at nine hospitals across Australia.

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**PS008**

**“I CAN DISCUSS THINGS I DON’T USUALLY TALK ABOUT”: EXPERIENCES OF A TIME ALONE MODEL FOR ADOLESCENT ONCOLOGY PATIENTS AND THEIR PARENTS IN THE PSYCHOSOCIAL REVIEW COMPONENT OF A LONG-TERM FOLLOW-UP CLINIC**

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**Purpose:** Improving healthcare services for adolescent survivors of childhood cancer involves implementation of developmentally appropriate care, including increased participation of the young person in decision-making and self management and increased attention toward issues of patient confidentiality and privacy. This study evaluated a “time alone” model implemented into the psychosocial component of a long-term follow-up program (LTFP). The model involves time alone for adolescents and parents with a psychologist and social worker respectively, followed by a joint consultation for shared discussion and planning. Specifically this study investigated adolescent, parent and staff members’ perceptions and experiences of the “time alone” model.

**Methods:** A study-specific survey, which included questions on previous experience of time alone with health professional, was conducted with 25 young people and their parents immediately following the consultation. Additionally, individual semi-structured interviews were conducted with 5 clinic staff members. Quantitative and qualitative data analysis was undertaken.

**Results:** For the majority of participants, this was their first experience of time alone with a health professional. Most participants were positive about their experience. They valued the opportunity to ask questions, to raise concerns privately and (for the young people) to practice independence in their health care. Participants’ understandings of confidentiality varied. Staff members were generally supportive of time alone for adolescents and believed that the model had improved patient care. They also highlighted organisational challenges that had arisen in the clinic as a result of the model, primarily around length of consultations.

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**PS009**

**RISKY SEXUAL BEHAVIOR IN ADOLESCENT SURVIVORS OF CHILDHOOD CANCER: A REPORT FROM THE CHILDHOOD CANCER SURVIVOR STUDY**

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**Purpose:** Identify factors associated with risky sexual behavior among adolescent survivors of childhood cancer.

**Methods:** The Child Health and Illness Profile-Adolescent Edition (CHIP-AE), a self-report measure of health-related quality of life and behavior, was completed by 307 survivors (mean age at diagnosis 1.5 years; range 0–3.76) aged 14–20 years. Univariate analyses were performed using Chi-square and Fisher’s exact tests. Multivariable logistic regression models were used to calculate odds ratios (OR) and 95% confidence intervals (CI) for risky sexual behaviors.

**Results:** History of sexual intercourse was reported by 35.8% of survivors. Of those sexually active, early initiation of intercourse (<16 years of age) and history of multiple lifetime sexual partners (≥2) was reported by 34.5% and 58.1% of survivors, respectively. Method to prevent pregnancy (83.6%) or sexually transmitted infection (71.8%) at last intercourse was also reported. Diagnosis of central nervous system cancer (OR = 13.95, 95% CI: 82–96, p = .05), no history of beer/wine consumption (OR = 20, CI: 0.68–12.53, p = .01), and lower peer influences (OR = 28, CI: 0.99–8.4, p = .02) were associated with a decreased likelihood of having engaged in sexual intercourse. Survivors not at-risk for psychological problems (scores >1.5 SD on the CHIP-AE Emotional Conformity subsdomain) were less likely to have initiated early sexual intercourse (OR = 0.19, CI: 0.05–0.77, p = .02), whereas those with well-educated parents (college degree or less) were less likely to report having multiple sexual partners (OR = 4.22, CI: 1.42–12.53, p = .01). Older age at diagnosis (OR = 4.22, CI: 1.42–12.53, p = .01).

**Conclusion:** Adolescent risky sexual behavior in survivorship is associated with psychological health, alcohol use, and peer influences, which may provide direction for future intervention strategies designed to reduce adverse health outcomes.

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**PS010**

**YOUNG ADULT CANCER SURVIVOR’S EXPERIENCES OF PSYCHOSOCIAL REHABILITATION**

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**Purpose:** The objective of this study was to establish innovation incentives based on young adult cancer survivor’s experiences of psychosocial rehabilitation following their treatment.

**Methods:** Eligibility for the study cohort included diagnosis and treatment for paediatric acute lymphoblastic leukemia in Sweden prior to age 15 years between 1985 and 1997 and survival for at least 10 years (n = 416). A brief questionnaire including both closed and open questions were sent out by mail to all eligible subjects still living in Sweden and with a valid address in the population register (n = 374). Responses (n = 213, 57%) were analysed by descriptive statistics and qualitative content analysis.

**Results:** Only a few of the survivors in the cohort had maintained contact with their paediatric oncology clinic (n = 30, 14%). However, continuation of regular clinical check-ups related to cancer treatment (n = 61, 28%) were more common. Of those who had no contact with health services, 61% were satisfied and 39% dissatisfied with the contact being terminated. A majority of survivors reported that they did not have experience of psychosocial rehabilitation focused on knowledge formation (58%), strategies for action (58%), or support (58%) to continue life the best way possible.

**Conclusion:** This study highlights the potential for innovative resources for psychosocial rehabilitation during adolescence and the importance of supporting children’s and young adult’s initiatives to re-establishing contact with health care related to psychosocial rehabilitation. The school nurse can play a significant role in communication of such resources due to their proximity to children’s daily life post treatment.

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**PS011**

**THE IMPACT OF CANCER DIAGNOSIS ON PSYCHOSOCIAL HEALTH IN CHILDHOOD CANCER SURVIVORS – SINGLE INSTITUTION LONGITUDINAL STUDY QIOLP**

Pediatr Blood Cancer DOI 10.1002/pbc
Purpose: The study deals with psychosocial problems of childhood cancer survivors. Brain tumour survivors suffer from the hardest adverse late effects of treatment. Adolescents are more vulnerable compared to younger children due to the many physical and psychological changes taking place in adolescence. Cancer survivors can experience PTSD or PTG, or both.

Methods: The study sample consisted of 147 cancer survivors (52% girls, 2–5 years old at treatment) aged 8 to 19 years who were compared to healthy children as a control group. Participants from both the study and control group were asked to complete the Minnesota–Minnesota Quality of Life Instrument (MMQL) and the Children’s Depression Inventory (CDI). Three groups of cancer survivors - leukemia, brain tumors and extracranial solid tumors - were compared to the control group using the Kruskal–Wallis test. Analyses were performed separately for younger (8 to 12 years) and older individuals (13 to 19 years).

Results: The lowest quality of life was reported by brain tumour survivors, average quality of life by survivors of childhood extracranial tumours, and the highest quality of life by adolescents after the therapy of leukemia. Comparison with healthy children showed only three significant differences: brain tumour survivors reported poorer physical functioning, leukemia survivors reported higher satisfaction with their body and a lower level of depression. All differences were observed only in the adolescent group.

Conclusion: The differences in measured QoL between the three groups of survivors reflect apparently the intensity of treatment, post-traumatic growth/post-traumatic stress disorder, and the severity of late effects. E.g. high-intensive leukemia protocols associated with a broad spectrum of treatment-related complications might make leukemia survivors stronger than the others (post traumatic growth). Given the short time after therapy (2–5 yrs), understanding possible changes in the perception of QoL, in time necessitates further monitoring of the research sample. Supported by GACR P407/11/2421.

PS012

EMOTIONAL DISTRESS IN 652 DUTCH VERY LONG-TERM SURVIVORS OF CHILDHOOD CANCER, USING THE HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS)

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Purpose: Following more successful treatment of paediatric cancer, the number of childhood cancer survivors is progressively increasing. Consequently, awareness of not only physical but also psychological late sequelae is important. The aim of this study is to identify adolescent and adult long-term survivors of childhood cancer that suffer from emotional distress.

Methods: The Hospital Anxiety and Depression Scale (HADS) was used as a screening tool for emotional distress in a complete single centre cohort of 652 childhood cancer survivors (median age 23 years (range 15–46), median follow-up time 16 years (range 5–42)). Higher HADS scores linearly reflect a higher level of emotional distress.

Results: Mean HADS score of the childhood cancer survivors was not different from controls (p = 0.38). Survivors of leukemia or a lymphoma who received central nervous system (CNS) irradiation had significantly higher HADS scores (8.3 ± 6.6, p = 0.05). Forty-three survivors (7%) had a HADS score ≥15. The proportion of CNS irradiated survivors of leukemia or a lymphoma (n = 9/76) was higher in the group with a score ≥15, than in the group with a score <15 (5.2 ± 3.85, p = 0.05). However, linear regression analysis showed that only educational achievement (β = −0.91, p = 0.01) was independently associated with emotional distress.

Conclusion: Emotional distress does not occur more often in childhood cancer survivors than in the healthy population. Although CNS irradiated leukemia or lymphoma survivors showed more distress, this was not an independent predictor for emotional distress.

PS013

SOMATIC COMPLAINTS IN SURVIVORS OF PEDIATRIC CANCER: THE ROLE OF EMOTION REGULATION

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Purpose: Some childhood survivors of cancer show heightened levels of somatic complaints. Since these complaints are often of undetermined physiological origin, they may be accepted for by psychological factors. Children’s ability to regulate emotion, as measured by respiratory sinus arrhythmia (RSA), is a well-documented physiological index of emotion regulation that is associated with psychosocial and health outcomes. In this paper, we test whether a diagnosis of cancer moderates the relation between RSA and children’s somatic complaints.

Methods: Participants were 257–12-year survivors of Acute Lymphoblastic Leukemia and 26 age-matched controls. Average time since treatment was 4.5 years. Respiratory sinus arrhythmia was measured at baseline from electrocardiogram recordings of heart rate and calculated using spectral time-series analysis. Mothers completed the Child Behavior Checklist, and the T-score on the somatic complaints subscale was used in analyses.

Results: As expected, there was a significant association between cancer diagnosis and somatic complaints (r = .39, p < .01). Moderation analyses indicated that a diagnosis of cancer moderated the relation between RSA and child somatic complaints. For childhood survivors of cancer, low levels of RSA was associated with higher levels of somatic complaints (t(56) = -3.01, p < .01). For controls, the relation between RSA and somatic complaints was not statistically significant.

Conclusion: Children’s emotion regulation abilities are central to development of a range of behavior problems. Children with low emotion regulation abilities also show greater vulnerability to stressors. In this study, we found that RSA, an index of emotion regulation, is an important factor in predicting somatic complaints in childhood survivors of cancer. Children with low RSA may be more vulnerable to the stress associated with a cancer diagnosis, and show poorer functioning even several years after diagnosis. Behavioral interventions can be developed to increase children’s emotion regulation abilities and reduce emotional reactivity.

PS014

VERY LATE ONSET AND RECURRENT SUICIDE IDEATION IN ADULT SURVIVORS OF CHILDHOOD CANCER: A REPORT FROM THE CHILDHOOD CANCER SURVIVOR STUDY

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Purpose: To examine late onset (> 10 years following diagnosis) and recurrent suicide ideation (SI) in adult survivors of childhood cancer. Subgroups of survivors are at-risk for psychological distress, including SI, though the prevalence and predictors of late onset and recurrence during adulthood are unknown.

Methods: Participants included 7,561 adult survivors of childhood cancer who completed a measure of psychological distress (Brief Symptom Inventory-18) at least twice among 1994–1996 (baseline), 2003–2005, and 2007–2010 surveys, and a randomly selected subset of sibling controls (n = 2,408). Very late onset SI was defined as SI reported on a second survey without previous report. Recurrent SI was defined as endorsement of SI on ≥2 surveys. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using multivariable logistic regression models to identify predictors of SI in survivors.

Results: Compared to siblings, survivors were significantly more likely to report very late onset (7.5% vs. 4.1%, p < 0.0001) and recurrent (3.1% vs. 1.5%, p < 0.0001) SI. Survivors endorsing very late onset SI were, on average, 26 years (SD = 5.1) from diagnosis. After controlling for symptoms of depression, fair/poor physical health status (OR = 1.69, 95% CI 1.16–2.46), cancer-related pain (OR = 1.66, 95% CI 1.16–2.38), and seizures (OR = 2.64, 95% CI, 1.32–3.17), were significantly associated with late onset SI. Recurrent SI was predicted by fair/poor physical health status (OR = 1.91, 95% CI 1.32–2.98), not having health insurance (OR = 1.79, 95% CI, 1.16–2.77), headaches (OR = 1.65, 95% CI, 1.13–2.41), and seizures (OR = 2.56, 95% CI, 1.44–4.56). The presence of initial elevated depressive symptoms was associated with an 8-fold increased likelihood of recurrent SI (OR = 8.64, 95% CI 5.99–12.4).

Conclusion: Survivors of childhood cancer appear to be at persistent risk for SI several decades following their original cancer diagnosis. A multidisciplinary approach toward survivor care, including routine screenings for psychological distress, especially in the context of poor physical health and pain, is necessary.

PS015

FAMILY ADAPTATION TO CHILDHOOD CANCER AND THE NEED FOR PSYCHOSOCIAL INTERVENTION

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Purpose: As a result of increased survival rates in pediatric oncology, a new field of research emerged, that of psycho-oncology, which studies the psychosocial aspects of cancer and indicates family support as part of the therapeutic regimen. Our aim is to assess the...
adoption of the family to the diagnosis of childhood cancer in the Greek population and indicate the need for intervention.

Methods: The following measures were used, translated and adjusted for the Greek population: Psychosocial Assessment Tool (PAT) (Patient & Staff Perceptions), Zung Depression Rating Scale, State Trait Anxiety Inventory (STAI), Hospital Anxiety and Depression Scale (HADS). Families and corresponding staff members were interviewed within 10 days following the diagnosis.

Results: 61 families with children that were diagnosed with malignancies were included in the study (one parent per family, 52 female:9 male, aged 23–47). According to the PAT, 33% were in need of universal psychosocial care, 52% in need of more targeted psychosocial care, and 15% had many risk factors and required clinical psychosocial care. Factors that statistically affected the PAT outcome were education level (less than high-school = high risk, p = 0.0005), and nationality (Non-Greek = high risk, p = 0.0001). Diagnosis (i.e. leukemia vs. brain tumor) was not statistically significant at this stage. In PAT Staff Perceptions, physicians correctly evaluated the situation in 26% of the families, and understated the family’s needs in 57%. Nursing staff were correct in 31% and underestimated in 61%. Anxiety levels were increased in 77% of the families according to HADS and 86% according to STAI. HADS revealed depression signs in 82% of the families, and depressive symptoms were prevalent in a substantial proportion of the parents. Further, optimism and especially mastery are useful resources for parents of children with cancer. Mastery should be promoted by tailored interventions.

Conclusion: In pediatric oncology, the parents experience high levels of anxiety and depression in the immediate period after diagnosis. The need for psychosocial intervention is clear, in order to facilitate the family’s adaptation to the diagnosis.

FAITH AND PROTECTION: THE CONSTRUCTION OF HOPE BY PARENTS OF CHILDREN WITH LEUKEMIA AND THEIR ONCOLOGISTS

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Purpose: Oncologists are criticised for fostering unrealistic hope in patients or families, but criticisms reflect a perspective that is over-simplified and “expert” guidance that is ambiguous or impractical. Our aim was to understand how paediatric oncologists/haematologists manage parents’ hope in practice and to evaluate how they address parents’ needs.

Methods: Participants were 53 parents and 12 oncologists whom they consulted at six UK centres. We audio-recorded consultations at approximately 1–2, 6 and 12 months after diagnosis. Parents were interviewed after each consultation to elicit their perspectives on the consultation and clinical relationships with staff. Transcripts of consultations and interviews were analysed qualitatively.

Results: Parents needed hope in order to function effectively in the face of despair, and all wanted the oncologist to help them be hopeful. Most parents focussed hope on the short-term. They therefore needed oncologists to be authoritative in taking responsibility for the child’s long-term survival, while cushioning parents from information about longer-term uncertainties and being positive in providing information about short-term progress. A few parents who could not fully trust their oncologist were unable to hope.

Conclusion: Oncologists’ pivotal role in sustaining hope was one that parents gave them. Most parents’ “faith” in the oncologist allowed them to set aside, rather than deny, their fears about survival whilst investing their hopes in short-term milestones. Oncologists’ behaviour generally matched parents’ needs, contradicting common criticisms of oncologists. Nevertheless, oncologists need to identify and address the difficulty that some parents have in fully trusting the oncologist and, consequently, being hopeful.

REFERENCES


MASTERY AND OPTIMISM AS PREDICTORS OF DISTRESS IN PARENTS OF CHILDREN WITH CANCER

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Purpose: Parents of children with cancer experience multiple stressors. This may lead to a range of emotional reactions (e.g. anxiety, depression, stress). Some parents, however, are more distressed than others. Candidates to predict differences in distress are optimism and mastery. The objectives of this study are to examine: (1) the amount of distress in parents of children with cancer (3 months post-diagnosis), and (2) the predictive value of mastery and optimism in ratings of parental distress (e.g. anxiety, depressive symptoms, illness-related parenting stress).

Methods: Participants were 96 parents of newly diagnosed pediatric cancer patients (all ages, 3 months post diagnosis). Measures included the Revised Life Orientation Test (LOT-R), Pearlin & Schooler Mastery List, State Trait Anxiety Inventory (STAI), Center for Epidemiologic Studies Depression Scale (CES-D), and the Pediatric Inventory for Parents (PIP).

Results: Fifty one percent of the parental ratings of anxiety and 37% of ratings of depressive symptoms were above the clinical cut-off. Regression analyses showed that parental age, optimism and mastery were inversely related to parental distress. The full model explained resp. 40% of the variance in anxiety, 44% of the variance in depressive symptoms and 42% of the variance in illness-related parenting Stress. When mastery was entered in the models of anxiety and illness related parental stress, optimism was no longer significant.

Conclusion: At 3 months after the diagnosis of childhood cancer elevated levels of anxiety and depressive symptoms were prevalent in a substantial proportion of the parents. Further, optimism and especially mastery are useful resources for parents of children with cancer. Mastery should be promoted by tailored interventions.

AVOIDANCE AND HYPERAROUSAL MEDIATE THE RELATIONSHIP BETWEEN REEXPERIENCING AND DYSPHORIA IN PARENTS OF CHILDREN WITH CANCER: A LONGITUDINAL ANALYSIS

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Purpose: Cognitive processing theory stipulates that avoidance mediate the relationship between intrusive thoughts about trauma and psychological distress (Cramer, et al., 1992). Evidence also suggests that hyperarousal predicts emotional numbing in response to trauma (Litz, et al., 1997). The purpose of this study was to investigate the mediating role of avoidance and hyperarousal in the relationship between reexperiencing and dysphoria among parents of children on cancer treatment.

Methods: We used data from a longitudinal study with three assessment points: T1 = 2 weeks after the child’s diagnosis (n = 249), T2 = two months after the child’s diagnosis (n = 234), and T3 = four months after diagnosis (n = 203). The PTSD-Checklist Civilian was used as a measure of symptoms of traumatic stress interpreted with Simms et al. (2002) four-factor theory of traumatic stress. Two models were evaluated with mediation analysis using bias corrected bootstrap estimation of indirect effects and 95% confidence intervals (CI, Preacher and Hayes, 2008). Model 1 included two indicators of avoidance at T2 as mediators of the relationship between reexperiencing at T1 and dysphoria at T3, while controlling for initial levels of included variables and gender. In model 2 hyperarousal at T2 was added as a mediator.

Results: In model 1 there was a significant total indirect effect from reexperiencing to dysphoria via avoidance (0.048, CI = 0.012–0.116). However, only avoidance of activities or situations remaining of the child’s disease had a significant specific indirect effect (0.044, CI = 0.009–0.097). In model 2 there was a significant total indirect effect from reexperiencing to dysphoria via avoidance and hyperarousal (0.140, CI = 0.076–0.233). However, only hyperarousal contributed with a significant specific indirect effect (0.110, CI = 0.061–0.212).

Conclusion: The current analyses suggest that avoidance and hyperarousal both are important targets for intervention in parents of children on cancer treatment.

PARENTING A CHILD WITH CANCER: PARENT AND ADOLESCENT SURVIVORS’ PERCEPTIONS OF PARENTING STRATEGIES UTILISED DURING TREATMENT AND INTO SURVIVORSHIP

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Purpose: There is limited evidence of the continuing psycho-social impact of childhood cancer on parenting. The purpose of this presentation is to report adolescents’ and parent’s perceptions of parenting in the context of childhood cancer 2–5 years post-end of treatment.

Methods: Fifty-seven semi-structured interviews were conducted with 36 parents and 21 adolescents. Interviews were transcribed and coded. Inductive thematic analysis was used to develop and interpret themes.

Results: Parents and adolescents reported increased intimacy, closeness and emotional support following the cancer diagnosis. Parents also reported epitomising their ill child and using gifts as bribes to attend appointments. Differential parenting between the ill child/adolescent and their sibling(s) was discussed; with acknowledgement that the ill child received more attention and emotional support than sibling(s). Parents reported wanting more information relating to potential treatment late effects, fertility issues and parenting strategies to manage problematic behaviors exhibited by their child. Parents reportedly withheld medical
information deemed too upsetting for their child, a strategy not well received by adolescents. Parents also mentioned a need to provide their ill child with a stable and predictable environment post diagnosis, including a desire for continuity in pre-diagnosis activities. Many aspects of parenting attitudes and behaviors appeared to persist beyond diagnosis and treatment, highlighting that several parenting strategies used during ‘active’ stages of the disease continue into survivorship.

Conclusion: Building on previous research, we document adolescent and parent perceptions of parenting strategies utilised both during treatment and into survivorship. Our results highlight the importance of understanding parenting processes that may operate throughout the disease trajectory for families experiencing pediatric cancer.

PS020

PREDICTORS OF PSYCHOPATHOLOGY IN CHILDREN WITH ACUTE LYMPHOBlastic LEUKAEMIA UNDERGOING CHEMOTHERAPY

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Purpose: Acute lymphoblastic leukemia (ALL) has achieved high cure rates in children with intensive chemotherapy. However, treatment requires prolonged and repeated hospital visits which may have adverse psychological effect on young children. Aim of the present study was to evaluate the psychopathology and risk factors in children with acute lymphoblastic leukemia undergoing chemotherapy in the oncology unit of Department of Pediatrics. Parents/ guardians were interviewed at least 6 months after starting chemotherapy. Inclusion criteria were: age 6–14 years, both parents alive and staying together, no family history of psychological illness, 50% age and sex matched children suffering from non-hematologic chronic illness served as control. Childhood psychopathology measurement schedule (CPMS) was used to assess psychopathology. CPMS is an Indian adaptation of Child Behavior checklist (CBCL) by Achenbach and Edelbrock. A cut-off of > 10 on total score was taken as significant.

Results: Mean age of the patients was 8.93 years with a female to male ratio of 1.81 in both study and control groups. Groups were comparable in relation to demographic profile. Mean CPMS score was 9.59 ± 4.68 (range 2–21) and 5.80 ± 3.54 (range 1–13) in study and control groups respectively (p < .001). 14 of (35%) children with ALL had a mean CPMS score of > or = 10 as against 8 of 50 (16%) children in control group. Children scored higher on the conduct disorder (p < .001) and depression (p < .05) subscales in the study group. Age and type of family (urban, nuclear) had significant correlation with psychopathology.

Conclusion: Children undergoing chemotherapy for ALL had significant psychopathology. Older children from urban, nuclear families were at more risk.

PS021

Course of emotional adjustment of children diagnosed with acute lymphoblastic leukaemia (ALL) from diagnosis until end of treatment

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Purpose: In this study we aimed to: 1) describe the course of emotional adjustment of children with Acute Lymphoblastic Leukaemia (ALL) from diagnosis until end of treatment, and 2) investigate to what extend sex, age and ALL-risk category contributes to the course of the child’s emotional adjustment.

Methods: 131 parents of children aged 1–17, diagnosed with ALL, agreed to participate in this multicenter longitudinal study. Data were gathered by means of a behavior questionnaire (Child Behavior CheckList) at time of diagnosis (T0), halfway treatment (T1) and at end of treatment (T2). 90 parents returned questionnaires on both T0, T1 and T2.

Results: Analyses revealed that the children with ALL in our study experienced significantly higher on the conduct disorder (p < .001) and depression (p < .05) subscales in the study group. Age and type of family (urban, nuclear) had significant correlation with psychopathology.

Conclusion: Children undergoing chemotherapy for ALL had significant psychopathology. Older children from urban, nuclear families were at more risk.

PS022

ACUTE NEUROPSYCHIATRIC EPISODES OF CORTICOSTEROIDS DURING INTENSIVE TREATMENT FOR ALL IN ADOLESCENT PATIENTS

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Purpose: Systemic corticosteroids, prednisone or dexamethasone (PRED or DEX), are an important component of leukemia treatment protocols. Prolonged, and high dose admitting of corticosteroids can have some neurotoxic effects, which can display some behavioral side-effect especially in young children. We evaluated an incidence of acute neuropsychiatric episodes in ALL adolescent patients treated BFM 93 and ALL-IC 2002 protocols.

Methods: 49 consecutive adolescent patients (59.2% boys) with ALL entered the study. Patients treated BFM 93 Protocol were diagnosed between Jan 1996 and Dec 1998, and ALL-IC 2002 Protocol between Jan 2007 and March, 2012, in pediatric onco-hematology ward in Lublin, Poland. Mean age at the diagnosis was 14.1 y, and median was 13.9 y. During intensive treatment patients were provided with planned psychosocial support program. Within first 2–3 weeks of treatment, evaluation of PIQ, VIQ and PIQ of patients were performed. Behavioral side-effects and neuropsychiatric episodes were rated using clinical interview.

Results: Mild intensity of behavioral side effects during corticosteroids therapy were observed in 28.6% of studied patients. The most frequently diagnosed symptoms were: anxiety, weepiness, decreased mood and withdrawal. Only in the ALL-IC group, 5.4% of patients received antidepressant treatment. Remaining patients, in both treatment groups, with symptoms of behavior disorders received only hydroxyzine. 10.2% of adolescent patients (18BMF, 4/ALL-IC) revealed acute neuropsychiatric episodes (with high anxiety, with seeing and hearing things, lack of consciousness) when corticosteroids were reduced. Three boys revealed acute neuropsychiatric symptoms twice: when both PRED and DEX were reduced, and they received antipsychotic treatment.

Conclusion: (1) Symptoms of mild intensity behavioral corticosteroids side effects were observed in one third of adolescent ALL patients. (2) ALL adolescent patients are at risk of neuropsychiatric episodes at the moment of corticosteroids reduction. (3) Neuropsychiatric effects during active treatment of ALL in adolescence needs further studies.

PS023

“HIT AND MISS”: PARENTS AND TEACHERS PERCEPTIONS OF EDUCATIONAL NEEDS FOLLOWING TREATMENT FOR A BRAIN TUMOR

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Purpose: Survivors of pediatric brain tumors (PBT) are at increased risk of reduced educational and vocational outcomes following treatment. Few studies have investigated the retrospective experiences of parents and teachers of school-age PBT survivors to inform the development of educational intervention strategies. The primary objective of this qualitative study was to explore parent and teacher perceptions of educational provision for their child student in the years following PBT treatment.

Methods: Semi-structured individual interviews were conducted with parents (N = 15) of children aged 4–18 years treated for PBT and more than one year post-treatment, and their teachers (N = 9). Template and inductive thematic analysis was used to construct and interpret themes arising from the parent and teacher interview data.

Results: Parents of school-aged PBT survivors described a significant burden in relation to obtaining and sustaining an appropriate level of educational support for their child post-treatment. This was a common theme for all parents regardless of the child’s age, diagnosis, age at diagnosis, treatment, or type of school. This burden was reported as being created and sustained by variable availability of services and resources within government and educational systems, a lack of appropriate and timely information, and unpredictable late-effects of treatment. Teacher perspectives described a resilient and resourceful approach to teaching children following PBT within a context of limited resources, funding and information. Common to both parents and teachers was a perceived lack of expertise in understanding and providing for the school-based needs of these children and adolescents.

Conclusion: Findings suggest the ongoing educational needs of children post-PBT treatment are not adequately managed by current services. A systematised model of service provision, such as a case management model, is recommended to address the needs of parents and schools in providing appropriate supports to maximise quality of life outcomes for the growing PBT survivorship population.
1126 SIOP ABSTRACTS

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Purpose: Children with brain and spinal tumors in remission, who reintegrate into Japan’s public education system, face many challenges related to academic performance after long absences and cultural inhibitions regarding their academic level. A comprehensive understanding of these issues will provide a framework for a guideline to be developed. This guideline will help children, their families and teachers have realistic expectations regarding student performance and what the community can do to help the student succeed.

Methods: This retrospective analysis is based on social work progress records of 210 children with brain and spinal tumors in our hospital from April 2007 to March 2012.

Results: This study focused on the following variables in determining a child’s successful reintegration: Child’s length of stay in the hospital. Child’s contact with their teachers and classmates from the school they were attending prior to hospital stay. Child’s academic work product at the hospital school during the hospital stay. Empowerment of the parents to be the primary advocate for the child in the academic environment. Teachers and school staff prior experience with students returning to school after a long illness. Community members general understanding of brain and spinal tumors. Whether or not a reintegration conference was conducted with relevant parties. This study showed all the above factors affected a child’s ability to successfully reintegrate. Additionally, conferencing with the teacher was the key area a social worker had to influence to a successful outcome.

Conclusion: The social workers primary goal in this situation is to facilitate understanding regarding a child’s need for individualized differentiated instruction. This is a significant concern in Japan’s conformist society. Children, who have courageously survived so traumatic an experience such as cancer and face new challenges of modified abilities, can be successful contributing members of our society if we help them to do so.

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Purpose: Monitoring Health Related Quality of Life Scores (HRQOL) by providing PROs to paediatric oncologists during routine follow-up consultations, leads to increased discussion of psychosocial functioning and improved identification of emotional and cognitive problems (Engelen et al., 2011). At the same time, it does not lengthen the consultation effectively. A PROfile is therefore an effective tool to discuss systematically and pay attention to HRQOL. However, do paediatricians and parents perceive it to be feasible for standard use in clinical practice?

Methods: Twenty-one oncologists (48% male) from four Dutch pediatric oncology centers and 74 parents of children aged 0–18 (80% mothers, after end of treatment), completed a (self constructed) feasibility questionnaire after finishing three consecutive consultations in which PROs regarding HRQOL were discussed (the QLC-ON PROfile study intervention). Participants were asked for their opinion concerning the use of the PROfile as part of standard care in paediatric oncology practice.

Results: Oncologists. The majority of the oncologists experienced the QLC-ON PROfile as a supplement to the conversation (62%). More than half of the oncologists recommended standard use in future paediatric oncology practice (67%), and use during treatment (67%). Frequency of use should be once per 3 months or more (71%). Eighty-five percent considers using a future internet version of the PROfile. Parents. Parents indicated the QLC-ON PROfile to be a good addition to current care (76%). According to the majority of the parents (78%), it should be implemented in future paediatric oncology practice. Most of the parents (67%) define the treatment period as a good moment for discussing the PROfile. Parents prefer the PROfile to be discussed by the oncologist once in every 3 months or more often (84%).

Conclusion: Systematic monitoring of HRQOL by providing PROs to paediatric oncologists during treatment seems feasible for implementation in clinical practice (see www.hetklik.nl).

References

P027

HELPING THE HELPERS: A PILOT STUDY OF MINDFULNESS TRAINING TO DECREASE BURNOUT AMONG PEDIATRIC ONCOLOGY STAFF MEMBERS

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Purpose: Burnout, a syndrome of emotional depletion, personification, and diminished feelings of accomplishment, is estimated to affect up to 40% of pediatric hematologist/ oncology staff members. Mindfulness based stress reduction (MBSR), which focuses on self-care, present moment awareness and compassion, can reduce feelings of burnout among healthcare workers, but requires a prolonged training process.

Methods: We developed an abbreviated MBSR (aMBSR) training program and tested the feasibility of its implementation on pediatric oncology staff members in two academic centers. We also assessed the program’s effect on burnout symptoms using the Maslach Burnout Inventory (MBI) and the Perceived Stress Scale (PSS) at study entry and completion. Logbooks detailing participant experiences, attendance logs and practice logs were maintained. Subjects randomized to the aMBSR intervention participated in a 17 hour skill-training course spread over 8 weeks that consisted of didactic and experiential exercises in MBSR.

Results: Five physicians, 25 nurses, 5 social workers, and 7 child-life specialist were enrolled; 23 subjects received the intervention. Attendance was excellent and subjective enthusiasm levels of participants were high. MBI scores revealed that 100% of the intervention group subjects and 96% of the control subjects showed signs of burnout at both time points on personification and personal accomplishment subscales. PSS scores were nearly double that of population norms, but did not change significantly from baseline to follow up in the two groups.

Conclusion: Our abbreviated MBSR program aimed at decreasing burnout can be easily implemented into the routine of a busy academic pediatric hematology oncology program. The impact of this program on burnout scale scores was not manifest at 8 weeks in this small pilot study. Ongoing modification of the aMBSR program and a larger study cohort will be required to improve the efficacy of this technique among our at risk co-workers.

P0026

PATIENT REPORTED OUTCOMES (PROs) IN PEDIATRIC ONCOLOGY PRACTICE: PERCEIVED FEASIBILITY BY ONCOLOGISTS AND PARENTS

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Purpose: Treatment abandonment is a leading cause of treatment failure in children with cancer in countries with limited resources. Previous research into determinants of treatment abandonment is scant. This study aimed to address this gap by gathering information from childhood cancer providers from around the world.

Methods: A 32-item self-administered online survey was created by members of the Working Group and distributed to regular users of the freely accessible Cure4Kids website (3234 clinicians, nurses, social workers and psychologists). The survey was launched in February of 2012 and will continue to accrue until April 2012.

Results: Of 280 responses from 78 countries, respondents were female (60%), physicians (87%), pediatric hematology/oncology specialists (83%) and in practice for > 10 years (52%). Reported likelihood of abandonment increased as the country’s income (GNI per capita) decreased. Abandonment rate ≥16% was reported in 1% of high-income countries, 12% of upper-middle-income countries, and 49% and 67% of low-middle and low-income countries respectively (p < 0.0001). Reported abandonment rate also increased as the country’s health expenditure per capita decreased (r = -0.616, p < 0.0001). Factors reported by ≥50% of respondents to increase abandonment likelihood included: low education or socioeconomic status, long travel time, high treatment toxicity, preference of alternative medicine, strongly held religious beliefs, and belief in cancer’s incurability. Over 65% reported that gender, nutritional status, and HIV status were unlikely to increase abandonment. In low- and middle-income countries, abandonment was reportedly lowest for Wilms tumor (21%) and Hodgkin lymphoma (24%) and highest for bone sarcomas (52%). Among treatment-related factors, relapse and amputation were considered of highest risk for abandonment (25–35% and 33% of responses, respectively).

Conclusion: This is the first global survey of provider’s perspectives on determinants of treatment abandonment in pediatric cancer. Results point to socioeconomic, disease-specific and treatment-specific determinants of treatment abandonment and will guide continued efforts to address this issue globally.

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The impact of this program on burnout scale scores was not manifest at 8 weeks in this small pilot study. Ongoing modification of the aMBSR program and a larger study cohort will be required to improve the efficacy of this technique among our at risk co-workers.
**PS028**

**PSYCHOSOCIAL RISK IN FAMILIES CARING FOR A CHILD WITH CANCER: USE AND VALIDATION OF THE PSYCHOSOCIAL ASSESSMENT TOOL (PAT2.0) IN AN ITALIAN MULTICENTER SAMPLE**

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**Purpose:** The impact of the psychosocial environment in children with cancer can alter emotional and developmental programming and influence behavior or interfere with the efficacy of treatment. Therefore, early psychosocial screening may help identify the unique needs of each child and its family, guide treatment and improve prevention. The purpose of this study was twofold: 1) to validate the PAT2.0 in an Italian multi-center sample of children diagnosed with cancer, and 2) to study the critical role of predisposing environmental factors in differentially mediating psychosocial needs and psychological risk over time in families caring for a child with cancer.

**Methods:** Parents of 120 children recently diagnosed with cancer belonging to four pediatric oncology centers were enrolled and completed the Italian version of the PAT2.0 within one month after diagnosis. About half of the sample was tested again six months later.

**Results:** The PAT2.0 separated the psychosocial risk of families into three levels reflecting the data from the authors of the scale. However, the proportion of families belonging to distinct risk levels differed. About forty percent of the families belonged to the lowest, universal risk level. Surprisingly, a substantial number of families – almost fifty percent – displayed an intermediate risk level while only 9% scored in the clinical range of the scale. Interestingly, families in the targeted and clinical risk group displayed a particular pattern of subscores. Risk assignment according to PAT2.0 scores did not differ among the participating centers nor did time of administration affect the proportion of families in need of targeted or clinical intervention.

**Conclusion:** The PAT2.0 proved a useful tool in identifying psychosocial risk in diverse clinical settings. However, particular attention should be directed to study subgroups with specific patterns of needs, how to identify them and how to best guide interventions to address their needs.

**References**


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**PS029**

**THE VALUE OF INFORMATION IN GAINING TRUST – EXPERIENCES FROM CHILDREN'S CANCER HOSPITAL IN EGYPT**

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**Purpose:** Providing adequate information regarding treatment may increase trust among parents of children with cancer. Little is found in the literature regarding predictors of trust.

In interviews we have documented mistrust between the family and health care professionals in pediatric oncology in Egypt. This mistrust, we believe, will impact the quality care for children with cancer in Egypt.

**Methods:** A study specific questionnaire was distributed to 304 parents of children with cancer in Egypt. In interviews we have documented mistrust between the family and health care professionals. We believe that this mistrust, if not addressed, will impact the quality care for children with cancer in Egypt.

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**Results:** A study specific questionnaire was distributed to 304 parents of children with cancer in Egypt. In interviews we have documented mistrust between the family and health care professionals. We believe that this mistrust, if not addressed, will impact the quality care for children with cancer in Egypt.

**Conclusion:** The impact of the psychosocial environment in children with cancer can alter emotional and developmental programming and influence behavior or interfere with the efficacy of treatment. Therefore, early psychosocial screening may help identify the unique needs of each child and its family, guide treatment and improve prevention. The purpose of this study was twofold: 1) to validate the PAT2.0 in an Italian multi-center sample of children diagnosed with cancer, and 2) to study the critical role of predisposing environmental factors in differentially mediating psychosocial needs and psychological risk over time in families caring for a child with cancer.

**References**


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**PS030**

**REVIEW OF INTERVENTIONS FOR PROMOTING PARTICIPATION IN SHARED DECISION-MAKING FOR CHILDREN WITH CANCER**

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**Purpose:** Cancer is a potentially life-threatening illness where important decisions are made at key points in the disease process. It is important for children’s psychological welfare that they are allowed a role in decision making. Children with cancer generally prefer to be involved in decision making (Siegenga 2008; Zwaanswijk 2007) and want to have the opportunity to take part in decisions concerning their healthcare, even in end-of-life decisions (Hinds 2001). International Society of Paediatric Oncology (SIOP) encourages doctors to share developmentally relevant information with children that will improve their ability to participate in the decision making process (Spinitta 2003). Despite increasing interest in children’s participation in decision making, most research studies are essentially descriptive in nature, are mainly focused on proxy decision making by parents or health professionals and do not provide information about what interventions promote children’s participation in SDM.

**Methods:** To examine the effects of interventions for promoting shared decision making (SDM) for children with cancer who are aged 4–18 years. Systematic Cochrane review of randomised controlled trials (RCTs) of SDM interventions for children with cancer from 1980 to 2011. The types of decisions included: treatment, healthcare and research participation decisions. The primary outcome was shared decision making as measured with any validated scale.

**Results:** Two review authors undertook the searches, and three authors independently assessed trial quality and extracted data. We contacted study authors for additional information. The reviewers identified 4477 potentially relevant documents, of which 4171 we excluded by reviewing titles and abstracts. Of the remainder, we retrieved 18 full publications for more detailed screening. None of these studies met inclusion criteria, and hence no analysis could be undertaken.

**Conclusion:** This review has highlighted the dearth of high quality quantitative research on interventions to promote participation in shared decision-making for children with cancer.

**References**


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**PS031**

**PREVALENCE OF GRANDPARENTAL DISTRESS, SUPPORT SERVICE USAGE AND BARRIERS TO ACCESS: A COMPARISON OF GRANDPARENTS OF CHILDREN WITH CANCER AND MATCHED CONTROLS**

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**Purpose:** Positive grandparental relationships can be protective for families faced with a traumatic event, however grandparents may be forgotten caregivers in pediatric oncology. This study assessed the prevalence of distress, support service usage and barriers in grandparents of children with cancer, compared with age, gender and rurally-matched grandparents of healthy children.

**Methods:** Grandparents completed self-report questionnaires assessing four predictors (distress, anxiety, depression, anger) and one outcome (‘need for help’) (validated Emotion Thermometers Tool); support service usage and barriers to access.

**Results:** 197 grandparents participated (76 in the cancer group; 121 controls; mean age = 65.76 years (SD = 7.05), 33% male). Grandparents of children with cancer reported significantly higher levels of clinically relevant distress (34.2% versus 13.2%; p = 0.001), anxiety (52.1% versus 21.5%; p < 0.001), depression (26% versus 5%; p < 0.001) and anger (23.6% versus 6.7%; p = 0.001). They also reported a greater need for help (14.1% versus 3.4%; p = 0.006). After controlling for group, gender and age, depression, anxiety and anger were significant predictors of need for help (R² = 0.446%, p < 0.001).

Grandparents of children with cancer were more likely to utilize support (71.1% versus 40.8%; p < 0.001), however formal psychosocial support was rarely accessed (<3%). Grandparents of children with cancer were more likely to find support in church/religious groups than staff (relative risk 3.3%; p = 0.002), and were also more likely to report that they did not know how to access support when needed (p = 0.010) and that their concerns were ‘too private to share’ (p = 0.048).

**Conclusion:** Grandparents of children with cancer are more distressed, and are in greater need of help, than the norm. Their capacity to support their families may be limited by their own, untreated, distress. While anxiety is most prevalent, depression and anger are also important targets, given their relationship with need. Grandparents rarely access evidence-based psychosocial support, possibly due to lack of information and privacy concerns.

**References**

THE LONG-TERM CONSEQUENCES OF UNRESOLVED GRIEF IN YOUNG ABDULT SIBLINGS WHO HAVE LOST A BROTHER OR SISTER TO CANCER

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Purpose: This study examined unresolved grief and its associated long-term effects on psychological health, in young adult siblings 2–9 years after losing a brother or sister to cancer. It was hypothesized that siblings with unresolved grief would have more psychological problems than siblings with resolved grief.

Methods: In a Swedish population-based cross-sectional study of young adult siblings, who between 2000 and 2007 had lost a brother or sister to cancer, 174 (73%) of 240 eligible siblings completed a study-specific questionnaire.

Results: Of 174 siblings, 92 (54%) reported not have resolved their grief. Neither gender was any more or less likely to have resolved their grief. However, female siblings with unresolved grief reported more symptoms of anxiety (P = .001) and depression (P = .001), worse psychological well-being (P < .001), and poorer quality of life (P = .001) than female siblings with resolved grief. They were also more likely to have sleeping difficulties (RR, 2.5; 95% Confidence Interval, 1.1–5.7). Among male siblings, those with or without resolved grief only differed with regards to psychological well-being (P = .02).

Conclusion: The majority of bereaved siblings reported not having resolved their grief several years after the loss of a brother or sister to cancer. The siblings with unresolved grief reported more psychological health related problems, than those who had resolved their grief. A tentative conclusion is that female siblings with unresolved grief are more emotionally distressed than male siblings.

P0033

PEDIATRIC PATIENTS’ WITH CANCER AND PARENTS’ OPINIONS ABOUT THE PAIN THEY SUFFERED DURING THE HOSPITALIZATION AND THE IMPACT OF PAIN UPON PARENTS’ QUALITY OF LIFE

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Purpose/Introduction

Pain is a major problem during children’s and adolescents’ hospitalization. It is estimated that almost 15–20% of the pediatric patients suffer from chronic pain during their hospitalization. The aim of the study was to report and assess pediatric and parental opinions about the pain the pediatric patients suffer during their hospitalization, as well as the impact of that pain upon parents’ quality of life.

Methods/Material

The sample of the study consisted of 92 pediatric patients with cancer and one of their parents. The Pediatric Pain Questionnaire (Parent Version) and the PedsQL-Family Impact Module (PedsQL-FIM) were used for the assessment of pain and the quality of life by the parents. Children and adolescents completed the pediatric version of the Pediatric Pain Questionnaire for the evaluation of pediatric pain.

Results:

The mean age of the children was 6.80 ± 4.31 years. The PedsQL-FIM was found to be a reliable tool for assessing patients’ quality of life (α = 0.94). The mean score for the PedsQL-FIM was 54.39 ± 17.24, the mean score for Health Related Quality of Life (HRQoL) was 55.61 ± 19.70 and the mean score for Family Functioning (FF) was 59.41 ± 22.04. No demographic factor was found to be statistically significant on the PedsQL-FIM scores. Moderate to high correlations were found on HRQoL mean scores, FF mean scores and total mean scores of PedsQL-FIM (r = 0.54 to 0.93, p < 0.000). Parents tended to overestimate their children’s acute and chronic pain, although no statistically significance was reported (acute pain: z = −1.29, p = 0.20; chronic pain: z = −1.40, p = 0.17). There were also positive high correlations on acute and chronic pain reported by children and parents (acute pain: Spearman’s rho = 0.48, ICC = 0.73, p = 0.00; chronic pain: Spearman’s rho = 0.53, ICC = 0.55, p = 0.00).

Conclusion: The PedsQL-FIM appears to be a suitable tool for measuring parental self-reported health related quality of life and family functioning in pediatric chronic pain. Children reported less acute and chronic pain than their parents. High correlations of the patient/parent responses strongly imply that relevant information might be obtainable through parents when children are unable to assess their pain.
As nurses, we intend to provide parents with enough skills prior to their child’s first discharge, to prevent potential complications. Our education program lasts three hours and potentially irrational, displeasure with his initial decision? 
Conclusion: Nursing adolescents presents real challenges. They need interest shown in what their lifestyles, impact of cancer on their daily living, and risky sexual behaviour. All of those interviewed felt angry and were in denial about their illness. Factors relating to side effects of treatment were expressed by 73% of teenagers and included stress, anger, denial and withdrawal symptoms. Twenty percent were stigmatised by their peer group. Lack of family support predominated with only 18% having support. Cultural and religious beliefs including witchcraft, holy oil and Jehovah Witness played a role in different ways. Their “I don’t care” attitude and conflict with the hospital were also contributing factors. Twenty percent were angry with their parents due to a genetic factor, and a small number had anger due to their HIV status. Education was affected in 80%. Only 9% were sexually active, but fear and anger were expressed on minimisation of their ability to procreate. Risky behaviour and non-compliance occurred.

Conclusion: Nursing adolescents presents real challenges. They need interest shown in what they say or do as well as assistance with grieving. Adolescents are still young and need lots of positive feedback, compliments and affection from the nursing personnel. Hopefully a time will come when they can move on and love happily again.

RESULTS: Preoperatively, the patient’s mother favored amputation, but deferred to her son’s desire to have a “normal appearing” leg with an allograft reconstruction. Both individuals declined the opportunity to have undergone one of the surgical options. Confusion regarding his recovery and functional expectations after the limb-sparing procedure resulted in the patient’s request for an elective, non-inoculated amputation. The institutional ethics committee was consulted to address the following issues: (1) Should an amputation be performed on an elective basis without medical indication, given the risks of surgery and delay in chemotherapy, as well as the irreversible disfigurement from an amputation? (2) Was the patient’s request to change surgical treatments a result of a transient, and potentially irrational, displeasure with his initial decision?

Conclusion: Adolescents’ involvement in their medical care decision making demonstrates respect for their autonomy and promotes engagement and cooperation with the treatment plan. Effective measures for assessing adolescent maturity and medical decision-making competency are needed.

IMPACT OF CANCER ON TEENAGERS AND CHALLENGES ON NURSES

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Purpose: The focus of this study is the impact of cancer on teenagers, the outcome thereof, as well as the challenges facing nurses working with them.

Methods: The study was undertaken during 2010 through interviews with patients on the ward as well as folder reviews. Information pertaining to sexual activity, lifestyle and impact of cancer on their daily living was obtained. Confidentiality was maintained at all times.

Results: Thirty-two teenagers, 53% male and 47% female, were interviewed, focusing on their lifestyles, impact of cancer on their daily living, and risky sexual behaviour. All of the interviewed teenagers felt angry and were in denial about their illness. Factors relating to side effects of treatment were expressed by 73% of teenagers and included stress, anger, denial and withdrawal symptoms. Twenty percent were stigmatised by their peer group. Lack of family support predominated with only 18% having support. Cultural and religious beliefs including witchcraft, holy oil and Jehovah Witness played a role in different ways. Their “I don’t care” attitude and conflict with the hospital were also contributing factors. Twenty percent were angry with their parents due to a genetic factor, and a small number had anger due to their HIV status. Education was affected in 80%. Only 9% were sexually active, but fear and anger were expressed on minimisation of their ability to procreate. Risky behaviour and non-compliance occurred.

Conclusion: Nursing adolescents presents real challenges. They need interest shown in what they say or do as well as assistance with grieving. Adolescents are still young and need lots of positive feedback, compliments and affection from the nursing personnel. Hopefully a time will come when they can move on and love happily again.

SCHOOL FOR PARENTS: EXPERIENCE FROM A PEDIATRIC ONCOLOGY UNIT

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Purpose: The diagnosis of cancer in a child or teenager causes a great impact on the whole family, because it represents an important change on family stability. Parents will receive a wealth of information in a very short time therefore confusion and overwhelm is a common feeling. The lack of knowledge about cancer and all the child increases the insecurity feelings. For this reason, developing an educational program for parents appears potentially useful in order to teach families how they can support their child at home. Understanding illness might help decrease anxiety.

Methods: As nurses, we intend to provide parents with enough skills prior to their child’s first discharge, to prevent potential complications. Our education program lasts three hours and it’s organised in small meeting groups (parents and one nurse). Parents not only have enough time to express doubts, worries or feelings, but also have the opportunity of sharing all of this with other participants.

Results: Educational program contents include: port-a-cath care, early warning signs of chemotherapy side-effects, what to do in emergency situations, tips of hygiene, dietary advices, suggestions about how to deal with child behaviour and feelings, and practical management of G-CSF shots. Moreover, educational program’s supplies include: written material, CD with all the information and helpful samples, like moisturizing creams or mouthwash rinses.

Conclusion: Each family, whose child is diagnosed in our hospital, attended the educational program. From our experience, the level parents’ knowledge about the cancer disease, its care and prevention of complications improved after receiving the education program. The parents showed a high degree of satisfaction at the end of the education program. We try to evaluate the incidence of complications in the group of children whose parents received our education program.

MEASURING QUALITY IN CHILDREN AND YOUNG PEOPLES CANCER CARE: FOUNDATION ONCOLOGY SKILLS PROGRAMME DEVELOPMENT

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Purpose: To develop and evaluate a foundation oncology skills training programme for children and young people’s cancer nurses. In 2005, guidelines to improve outcomes for children and young people were introduced in the UK. In 2008, measures to assess the quality of provision were implemented and a programme of assessment for all children and YP cancer services was launched. All UK centres undergo a peer review process evaluating service provision against these measures. Although a key focus of the guidelines and measures was training of nursing staff, including the identification of 2 training levels, a review of London centres found a lack of consistent foundation level training.

Methods: Mixed methods evaluation including; an action research education development group to design the content of the training; pilot testing of the programme with nursing staff from Principal treatment centres; survey evaluation of programme with mixed nursing groups from principal treatment centres and shared care units.

Results: A pilot of 23 nurses across North and South London, found nurses reported the course enabled them to link clinical practice closely with theory/biology, and piece together fragmented knowledge. Evaluations from the courses since have shown a 100% record of achieving personal learning objectives. In particular, staff have stated it helps to “fill in the gaps when the patients are not in their centre.”

Conclusion: There is a demonstrable need for accessible foundation skills training within PTC & POSCU’s across the UK. In this project a course devised for the local workforce was taken up by over 300 nurses. Foundation skills training is effective in enabling services to meet Cancer measures. There remains a future requirement to evaluate with patient input, whether the training has had an impact on quality of care, and to survey more senior staff who sent nurses, to assess any impact they feel the course has had.

REFERENCES


CHILDREN’S CANCER NURSES’ EXPERIENCES OF PROVIDING PALLIATIVE CARE IN THE ACUTE HOSPITAL SETTING

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Purpose: Children’s palliative care is rarely hospital centred, but typically provided at home, with support from a paediatric oncology outreach nurse specialist (Hamman & Gibson 2005). Consequently, palliative care in the acute hospital setting is diluted which negatively impacts on nurses’ ability to learn and develop. Given the limited experience do nurses possess the right knowledge, skills, training and support to enable them to deliver effective patient care to these children? The study was undertaken to help inform supervision, education and palliative care strategies to support nurses in meeting the needs of children requiring palliative care.

Methods: Data were captured through semi-structured interviews. Four children’s oncology primary treatment centres across the UK were invited to participate of which three centres consisting of 7 participants accepted. Informed written consent was obtained. The study gained NHS ethical approval. Grounded theory was used to analysis the data.

Results: Limited exposure caring for this patient group resulted in participants feeling nervous and scared at the unknown in relation to symptoms management and how to give effective patient care. Participants felt due to having limited experience in providing palliative care this impacted on the support they gave to the family due to not knowing how to manage the symptoms. The relationship with the family impacted on how they delivered psychological support. Good team work and support enabled participants to provide better care as they were able to ask for help. None of the participants have had further training in palliative care since they qualified and participants expressed little training and education at a pre-registration level.

Conclusion: Participants have had limited exposure in providing palliative care which is most likely due to the advances is supporting families within the community. A lack of
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training at pre-registration level and continuing professional development has resulted in participants lacking knowledge in delivering palliative care.

References

PU007
LIVING AN EVERYDAY LIFE SHADED WITH TRACES FROM THE CANCER TRAJECTORY - FAMILIES’ LIVED EXPERIENCES IN A SIX YEAR FOLLOW UP

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Purpose: The aim of the study was to illuminate families’ lived experiences of having a child within the family surviving a minimum of six years after completing childhood cancer treatment.

Methods: This study is a part of an inductive and longitudinal research project about family members’ experiences of childhood cancer. Seventeen families with a child diagnosed with childhood cancer were followed during their child’s cancer trajectory. Inclusion criteria for taking part in the six years follow up was that the survivor had not had any relapses and was feeling well. Nine families were eligible and five of these declined to participate.

Results: Conversational interviews were performed with four mothers, three fathers, three siblings and three children from a total of four families. The interviews were analyzed with a hermeneutical phenomenological approach.

Conclusion: The preliminary results reveal that family members still feel vulnerable even if a long period of time has passed since completion of treatment. In varied degrees they even now need support. To be able to move forward in life, the family members are helped if they can reconcile with their memories and experiences deriving from the childhood cancer trajectory.

PU008
REWARDS AND CHALLENGES OF NURSES WORKING IN A DEVELOPING COUNTRY: WHAT DOES IT TAKE?

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Purpose: Cancer is emerging as a major cause of childhood death in developing regions of the world as the treatments for diarrhea, malaria, infection and malnutrition have improved. Collaborative efforts/twinning partnerships have been established to impact the survival of childhood cancer. The purpose of this presentation is to explore the role of the volunteer nurse, providing guidelines and practical advice to nurses who are interested in working in developing countries.

Methods: Key questions should be asked by any volunteer nurse (1) What are the goals and history of the project, (2) What will be your role (observing, participating, networking) once in-country and post visit, (3) How do you set realistic expectations and (4) How do you prepare for the trip? Answers to these questions will be explored using examples from SIOP nurses’ experiences partnering with twinning projects throughout different regions of the world. These projects demonstrate how to effectively work beyond your boundaries.

Results: Working beyond the borders of your country provides both rewards and challenges to even the most experienced oncology nurse. Confidence in nursing care, problem-solving skills, cultural sensitivity, organizational ability and political awareness are specific attributes that will lead to success. “Having what it takes” to work in developing countries requires being open-minded, flexible, ethical and a team player. The nurse must continually assess and re-evaluate these issues throughout all phases of the project.

Conclusion: Sustainability, daily observations, detailed documentation and applying practical clinical wisdom are some of the valuable lessons learned by volunteer nurses. As we partner with our nursing colleagues throughout the developing world, we have much to learn from each other. The impact from oncology nurses’ contributions to the care of children with cancer and their families is huge; however, it is the small and critical steps that build and establish practice models across the globe.

PU009
ENTERAL FEEDING-DOES IT HAVE A PLACE IN ADVANCED CANCER?

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Purpose: The law regards withholding and withdrawing treatment as the same. Food and drink by mouth is regarded as basic care and feeding by artificial means as a medical treatment. Few studies have examined the impact of medically assisted nutrition on survival or quality of life in palliative care. In the cancer population hunger is not a symptom often expressed during palliation. However children and young people (CYP) diagnosed with a diffuse pontine glioma often express hunger as a symptom; when their swallow becomes unsafe due to the progressive nature of their brain stem disease. In meeting the needs of this patient population our service supports insertion of a Naso Gastric Tube (NGT) to maintain hydration, relieve hunger and meet parental need to promote the best quality of life be maintained for the time the child and family has.

Methods: Retrospective data from over 12 years of patients diagnosed with a diffuse pontine glioma who died from the progressive nature of their disease will be presented. This data consists of 41 children and young people and will demonstrate our experience of use of artificial (naso gastric tube) feeding for symptom management within this population.

Results: 41 CYP died from their advanced Diffuse Intrinsic Pontine Glioma over the 12 years. 33 CYP had a NGT inserted, 8 CYP did not have a NGT inserted and it was unknown if 2 CYP had a NGT inserted during their palliative and end of life care.

Conclusion: To raise awareness of this small but significant group of children and young people and their symptom needs. To highlight professional complexity in supporting this patient population. This may have implications for those young adults who have a paediatric brain stem lesion receiving palliative and end of life care within an adult setting.

References

PU010
INDEPENDENT NON MEDICAL PRESCRIBING PRACTICE WITHIN A MULTIDISCIPLINARY TEAM OF ONE UK TERTIARY CHILDREN'S CANCER CENTRE

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Purpose: Clinical governance is “A framework through which NHS organisations are accountable for continuously improving the quality of their services and safeguarding high standards of care by creating an environment in which excellence in clinical care will flourish”. Independent non-medical prescribing practice has increased in the United Kingdom which had led to improvement in the patient experience.

Methods: In our tertiary children’s cancer centre we have developed and encouraged the expanded role of non-medical prescribing to enhance the quality of the paediatric pain service offered. The paediatric pain service provides inpatient, day-care and outreach support for children with cancer on treatment (receiving radiotherapy and chemotherapy). off treatment (with chronic pain issues) and in the palliative care setting. The prescribers within the Multi Disciplinary Team (MDT) include a paediatrician, children’s nurse and a paediatric pharmacist that bring together the perspective and experience of each individual discipline.

Conclusion: Awareness of the advantages/challenge to this approach. (1) understanding of the MDT approach to prescribing practice, (2) Current prescribing practice in a palliative care setting, (3) Limitation of independent non-medical prescribing practice in palliative care practice.

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PU011
CLINC SARGENT PAEDIATRIC ONCOLOGY SPECIALIST NURSE KEY WORKER PROJECT

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Purpose: To establish a potential model for Key Working in Paediatric Oncology which will allow survivors of childhood cancer to have improved emotional wellbeing, and that they are better able to participate in education, employment and training, at no additional cost to public service provision.

Methods: A total of 23 specialist nurse keyworker posts have been introduced between October 2010 and April 2011 in 18 Principal Treatment Centres across the UK. The project...
supports the implementation of the Improving Outcomes in Children and Young People with Cancer and the associated Children’s Cancer Measures. Independent evaluation of the project is being undertaken by London South Bank University, and is funded by NCIAT for cancer service in England.

Results: Initial data have been collected and analysed with regards to whether the following outcomes have been achieved as a result of nursing key worker support: (1) There is a benefit to patient and family experience of services. (2) Children and their families have improved emotional wellbeing and greater participation in education, employment and training. (3) Children and their families are able to spend more time safely at home during treatment where appropriate.

Conclusion: The study is on-going with data collection planned for between October 2010 and April 2015.

References

PU012
HOSPITAL-BASED HOME CARE FOR CHILDREN WITH CANCER – A QUALITATIVE EXPLORATION OF FAMILY MEMBERS’ EXPERIENCES IN DENMARK
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Purpose: The purpose of the study was to describe family members’ experiences of a hospital-based home care programme for children with cancer.

Methods: A purposeful sample of 12 families was selected to capture a wide range of experiences and differences among the families, e.g. the children’s diagnosis, family constellation, parents’ occupation, number of home care visits, and the duration of the participation in the home care programme. Fourteen parents representing 12 families were approached for interviews about their experiences. The parents decided whether both of the parents, the child, or the siblings would participate in the interview. This study was a part of a larger research project including a hospital-based home care programme and all interviews were conducted during the programme period at a time and place in accordance with the families’ wishes. The transcribed text from the interviews was analysed using qualitative content analysis.

Results: Two of the 12 families declined to participate because they felt overwhelmed by the burden the disease put on their family, thus 10 parents representing 10 families were interviewed. Five children participated in all or part of the interview. The findings indicate that hospital-based home care supports the families throughout the course of treatment by decreasing the strain on the family and their ill child, maintaining normality and an everyday life, and fulfilling the need for safety.

Conclusion: Hospital-based home care appears to support the families’ and the individuals’ perceived needs to maintain family functions while at the same time alleviating the perceived distress. The study highlights the importance of providing hospital-based home care in accordance with the family members’ need for the sense of safety by using experienced paediatric oncology nurses, and scheduling regular hospital visits and appointments with the paediatric oncologist.

PU013
adolescent and young adult views of daily life five years after a childhood cancer diagnosis
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Purpose: The aim of the study was to investigate adolescents’ and young adults’ views of what influence an experience of childhood cancer has on daily life five years after diagnosis.

Methods: In a cross-sectional design, a Swedish national cohort of 61 (response rate 86%) adolescents and young adults (ages 12–22 years) were interviewed a median of five years after start of initial treatment for childhood cancer. Semi-structured telephone interviews were performed based on an interview guide covering the following areas: current life situation, school situation/occupation, leisure and relation to friends. Interviews were recorded, transcribed verbatim and analysed using qualitative content analysis.

Results: Three overarching views on daily life were identified: Feeling different, the cancer experience has great influence on daily life such as often thinking back on the illness experience and presence of complications that limited activity (13%); Feeling almost like others, the cancer experience has left some persisting limitations but these appeared to be manageable (61%); Feeling like anyone else, the cancer experience has almost no influence on daily life (26%).

Conclusion: In line with previous reports, the findings show that cancer during childhood to a varying extent influences adolescents’ and young adults’ daily life a median of five years after diagnosis. Although participants most often viewed that life to some extent was influenced by the cancer experience, most of them appeared to get along well with their lives. However, the results also indicate that those reporting great influence on daily life should be offered targeted support and interventions.

PU014
important needs in care situations for teenagers and young adult cancer patients
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Purpose: The purpose of this study is to explore the needs of the teenagers and young adults (TYA) in care situations. The overall aim of this project is to highlight issues that are important to the TYA patient in order to develop a questionnaire based on these issues.

Methods: The chosen method for this study is focus group interviews and personal interviews with former cancer patients. The inclusion criteria for participants were patients who finished treatment and had a maximum of three years from the end of treatment. Participants were between 15 and 29 years when treated. Participants were recruited from university hospitals in Sweden. In every focus group there were a number of 2 and 6 participants. The interviews were recorded, transcribed into text and analyzed through content analysis.

Results: The preliminary results of the focus group discussion are as follows. Every TYA needs to be seen as an individual person during treatment. The health care professionals need to accommodate each individual TYA to their needs. One of the issues addressed by TYAs was that information on sex and fertility will have to be routinely delivered by health care professionals.

Conclusion: The issues addressed by TYA cancer patients can give health care professionals tools to improve the care. The result from this study will be used to develop a questionnaire for TYAs cancer patients.

PU015
sense of coherence over time for families with a child diagnosed with cancer
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Purpose: The aim of this study was to describe sense of coherence over time in a sample of parents with a child newly diagnosed with cancer.

Methods: The Swedish version of SOC (29 items) was used to measure the parents’ (n = 29) sense of coherence. Data were collected at four time-points: Time-point 1 at the time of diagnosis; time-point 2 during the treatment; time-point 3 after the child had completed their treatment and time-point 4 when the child had been off treatment for some years or had died.

Results: The results showed that SOC in the investigated population is not stable over time. The parents decreased in total SOC score between time-points 1, 2 and 3. Mothers had significantly weaker total SOC score including the components Manageability and Meaningfulness at time-points 1 as well time-point 2 compared to the fathers. However, no significant differences were shown between mothers and fathers concerning the component Comprehensibility.

Conclusion: This study found that parents’ SOC scores change over time when they have a child that is diagnosed with cancer. As the pattern in these changes varies between mothers and fathers during their child’s cancer trajectory, they may have different support needs.

PU016
a survey of stress resources among parents of critically ill children in pediatric oncology ward
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Purpose: Pediatric oncology ward has long been recognized as an emotionally changed & highly stressful place. Admission of a child to the oncology ward may be one of the most stressful events for parents, because the outcome is often uncertain, the procedures are often
painful and intense emotion of anxiety, sadness & anger are in constant flux. Therefore this study was done to determine stress resouces of parents in pediatric oncology ward.

Methods: A descriptive cross sectional study was carried out by using data obtained through "parental stressor scale" (POI) to examine sources of stress among parents. A convenience sample of 25 parents whose child had recently admitted to pediatric oncology ward were subjects for study. Demographic data were collected using an investigator designed questionnaire. The stress was measured with parental stressor scale. PS scale is a 37 item instrument in 7 subscales that uses a likert to measure sources of parental stress in pediatric oncology ward.

Results: After measurement of stress in parents with PS result revealed that in a comparison of means score on the 7 dimensions of the PS parent found the "Alteration in parental role" to be the greatest source of their stress (3.74 ± 0.61) and the second highest ranking stressor was a "Not knowing to what extent " (3.56 ± 0.70).

Conclusion: Our result suggests the need to prepare parents for role alteration when a child is admitted to pediatric oncology ward. They should also be encouraged to participate in the child’s care and provides comfort measures. We need to consider creating spaces that not only address family needs to remain present with their child, but also creating situations for parents to partner in decision making, information sharing and care planning.

PW001

NURSES AS STAKEHOLDERS AND PARTICIPANTS IN THE DEVELOPMENT OF A DATA MANAGEMENT SYSTEM FOR HEMATOLOGY/ONCOLOGY: LESSONS FROM A TERTIARY CARE INSTITUTION IN ETHIOPIA

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Purpose: High-quality clinical data management is essential for delivering effective cancer care and monitoring care and outcomes. We report our experience establishing systems to improve documentation and collect data in adult and pediatric hematology/oncology at Tikur Anbessa Hospital (TAH), Addis Ababa, Ethiopia.

Methods: Over six weeks, an initiative was undertaken by the Georgetown University/INCTR twinning program at TAH to develop a data management platform for adult and pediatric hematology/oncology. Multidisciplinary participation in process improvement and shared decision-making were central to our approach. Nurses from both units were integral to the team that worked to develop data collection tools and an electronic database, and establish the data manager role. Current clinical practices were observed and input was solicited from stakeholders. We sought to identify best data management practices at TAH. Individuals from NICU and Pediatrics ART were interviewed on their chart documentation and data collection strategies. Discussions were initiated with hematology/oncology departments on clinical data management; best practices were shared and new ideas elicited. Recommendations were presented, which included use of Clinical Shadow Charts, a Patient Registry and the Pediatric Oncology Networked Database (POND). Data collection tools captured demographic information, baseline clinical data, and longitudinal data on treatment, care and outcomes. We conducted an interactive workshop, during which interdisciplinary teams (18 physicians/residents and nurses) evaluated tools by analyzing data fields and inputting data from charts. The Director of the Clinical Trials office (a nurse) at INCTR-Brussels reviewed the proposed tools and data management plan and made recommendations based on past experiences.

Results: The outcome and current status of this initiative will be presented as well as continuing efforts by the nursing staff to address data collection.

Conclusion: Our experience has shown multidisciplinary engagement with active nurse involvement can be a useful strategy for improving clinical documentation and integrating systematic data collection into clinical practice.

SURGERY (IPSO)

PW002

POSTOPERATIVE INTUSSUSCEPTION IN PEDIATRIC ABDOMINAL MALIGNANCIES: A RARE FORGOTTEN CAUSE OF EARLY POSTOPERATIVE INTESTINAL OBSTRUCTION

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Purpose: The aim of this study was to review the incidence of postoperative intussusception (POI) in our patients with pediatric abdominal malignancies and the end result of management of these cases.

Methods: From Nov. 2007 till the end of April 2011 a total of 429 patients with different abdominal malignancies were operated upon by laparotomies in our hospital. Reoperations were required in 10 patients for post operative intestinal obstruction developed in the 1st postoperative month. Review of the identified cases focused on patient’s characteristics, tumor type, the primary surgical procedure, clinical and imaging features of the intussusceptions, timing and findings at the 2nd laparotomy and the end result of subsequent interventions.

Results: Early post operative intestinal obstruction (within 1 month) developed in 10 patients of whom 7 patients had POI. Four patients had adhesive intestinal obstruction (1 patient developed both). The median duration between the primary surgery and the onset of intestinal obstruction symptoms was 4 days in the POI group and 24 days in the adhesion group. Abdominal CT was done in all cases and it could properly diagnose POI and detect its site in the POI group while in the adhesion group it showed evidence of complete obstruction. Plain radiograph failed to detect signs of intestinal obstruction in 2 cases (one in each group). In POI group simple reduction was done in 6 cases while resection anastomosis was done in 1 case due to gangrene of the ileocecal region. Adhesiolysis was done in the 4 cases of intestinal adhesion group.

Conclusion: Early POI in pediatric abdominal cancer is a rare complication. Early diagnosis and intervention is essential for successful management. Abdominal CT is very helpful as it can detect the level and possible cause of obstruction.

PW003

DIDACTIC INTERACTIVE MULTIMEDIA “PEDIATRIC SURGICAL ONCOLOGY”

Andrés José Pi Onorcia1, MSc. Vilma Lopez Merino2, Ricardo Cabanas Armada2, Multidisciplinary Team for the Integral Treatment of Children and Adolescents with Cancer

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Purpose: To contribute to the educational needs of pediatric surgeons and the professionals related with children and adolescents health care.

Methods: By means of an attractive user interface, hyperlinks, videos and surgeries in real time, gallery of pictures, charts and diagrams, our Multimedia fulfills didactic objectives. The statistics showed are according to the National Register of Cancer. The informatics programs and licenses by CITMATEL.

Results: This Multimedia consists of five chapters: “Generalities” is about the history of General and Pediatric Oncology and Oncology Surgery synthesized up to now, both international and in Cuba. It also deals with statistics of each area, survival on the National Program and the main concepts. We clearly and accurately approach the criteria and principles of Pediatric Oncology Surgery, the main achievements, challenges and present difficulties and also our concept of Rescue Surgery in cancer. “The most important Tumors” deals it Renal Tumors, Embryonal Tumors, Neuroblastoma, Rhabdomyosarcoma, Burkitt lymphoma, Rhabdomyosarcoma, Thymus Tumours, Metastatic Tumors, among other topics with a comprehensive and up dated approach where we present our selection criteria for surgery treatment based on the cost-benefits-risk balance within the general treatment program, according to the approved surgical protocols. “Emergencies”. “Can cancer be cured?” deals with criteria about prognostic, diagnosis and life quality. “The family” is
about the impact on each members of the family, since the diagnosis to the cure or death and the behavior of the family health staffs. 

Conclusion: Pediatric cancer in Cuba represents 2% of all the annual cancer. However, this low incidence is a health problem with a serious impact on the family, health workers and society. This Multimedia is mainly addressed to Paediatric Surgeons as ones in charged of one of the treatment modalities. It has been validated by the Cuban Society of Pediatric Surgery.

**PW004**

**ADRENAL TUMORS IN CHILDREN**

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**Purpose:** Pediatric adrenocortical tumours (ACTs) are rare. We reviewed findings in 8 children. 18 years of age or younger, di-agrossed with ACT in our institution over the past 15 years.

**Methods:** We retrospectively reviewed 8 children with ACTs treated between 1996 and 2010.

**Results:** Three girls and 5 boys were treated for ACTs; their median age at presentation was 14 months (range, 28 months to 18 years). Seven patients showed signs of endocrine dysfunction, 4 with Cushing syndrome, 2 with virilization, and 1 with hyperadrenosteronism. One patient, with symptoms of hemarrhia, underwent a computed tomograpy scan, which showed an adrenal mass. The median duration of symptoms prior to resection was 6 months (range, 1 to 24 months). Five patients had adrenomas and 3 had carcinomas. All underwent complete resection of the tumor, with laparoscopic adrenalectomy performed on 3 patients with adrena and 1 with carcinoma. The median tumor weight was 12.5g (range, 1 to 130g) and the median tumor volume was 18.3cml (range, 2.2 to 299.3cml). At a median follow-up of 5.1 years (range, 4 months to 15 years), all 8 patients remain alive with no recurrence of disease.

**Conclusion:** The characteristics of pediatric ACTs vary considerably. Laboratory findings, clinical hormonal features, and tumor size could not distinguish adrenomas from carcinomas before surgery. Complete tumor resection was successful, with no tumor recurrence. However, the small number of patients and short follow-up period limit assessments of prognosis.

**PW005**

**CATHETER-RELATED INFECTIONS AND CATHETER THROMBOSIS IN CHILDREN WITH CANCER**

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**Purpose:** A long-term use of venous port systems essential in the treatment of child cancer patients is only possible with providing appropriate maintenance and care.

**Methods:** July 2010–March 2012 we observed 217 child cancer patients (6 months–17 years). 97 were implanted subcutaneous venous port-systems. 120 were introduced subclavian catheters. The following criteria were evaluated: local manifestations of infection, clinical manifestations of infection, and clinical manifestations of thrombosis. Of the patients implanted with subcutaneous ports, port-related bloodstream infections were noted. Port catheter thrombosis was observed in 7 cases (7.2%). In patients with subclavian catheters, puncture site infection was noted in 73 cases (60.8%). The development of catheter-related bloodstream infections was noted in 15 cases (12.5%). Catheter thrombosis was observed in 44 cases (36.6%). In cases of port thrombosis, we injected the system with a 25,000 IU dose of Urokinase with an exposure of 15 minutes. The treatment of 32 cases (72.7%) of the 44 occurrences of subclavian catheter thrombosis necessitated replacement under general anesthesia. To seal the catheter between courses of treatment, we used heparin or a solution containing cyclotaurolidin (when using which no catheter-related bloodstream infections were noted).

**Results:** All venous ports have worked satisfactorily. All cases of thrombosis of venous port systems were successfully treated.

Conclusion: The use of a cyclotaurolidin solution to seal the venous system between usage prevents infection. The treatment of catheter-related infections is better effected by a combination of cyclotaurolidin and urokinase, which provides lysis of the microtrombs and prevents infection. The treatment of catheter-related infections is better effected by a combination of cyclotaurolidin and urokinase, which provides lysis of the microtrombs and prevents infection. The treatment of catheter-related thrombosis of the neck, lymph nodes or lateral trigonum of the neck were found out 104 (62.7%), in an average line in 74 (44.6%). Metastases to lungs have been found initially in 14 (8.4%) and during dynamic supervision already in 40 (24.1%) patients. In 118 children FTC (1999–2011): metastases to lymphnodes or lateral trigonum of the neck were found out 92 (78%), in an average line in at 99 (84%). Metastases in lungs have been revealed initially in 11 (9%) and during dynamic supervision already in 43 (36%) patients. In 15 children FTC (from 1971 to 1986): metastases to lymphnodes or lateral trigonum of the neck were found out 1 (0.6%), in an average line in 1 (0.6%), metastases in lungs have been found in 1 (0.6%) patient. In 30 children FTC (1986–2011): metastases to lymphnodes of the neck and metastases to lungs were not cases. We found three cases of insular variant FTC (1986–2011), only in one case were metastases in the soft tissue of the neck and lymphnodes after 4–6 month after primary operation.

**Conclusion:** Treatment FTC needs to be aggressive (thyroidectomiy as tumor more than 1 sm. in diameter, radical operation on a lymphatic collector of a neck, radioiodotherapy, suppressive hormonal therapy). Treatment of FTC does not have to be aggressive (hemithyroidectomy, thyroidectomy).

**PW007**

**TREATMENT STRATEGY OF VAGINAL ENDODERMAL SINUS TUMOR - EXPERIENCE OF A SINGLE CENTER**

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**Purpose:** To evaluate the treatment modality for vaginal endodermal sinus tumor, exclusively with chemotherapy or combined with surgery/[Methods:] From October 2001 to October 2011, 18 cases of vaginal endodermal sinus tumor were enrolled. The age on diagnosis ranged from 6 months to 21 months. The most common symptoms were bloody excretion in vagina. All cases showed elevated alpha fetal protein. The diagnosis was determined by pathology in 16 cases and by clinical features in 2 cases. There was no metastasis to lung but to retroperitoneal lymph nodes in one case. The treatment and outcome were retrospectively analyzed.

**Results:** The primary treatment was chemotherapy. The protocol was VAC in one case and PEB in 17 cases. After 4 cycles, 8 cases reached CR and 10 cases PR. The 8 cases with CR finished consistent chemotherapy for 8 to 10 cycles. They were followed up for 6 months to 8 years and without recurrence. 8 of the 10 cases with PR underwent surgical removal, followed by adjuvant chemotherapy for 6 to 8 cycles. 2 of 10 cases with PR went on chemotherapy and reached CR after 6 and 8 cycles of chemotherapy. However, they found recurrence after 17 months respectively after finishing treatment. Later on they accept surgery to remove the tumor tissue and followed by chemotherapy for 6 to 5 cycles. For follow-up of 3 months to 10 years, 2 cases showed recurrence and died, 8 cases on event free survival.

**Conclusion:** Vaginal endodermal sinus tumor was very sensitive to chemotherapy. Chemotherapy should be the primary treatment to preserve vagina and uterus. Cases reached CR on 4 cycles of chemotherapy could avoid surgery. Cases reached PR on 4 cycles should accept surgery. CR could be reached on 5 to 8 cycles of chemotherapy, but longer regimen may be needed to prevent recurrence.

**PW008**

**JUVENILE GRANULOSA CELL TUMOR OF THE OVARY**

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**Purpose:** To assess the presentation, diagnosis, treatment and the outcome of the Juvenile granulosa cell tumors (JGCT) of the ovary in children.

**Methods:** All children less than 12 years and registered in the solid tumor clinic of our hospital from 2005 to 11 who were diagnosed to have JGCT were retrospectively studied for the presentation, diagnostic investigations, management and outcome.

**Results:** A total of 6 patients in the age range of 12–141 months (mean 70.8 months) were included. Four patients (66%) presented with an abdominal mass. Vaginal bleeding and breast enlargement was the most common presentation (66%). Other presenting symptoms were premature appearance of pubic hair (33%) and pain abdomen (33%) and abdominal distention (16.5%). One patient (16.5%) presented with obstructive symptoms of bladder and...
bowed and another had associated bilateral inguinal swellings. Diagnosis was made by raised serum estradiol (Range 162–110pg/ml) levels and ovarian mass on radiologic imaging and confirmed histologically after resection. All patients underwent salpingo-oophorectomy on the affected side (one laparoscopic, 5 open surgery). All of them were POG stage 1 tumors without any extension beyond the ovary and none received adjuvant chemotherapy. Patients were followed up with clinical examination, serum inhibin levels and serial ultrasonography.

The symptoms of isosexual precocious puberty regressed in all. There was no recurrence during a follow up of ranging from 3 to 72 months.

Conclusion: Juvenile granulosa cell tumors of the ovary presents with varied features of isosexual precocious puberty with or without palpable abdominal mass. POG Stage 1 JGCT have very good prognosis with complete excision with complete regression of features of isosexual precocious puberty and no recurrence without any chemotherapy.

**PW009**

**INTERNAL HEMIPELVECTOMY AS A TREATMENT OPTION IN BONE TUMORS IN CHILDREN AND YOUTH**

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**Purpose:** The standard treatment of primary bone tumors consists of chemotherapy, surgery and/or radiotherapy.

**Methods:** In the period 2009 to 2011 in our clinic, 17 patients underwent surgery for malignant bone tumors in the pelvis; 12 boys and 5 girls, in age from 10 to 21 years, average 13 years. In histopathologic diagnosis were sarcoma Ewingi in 8 pts., osteosarcoma in 6 pts., chondrosarcoma in 3 pts. Localization by Enneking classification; stage I were in 6 pts, stage II/III 2 pts and stage III/III in 6 pts. Total hemipelvectomy have been made in 3 pts and internal hemipelvectomy in 14 pts, in reconstruction were used bone grafts (6 pts.), modular endoprostheses and trevira tube (2 pts.). LUMIC endoprostheses (6 pts). Early and late complication were observed in 5 cases. Satisfactory functional results in 70%.

**Results:** Alive 14/17 pts. Follow up 3 yrs to 5/12 months, mean 2.2 yrs.

**Conclusion:** Patient’s experience is of basic importance for surgery. Possibility of internal hemipelvectomy depends on: (1) localization and extent of the tumor; (2) tumor reaction after neo-adjuvant chemotherapy; (3) patients age. Internal hemipelvectomy as limb salvage surgery is satisfactory, but satisfactory results of surgeon’s depend on extent of operation and rehabilitation.

**PW010**

**PROBLEMS AMONG CHILDHOOD CANCER SURVIVORS IN A PEDIATRIC SURGICAL CLINIC**

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**Purpose:** Recent improvements in the diagnosis and multimodal therapy of pediatric malignancies have increased the number of childhood cancer survivors (CCSs). The importance of the quality of life (QOL) of CCDS has now been recognized, and the late effects of cancer treatments are essential and important issues. This study analyzed the late effects of cancer treatments in CCDS followed in the pediatric surgical outpatient clinic.

**Methods:** Fifty-seven (age > 10 years old; follow-up period > 5 years) of the CCS patients the received surgical treatment and were followed in the surgical clinic were included in this study. The patients included 25 males and 32 females. The average age was 17 (10–28) years and the duration follow-up varied from 5 to 28 years (mean 14 years). They included 26 neuroblastomas, 12 Wilms tumors, 10 hepatoblastomas, 10 rhabdomyosarcomas, 7 germ line tumors and others. Seventeen patients (25%) received hemato poetic stem cell transplantation (SCT) and 10 (15%) received radiotherapy.

**Results:** Thirty-three patients (58%) had complications. Surgical complications: Fourteen patients underwent nephrectomy and one of them developed renal failure. Two patients with rhabdomyosarcoma received cystectomy with urinary tract reconstruction and one received vaginectomy. Other complications, such as ileus, sclerosis, and leg length discrepancies were seen in some patients. Medical complications: Eight patients showed growth retardation and two were treated with GH. Gonadal dysfunction was observed in 16 patients and 6 were treated with gonadal hormone. Low bone mineral density was observed in 7 patients. Other medical deficiencies, such as hearing loss, and hepatitis were seen in some patients. The rate of gonadal dysfunction and growth retardation were also significantly higher in the patients who received SCT.

**Conclusion:** Treatment-related complications may occur many years after the therapy. Lifetime medical surveillance and continuous follow-up by pediatricians, pediatric surgeons and endocrinologists are therefore required for childhood cancer survivors.

**PW011**

**LONG TERM IMPLANTABLE CATHETERS IN CHILDREN: EXPERIENCE OF THE PEDIATRIC ONCOLOGY INSTITUTE OF THE FEDERAL UNIVERSITY OF SÃO PAULO IN TWO PERIODS**

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Surgery, Pediatric Oncology Institute/GRAACC/Federal University of Sao Paulo, Sao Paulo, Brazil

**Purpose:** Evaluate the incidence of complications with long term catheters in two periods. Methods: The previous study showed complications related to the place of the puncture and catheter brand. Changes were made in implantation (site, brand, use of ultrasound). Prospective study of complications in 2 periods. Period 1: Puncture implantation from 2004 to 2006, with follow up until 2008. Period 2: punction implantation from 2007 to 2010, with follow up until 2011. Endpoints considered were those that let to catheter revision or removal. Complications and survival of the catheter (from implantation until removal, death or end of the study) were analysed.

**Results:** 77 catheters on period 1 and 52 on period 2. Age at implantation: period 1 75 ± 27.2 vs period 2 70.3 ± 8.9 months (p = 0.5227). Patient weight on period 1 was 26.4 ± 19.8 Kg and on period 2 29.2 ± 22.0 Kg.

**Diagnosis:** Hematologic malignancies 41.4% on period 1 and 40.4% on period 2; solid tumors 44.2% and 44.2% and central nervous tumors 14.3% and 15.4% respectively. Site of implantation was 49% jugular and 51% subclavian on period 1 and 96% jugular and 6% subclavian on period 2. Complications: Period 1 - 29 complications: 13 infections, 13 embolias, 1 thrombosis, 1 extrusion and 1 fracture. Period 2: 9 complications: 8 infections, 1 obstruction. Complication rate was 37% on period 1 and 17% on period 2 (p = 0.0001). Catheter survival was of 13.7 ± 10.6 months on period 1 and 20.0 ± 15.2 months on period 2 (p = 0.01).

**Conclusion:** Site of implantation and catheter brand influenced the complication rates. Jugular implanted catheters are associated with fewer long-term complications.

**PW012**

**BILATERAL WILMS TUMOR: EXPERIENCE OF THE PEDIATRIC ONCOLOGY INSTITUTE OF THE FEDERAL UNIVERSITY OF SÃO PAULO**

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1Surgery; 2Pediatric Oncology; 3Pathology, Pediatric Oncology Institute/GRAACC/Federal University of Sao Paulo, Sao Paulo, Brazil

**Purpose:** To evaluate the experience of one single institution in treating children with bilateral Wilms tumors.

**Methods:** Retrospective study of patients with Wilms stage V. Age, sex, clinical presentation, chemotherapy, need of biopsy for diagnosis, type of surgical resection, number of surgical procedures, radiotherapy, pathology, renal function and need for kidney transplantation were analysed.

**Results:** 15 patients with bilateral renal tumors were studied; including 67% female and 33% male. Age varied from 7 to 48 months, medium of 28 months. Abdominal mass was the clinical presentation in 80% of cases. Total nephrectomies were performed in 23%, partial nephrectomies in 33%, nodulectomies in 43%. 12 patients are alive without disease and 3 died. Creatinine varied from 0.39 to 0.85 and clearance varied from 58, 48 to 157. No patient had a submitted to renal transplant.

**Conclusion:** Patients with bilateral Wilms tumors need a multidisciplinary approach for treatment.

**PW013**

**PRIMARY CERVICAL NEUROBLASTOMA: SINGLE INSTITUTION EXPERIENCE**

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**Purpose:** To review the clinical presentation, management and outcome of primary cervical neuroblastoma complications at a tertiary cancer center in India.

**Methods:** Case records of patients with cervical neuroblastoma presenting at our institution between the year 2007 and 2012 were reviewed and analyzed.

**Results:** There were 7 patients (4 boys and 3 girls) with a median age of 20 months (12–54 months). The commonest presentation was a neck mass. Two patients had neurological symptoms, opso-myoclonus in one and behavioral changes in another. The median duration of symptoms was 12 weeks (2.0–32 weeks). At the time of presentation, 3 patients had received anti-tubercular drugs and two, prolonged antibiotics. Homer’s syndrome was present in two patients at presentation. None of the patients had metastatic disease. The mean
POSSIBILITY OF PARTIAL NEPHRECTOMY IN CHILDREN WITH WILMS TUMOUR - ANALYSIS OF PATHOLOGICAL POSTOPERATIVE SPECIMENS OF 12 CASES

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1Department of Pediatric Surgery; 2Department of Pediatrics, Kyoto Prefectural University

Purpose: Partial nephrectomy in children with nephroblastoma remains controversial. Aim of the study was to assess possibility of partial nephrectomy (PN) on the basis of the correlation between clinical and pathological features, results of imaging and anatomical relationships between the tumor and the remaining part of the kidney in the postoperative evaluation.

Methods: Data of 12 patients (age from 0.5–8 years) with classical complete nephrectomies was to assess possibility of partial nephrectomy (PN) on the basis of the correlation between clinical and pathological features, results of imaging and anatomical relationships between the tumor and the remaining part of the kidney. All patients underwent routine therapy: two patients did not get neoadjuvant therapy because of excisional biopsy of the renal tumor; leaving tumours not resectable by PN (central and polar localization) were IR, 1 (CS I) LR. PN based on imaging studies was not possible in 5 pts; however, in 1/3 appeared possible at autopsy leaving <1/3 of healthy renal parenchyma.

Conclusion: It is controversial. It seems that the group of potential candidates for PN is greater than the group based only on the imaging studies but usually at a cost of leaving less than 1/3 of functioning renal parenchyma.

ROLE OF PALLIATIVE RADIOTHERAPY IN THE MANAGEMENT OF ADVANCE PEDIATRIC CANCERS

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Purpose: To evaluate the role of palliative radiotherapy in the management of advance pediatric malignancies either as sole modality or in combination.

Methods: Retrospectively study of 36 pediatric patients treated between Jan ’2007 and Nov’ 2011 who received palliative radiotherapy for symptom control and was given either as sole modality or in addition to surgery, chemotherapy and along with symptom relieving drugs. Data collection was done for age, sex, disease extent, histology, major symptoms and treatment given. All the children presented in advance or metastatic stage.

Results: There were 30 boys and 6 girls in the age group of 1 to 16 years, with a median age of 12 years. Major symptoms were pain with or without swelling, bleeding, and weakness of lower limbs. The median duration of symptoms was 3 months. The diagnosis of these children varied with different histologies, most in the group of malignant round cell tumors (18), retinoblastoma (2), neuroblastoma (5), AML with chloromas (3), Osteogenic sarcoma and Ewing sarcoma (8). Out of 36 patients 18 (50%) had metastatic disease at presentation. 10 patients underwent surgery while 26 patients received chemotherapy and all patients received symptom relief drugs in addition to palliative radiotherapy. The various dose schedules were either 8 Gy single fraction, 20 Gy in 5 fractions or 30 Gy in 10 fractions. 20 patients showed good response, while 12 patients had partial, 4 patients had no relief. At the completion of multimodality treatment, 16 patients had partial response, 10 had stable disease, 6 patients had progressive disease and 2 patients had complete response. The disease status of 2 patients could not be known. Major symptoms that responded to palliative radiotherapy was pain and bleeding.

Conclusion: Radiotherapy as palliative modality in children with locally advanced lesions provides better symptom relief in combination with other modalities of treatment.

COMPARISON OF VOLUMETRIC MODULATED ARC THERAPY (VMAT) VS. CONVENTIONAL RADIOTHERAPY WITH INTENSITY MODULATED RADIATION THERAPY (IMRT) BOOST IN CRANIOSPINAL IRRADIATION (CSI) OF PEDIATRIC MEDULLOBLASTOMA

PX002

Purpose: To assess the outcome of Askin tumour in a centre with low case load.

Methods: From 1989 to 2012 Askin tumour was diagnosed in a nine patients (6 males) at the median age of 12 (range 1–15) years. none of the patients had metastases. In two patients tumour grew into vertebral column in one patient into the cupola of liver. Routine therapy consisted of biopsy, neoadjuvant chemotherapy, surgical excision and conventional or high-dose adjuvant chemotherapy and local radiotherapy. The main outcome measure was survival on after diagnosis, secondary outcome functional result after surgery.

Results: Tumors were situated from 7th to 12th rib, six at the left side, five posteriorly and four anteromedially, diameter ranging from 3 to 18cm. Seven patients underwent the routine therapy. Two patients did not get neoadjuvant therapy because of excisinal biopsy of the whole tumour (n = 1) and excision of the primary tumour in conjunction with decompresive laminectomy (n = 1). After surgery eight patients underwent adjuvant chemotherapy and four with poor chemotherapeutic response had high-dose chemotherapy and local irradiation. One patient is still waiting for tumour histology after surgical resection. A median of 3 (range 1–6) ribs were resected. Surgical reconstruction methods included pedicled latissimus dorsi musculocutaneous flap (n = 2), Gore-Tex/Bio patch (n = 6), rib plasty (n = 2). After median follow up of 1.7 (0.1 – 20) years eight patients are alive. A patient with primary excision of the tumour died of recurrent tumour 1.7 years after diagnosis. Functional result in chest wall is satisfactory in two and good in five patients, and not yet assessed in one.

Conclusion: With a structured therapy regimen Askin tumour can be successfully treated with good long term result. Good functional result after surgical excision of the chest wall requires various plastic surgical reconstruction techniques.

RADIATION ONCOLOGY (PROS)

PX001

Radiology, AMRI Hospital, Kolkata, India

Purpose: To evaluate the role of palliative radiotherapy in the management of advance pediatric malignancies either as sole modality or in combination.

Methods: Retrospectively study of 36 pediatric patients treated between Jan ’2007 and Nov’ 2011 who received palliative radiotherapy for symptom control and was given either as sole modality or in addition to surgery, chemotherapy and along with symptom relieving drugs. Data collection was done for age, sex, disease extent, histology, major symptoms and treatment given. All the children presented in advance or metastatic stage.

Results: There were 30 boys and 6 girls in the age group of 1 to 16 years, with a median age of 12 years. Major symptoms were pain with or without swelling, bleeding, and weakness of lower limbs. The median duration of symptoms was 3 months. The diagnosis of these children varied with different histologies, most in the group of malignant round cell tumors (18), retinoblastoma (2), neuroblastoma (5), AML with chloromas (3), Osteogenic sarcoma and Ewing sarcoma (8). Out of 36 patients 18 (50%) had metastatic disease at presentation. 10 patients underwent surgery while 26 patients received chemotherapy and all patients received symptom relief drugs in addition to palliative radiotherapy. The various dose schedules were either 8 Gy single fraction, 20 Gy in 5 fractions or 30 Gy in 10 fractions. 20 patients showed good response, while 12 patients had partial, 4 patients had no relief. At the completion of multimodality treatment, 16 patients had partial response, 10 had stable disease, 6 patients had progressive disease and 2 patients had complete response. The disease status of 2 patients could not be known. Major symptoms that responded to palliative radiotherapy was pain and bleeding.

Conclusion: Radiotherapy as palliative modality in children with locally advanced lesions provides better symptom relief in combination with other modalities of treatment.

Clinical features and surgical intervention of renal tumors diagnosed during early infancy

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Purpose: Renal tumors diagnosed during early infancy are uncommon. The problem of this age group is an accompanied paraneoplastic syndrome such as hypertension and associated congenital anomalies, however, the clinical features and outcomes are still unclear.

Methods: From 1977 to 2011, we treated 38 pediatric renal tumors in our institute. Among them, we retrospectively reviewed the clinical presentations, pathology, surgical treatment, and outcomes of renal tumors in infants less than 6 months of age.

Results: There were 7 early infants with renal tumors (20%). Pathological diagnosis was Wilms tumor (WT) in 3 cases, malignant thalidoblast tumor (MRTK) in 2, and congenital mesoblastic nephroma (CMN) in 2. Renal mass was antenatally detected in 2 cases. All 7 infants had a palpable abdominal mass, 3 had hypertension, and 1 had macrohematuria. Hypercalcemia was noted in 1 child with MRTK. One case with WT had bilateral tumors with familial history. Regarding surgical intervention, all but one underwent nephrectomy, and one with bilateral WT underwent palliative nephrectomy with incisional biopsy of the contralateral kidney. A case with antenatally diagnosed WT showed an intratumoral hemorrhage causing hypovolemic shock just after birth. She required transcatheter arterial embolization, and chemotherapy preceded the surgical resection. Adjuvant chemotherapy was performed in 4 cases. Finally, 2 cases with MRTK died of tumor recurrence in spite of resection. Overall survival of these tumors was 71.4%.

Conclusion: Paraneoplastic syndromes such as hypertension, hypercalcemia, and tumoral hemorrhage were common in these early infants with renal tumor. Palpable mass and hypertension were caused by a large space occupying mass for infantile trunk. CMN showed excellent outcomes with surgical resection only. MRTK had poor prognosis in spite of aggressive resection and chemotherapy. Surgery is the appropriate initial treatment for early infants with renal tumors, and mortality depends on the tumor pathology.
Purpose: To compare volumetric modulated arc therapy (VMAT) and conventional radiotherapy with Intensity Modulated Radiation Therapy (IMRT) boost in cranial irradiation with respect to dose conformity (CI), homogeneity (HI) and reduced dose to organ at risk (OAR).

Methods: CT simulation scans (3mm slice thickness) of three children with standard risk medulloblastoma who had been simulated in supine position for CSI were planned using VMAT technique and conventional radiotherapy (parallel opposed portal for whole brain and direct posterior spinal field) followed by tumor bed boost by IMRT (6 field sliding window technique including one non coplanar beam) using 6 MV photons. The plans were optimized with high weightage for planning target volume (PTV) coverage. Conformity and heterogeneity indices, monitor units and doses to OARs namely eye, cochlea, heart, lung, esophagus, thyroid, liver and kidney were analysed for a prescription dose of 25.2 Gy to whole brain, 23.4 Gy to whole spine followed by a tumor bed boost of 29 Gy.

Results: Planning objectives were met for all the plans. The mean and maximum PTV doses were higher with VMAT plan (55.5 Gy and 59.78 Gy) as compared to the conventional plans (54.4 Gy and 58.7 Gy). The median (range) conformity index for VMAT for brain was 1.04 (1.02–1.05) compared with 1.11 (1.02–1.11) for conventional plans. The median (range) conformity index for VMAT for spine was 2.25 (1.68–5.14) compared with 5.62 (4.9–9.2) for conventional plans. The heterogeneity index was also lower for the VMAT plans. The mean doses to OARs, V20 of lung and monitor units were lower with the VMAT plans.

Conclusion: The VMAT technique increases the homogeneity and conformity which along with lower number of monitor units translates to decreased integral dose and shorter treatment times with increased OAR sparing and elimination of field junction dose uncertainties but at the expense of increased low dose volumes.

PX003

IMPACT OF RADIATION TECHNIQUES 3D VS IMRT ON ACUTE TOXICITY AND LOCAL CONTROL IN PATIENTS WITH RHABDOMYOSARCOMA

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Purpose: Rhabdomyosarcoma is an extremely rare tumor which in many cases necessitates optimal dosimetric conformity for normal tissue sparing and better target dose coverage. In this study with compared locoregional control and acute toxicity of intensity modulated radiotherapy (IMRT) vs three dimensional conformal radiotherapy (3D RT) in patients with rhabdomyosarcoma.

Methods: This is a retrospective analysis of 61 patients treated with IMRT (n = 27) and 3D (n = 34) CRT between June 2004 and June 2011. Radiation treatment was correlated with clinical outcome (local and distant control) and acute toxicity. The Chi-Squared test was used to compare the patients characteristics and radiation parameters between the two arms.

Results: The mean follow up was 20.7 months and the mean age was 15.3 years. The primary histology was embryonal (65.6%) and the main location was non-parameningeal head and neck (32.8%). Fifty-five patients received chemotherapy under Protocol. The mean total dose was 42.7 Gy in the IMRT arm and 47 Gy in the 3DRT arm (p = 0.482). At last follow up 38 patients had no evidence of disease (62.3%), with a crude locoregional recurrence rate of 8.2%, distant metastasis rate of 16.4%, and both distant and local recurrences were seen 13.1%. Forty-six were alive at last follow up (75.4%). No statistically significant differences in locoregional control were found between IMRT (88.9%) and 3D CRT (70.6%) (p = 0.08) nor in acute toxicity (p = 0.01) or when comparing grades 0–1 vs 2 - 3 toxicity (p = 0.79). The analysis by primary site revealed no differences between both techniques in acute toxicity (p = 0.18).

Conclusion: Local control and acute toxicity of IMRT vs 3D CRT in patients with rhabdomyosarcoma appears potentially better at two years follow-up, final evaluation will require longer follow up and a large number of patients.

PX004

AGE RELATED CHANGES IN Frontal LOBE ANATOMy REQUIRE PATIENT SPECIFIC CRANIOsPINAL IRRADIATION TREATMENT MARGINS

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Purpose: To explore the anatomy of the frontal and temporal lobes as it concerns pediatric radiation therapy, in particular for craniospinal and whole brain scenarios, and to define the temporal frontal angle (TFA), determine the age related variability of the TFA, and discuss implications of these findings regarding cranial irradiation.

Methods: Eclipse treatment planning software CT images for 122 patients were analyzed for frontal lobe excursion, defined as the TFA. TFA was compared as a function of age and gender.

Results: The TFA decreases linearly in pediatric patients (p < 0.001), however, this linear relationship disappears after age 20 (p = 0.839). Anterior excursion up to age 20 varies significantly for both boys (p = 0.0011) and girls (p = 0.0007). Lateral excursion up to age 20 varies by age significantly for girls (p = 0.0002) but not for boys (p = 0.3229).

Conclusion: Because relative frontal lobe position varies with age, innovative approaches are needed for orbital sparing while effectively treating disease in very young children. If class solutions become the standard form of management of this issue, these class solutions may need to be different for boys and girls. It is critical that our specialty review the current guidelines for cranial irradiation given the issues presented for whole brain treatment as part of leukemia and craniospinal therapies. Both proton therapy and intensity modulated photon therapy can be used to solve the issues the frontal lobes present in very young children.
plans were 10.8 and 10.1 Gy respectively, compared to 3.0 and 3.2 Gy for the IMRT plans (p < 0.01). The IMRT plans resulted in significantly decreased max eye dose (p < 0.006), with no significant difference in the max or mean layerns or spinal cord dose. There was a significant increase in the max dose to the dental and facial regions with the IMRT plans, but no difference in the volume receiving > 10 Gy.

Conclusion: HS-CSS is dosimetrically feasible and allows for acceptable target coverage and dose to OAR. There is concern for an increase in second malignancy using IMRT in pediatric patients; however, there was no increase in MU’s for the spinal posterior beam. A phase II protocol is being developed to evaluate the feasibility of this treatment.

PX007
CONFORMAL PEDIATRIC RADIOTHERAPY IN SERBIA
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Purpose: Institute for Oncology and Radiology of Serbia has a 30 years long tradition in pediatric radiotherapy and oncology. With 60 to 70 children for radiotherapy treatment per year Institute is the main center for pediatric radiotherapy in country. From 2006 we provide equipment for conformal radiotherapy and start with new radiotherapy techniques.

Methods: From September 2006 to December 2010 radiotherapy was performed for 253 children with malignancy. There were 152 (60%) girls and 101 (40%) boys, age from 1 to 18 years. 23 (9%) children was under 3 years of age. Most of pts were with central nervous system tumors (CNS) 28.88%, leukemia 17.65%, bone tumors 15.51%, limfomas 14.44%, soft tissue sarcoma 9.63%, neuroblastoma 5.88%, nephroblastoma 3.21%, retinoblastoma 2.14% and other rare tumors 2.67%. 208 pts received chemo and radiotherapy, in 45 pts radiotherapy was only treatment approach. In 102 children chemotherapy treatment was performed at our Institute, at Pediatric Department and 106 received chemotherapy in some other pediatric oncology departments.

Results: Conformal radiotherapy was performed in 191 (75.4%) pts. using 3D planning system (XIO) but 62 (24.6%) were treated with conventional (2D) radiotherapy. Almost all children with CNS tumors had conformal radiotherapy treatment (94.44%), than with soft tissue sarcoma (83.3%) and bone tumors (72.41%).

Conclusion: With further education of all in radiotherapy team and with better possibilities to use radiotherapy equipment we continually improve conformal radiotherapy at our Institute with aim to start with advance radiotherapy techniques.

PX008
DIFFUSE PONTINE GLIOMAS OF THE CHILDHOOD: DOES TEMOZOLOMIDE IMPROVE SURVIVAL?
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Purpose: Diffuse pontine gliomas (DPG) are highly mortal tumors occurring in young children. Usually surgical resection is not possible and radiotherapy is the main treatment. Chemotherapy has not shown to prolong survival so far. The role of temozolomide (TMZ) – which is an effective drug in the treatment of high grade gliomas in adults, is not clear yet.

Methods: 72 children having a diagnosis of DPG were treated with radiotherapy in Ege University Hospital from 1988 till 2012. Median age was 8 (range 2–17), 41 were females and 31 were males. Radiotherapy dose was 54–59.4 Gy with 2 daily fractions. Concomitant and adjuvant TMZ was used routinely since 2007, thus 19 patients received TMZ. Various chemotherapy drugs were used in case of progression as well.

Results: Survival was analyzed in February 2012. Only 6 patients were alive. Median survival was 9.1 months (+/- 6.8) in the whole group. Median survival was longer (14.0 vs. 6.8 months) and survival at 1 year was better (0.62 vs. 0.23) in the patients receiving TMZ, however these promising early results faded way during the second year (survival at 2 years: 0.07 vs 0.13). Overall the survival difference between the two groups was not significant.

Conclusion: The addition of TMZ to radiotherapy delayed the progression of tumor approximately 6 months, unfortunately did not provide long term remission and cure. Results are in consistency with previously published reports. DPG should be target of novel agents in combination with TMZ.

PX009
IMPACT OF MOTION IN ADVANCED PAEDIATRIC ABDOMINAL RADIOTHERAPY
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Purpose: Advances in radiotherapy have sought to mitigate the effects of patient movement, organ motion and anatomical deformation on the efficacy of treatment delivery. The irradiation of abdominal tumours such as Neuroblastoma in paediatric patients presents a challenge to deliver an adequate dose to the target dose whilst minimising dose to surrounding tissues. The majority of the published data for motion for abdominal organs have been acquired from the adult population. Paediatric data is limited to one article on 4DCT on 20 free-breathing patients and a second evaluating CBCT for 9 patients under general anaesthesia.

Methods: The radiotherapy database at UCH was reviewed to extract those paediatric patients that were treated for abdominal tumours with Intensity Modulated radiotherapy with Cone Beam CT (CBCT) verification during treatment for 2011/2012. The CBCT scans were then ‘matched to the reference vertebral bones of the planning ct’ in the planning system in order to demonstrate relative soft tissue motion. In the planning system, both kidneys and the liver were re-delineated from the matched dataset onto the reference planning scan. In addition, areas of bowel gas were re-delineated in the same manner.

Results: Six paediatric patients were able to be included in this review. All patients demonstrated kidney and liver positions different from the planning ct. All patients demonstrated large variations in bowel gas volume and distribution. Anatomical positional variations and bowel gas changes led to changes in delivered dosimetry.

Conclusion: Highly conformal plans based on a helical CT in this patient cohort may not be able to deliver the planned dose due to the variations in anatomy described. Methods to characterise the motion such as 4dct or limit the motion such as abdominal compression should be used. Interventions such as those used in the adult practice to reduce the impact of bowel gas should be considered.

PX10
MYXOPAPILLARY EPE NDY MOMAS OF THE FILUM TERMINALE IN CHILDREN TREATED WITH SURGERY AND RADIATION
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Purpose: Ependymomas are the most common intraparenchymal tumors and comprise approximately 60% of intraparenchymal tumors of the spine. The myxopapillary variant represents only about 13–15% of ependymomas. It has been observed that most myxopapillary ependymomas arise in the filum terminale or cauda equina region. They are usually characterized as slow-growing and are histologically benign. While local recurrence may occur, tumors rarely metastasize.

Methods: Seven children with myxopapillary ependymomas were treated in our department over a seven year period. All 7 patients presented with low back pain. One patient also presented with bilateral lower extremity weakness, numbness and occasional urinary incontinence. All patients initially underwent a gross total resection (GTR) by the same neurosurgeon. In 4 cases, recurrence was observed at 13, 18, 22 and 23 months, respectively, following initial resection. In the other 3 cases, while GTR was achieved, there was concern that microscopic disease remained.

Results: All 7 patients received post-operative RT. Four of the patients received RT after recurrence was resected, while the other 3 received adjuvant RT. RT doses ranged from 4320 to 5400 cGy. With a median follow-up of 81 months, all patients are NED. All 7 patients tolerated RT with minimal morbidity. None of the patients have reported any pain or neurologic dysfunction. One patient reported occasional bouts of nausea. Growth for all seven patients has been normal.

Conclusion: In our experience, RT for recurrent or residual myxopapillary ependymoma given post-operatively in children yields excellent control of disease with little or no morbidity. Our data confirm prior reports regarding the efficacy of resection plus RT in this disease. With a median follow-up time of 81 months, all seven patients continue to do well.

References
GTR = Gross Total Resection, STR = Subtotal Resection, RT = Radiotherapy, NED = No Evidence of Disease.