

weeks. The 5-year actuarial disease-free and overall survivals were 91% and 95%, respectively (CI: 62%-98%).

Conclusion: Our study indicates that paediatric ENB is a chemo-sensitive tumour, thus support the role of a combined therapy including neoadjuvant chemotherapy, surgery and radiation therapy.

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POSTER

Identifying medical and psychosocial needs of teenagers and young adults with ependymoma

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Background: Teenagers and young adults (TYA) with cancer form a specific group of patients with different biological, clinical and social characteristics. We report the Royal Marsden Hospital experience treating TYA with ependymoma and aim to analyze the medical and psychosocial needs of this group.

Material and Methods: Twenty TYA (aged 13 to 24 years) were treated for ependymoma from 1971 to 2004 and are compared to 27 children (not infants) treated in the same period. Data regarding clinical presentation, outcome and need for ancillary services were gathered. Comparisons were made between TYA and children and according to department where treatment was delivered (Paediatrics vs. Neuro-Oncology). Institutional Review Board approval was obtained.

Results: Four out of 20 TYA had grade 3 ependymoma. Only 20% of TYA achieved gross-total resection (vs. 66.7% of children, $p = 0.003$), all of them received radiotherapy, and 5 of them received adjuvant chemotherapy. There were 7 relapses, all of them were local vs. 50% of metastatic relapses in children ($p = 0.02$). Five-year overall survival was $78\% \pm 9.8$ for TYA vs. $71.6\% \pm 9.2$ for children ($p = 0.368$) and 5-year progression-free survival was $63.6\% \pm 11.1$ for TYA vs. $46.4\% \pm 9.9$ for children ($p = 0.14$).

Average time from symptoms to diagnosis was 264.4 days for TYA vs. 87.1 for children ($p = 0.018$). Treatment was given in a paediatric unit in 30% of TYA and 100% of children. Only two TYA (10% vs. 25.9% for children) were enrolled in a clinical trial. None of the cases was enrolled in any adult clinical trial. According to the unit where treatment was given (Paediatrics vs. Neuro-Oncology), patients were referred for psychosocial support in the following proportion: Psychology (44.8 vs. 25%), Physiotherapy (31 vs. 0%), Occupational Therapy (24.1 vs. 0%), Speech Therapy (13.8 vs. 0%) and Dietetics (34.5 vs. 12%).

Conclusions: Ependymoma in adolescents and young adults is an infrequent entity, with perhaps better outcome compared to children. In our experience, needs of Teenagers and Young Adults with ependymoma summarize current issues about treatment of TYA with cancer: need for dedicated multidisciplinary adolescent units, access to clinical trials (either adult or paediatric), delays in diagnosis and psychosocial support.

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POSTER

A prospective, multicentre trial of high-dose methotrexate/doxorubicin or cisplatin/doxorubicin for children and young adults with osteosarcoma – decision making analysis

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Background: This prospective, multicentre trial was designed to compare two protocols: high-dose methotrexate+doxorubicin (MTX/DOXO) vs cisplatin+doxorubicin (cDDP/DOXO) in localized osteosarcoma.

Material and Methods: Between 1998–2005, 146 patients aged 4–24 years (mean 14 years) with non-metastatic operable high-grade primary osteosarcoma were assigned preoperatively to the MTX/DOXO regimen, or to the cDDP/DOXO regimen. After surgery, the regimen was continued, when histological response was below 5% of viable tumour cells, or was changed to VP-16+IFO in case of poor histological response. For statistical analysis, log rank test and χ^2 test were used, and the probabilities of events were included into clinical decision tree model.

Results: 126 patients fulfilled inclusion criteria. Before surgery, 25 of 51 patients (49%) in the MTX/DOXO group had disease progression in

contrast to 2 of 75 patients (3%) in the cDDP/DOXO group ($P = 0.000$). Due to progression in the MTX/DOXO group, 22 patients received cDDP/DOXO and 1 patient – VP-16/IFO (with response). The rest of population underwent surgery. In clinical decision tree model, three group of patients were analysed: (1) responders-MTX/DOXO, (2) non-responders-MTX/DOXO and (3) cDDP/DOXO. The proportion of good histological response was as follow: cDDP/DOXO (41%), responders-MTX/DOXO (43%), and non-responders-MTX/DOXO (28%). With a median follow-up of 80 months, there was a trend for higher overall survival in the cDDP/DOXO arm (85%), comparing to the responders-MTX/DOXO arm (77%) and the non-responders-MTX/DOXO arm (68%); $P = 0.056$. Toxicity was manageable with different acute toxicity profiles.

Conclusion: Clinical and histological response to primary chemotherapy were identified as the most significant prognostic factors in localised osteosarcoma.

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POSTER

Influence of the GGH -401C>T and the RFC1 A(80)G polymorphism on methotrexate toxicity in children with osteosarcoma

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Background: The human gamma-glutamyl hydrolase (GGH) plays an important role in antifolate-resistance in tumour cells. The presence of the -401T allele in the promoter of the GGH gene causes increased gene expression in leukemic cell lines. G(80)A polymorphism has been described in the reduced folate carrier (RFC1) gene, which encodes the major methotrexate transporter. Children with acute lymphoblastic leukemia homozygous for A(80) had worse prognoses and higher levels of MTX than the other genotype groups. During this study, we examined the association of the GGH promoter polymorphism and the RFC1 G(80)A polymorphism with respect to toxicity of methotrexate treatment in children with osteosarcoma.

Material and Methods: We examined the data of 571 methotrexate blocks administered to 72 patients treated with COSS 86 or 96 protocol between 1987 and 2004. From the medical records we examined the following parameters: the serum drug levels 6, 24, 36, 48 hours after methotrexate infusion; the highest serum GPT, GGT and bilirubin values and the lowest number of granulocyte and serum protein levels in the first two weeks after the methotrexate treatment. The two polymorphisms were determined by a PCR-RFLP method using DNA extracted from peripheral blood.

Results: The incidence of grade IV. acute hepatotoxicity was less frequent ($p = 0.007$) in patients homozygous for the GGH -401T allele than in the group with -401CC or CT genotype. Serum protein was significantly lower ($p = 0.0005$) and the frequency of grade IV. acute hepatotoxicity was significantly higher ($p = 0.001$) in patients with RFC1 80AA or AG than in those homozygous for the G allele.

Conclusions: Patients homozygous for the GGH -401T allele had less hepatotoxicity compared to those with the -401CC or CT genotype. The presence of RFC1 80A allele resulted in more toxicity than the homozygous GG genotype. Our results indicate that certain gene polymorphisms should be considered for treatment dose individualization in the future.

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POSTER

Endocrine dysfunctions in children transplanted with TBI-based conditioning regimens for hematological malignancies: a retrospective analysis

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Background: The progressively increasing number of long-term survivors after hematopoietic stem cell transplantation (HSCT) led researchers to focus on its late complications. Endocrine dysfunctions following HSCT are common and occur mostly in patients treated with Total Body Irradiation (TBI) as part of conditioning regimen. In this retrospective study, we evaluated incidence and severity of late endocrine dysfunction in a cohort of very long-term survivors.

Materials and Methods: Fifty-one patients (32 females, 19 males) surviving at least 5 years after HSCT were included. Median age at HSCT was 8.5 years (range: 2–16.4). The median follow-up was 8 years (range 5–17). Primary diseases were acute lymphoblastic leukemia ($n = 32$), acute ($n = 15$) or chronic ($n = 2$) myeloid leukemia, or non-Hodgkin lymphoma ($n = 2$). Median time interval from diagnosis to HSCT was 1.2 years (range

0.3–3.6). Thirty-two patients (63%) underwent allogeneic and 19 (37%) autologous transplantation. Six patients were treated with a total dose of 14.4 Gy/12 fractions, 42 with a total dose of 12 Gy/6 fr, 3 with a total dose of 9.9 Gy/3 fr. Hypothalamic, pituitary, gonadal and thyroid function were routinely assessed before and after HSCT.

Results: The most common observed endocrine dysfunction was hypogonadism, recorded in 24/47 evaluable patients (51%). Five-year and ten-year cumulative risk were 36.5% and 60.1%. In univariate analysis, age at transplantation was the most important risk factor for hypogonadism (cut-off value 8.5 yrs old, median age of the whole patients cohort, $p < 0.01$), with younger patients presenting a lower incidence. T-Student test confirmed this findings ($p = 0.01$). Twelve patients showed severe growth impairment requiring GH replacement therapy (12/50 evaluable patients, 24%). Cumulative incidence of severe growth impairment was 18% at 5 years and 29.9% at 10 years. Non-parametric analysis showed that younger patients had a significant higher incidence of delayed growth velocity ($p \leq 0.05$). Hypothyroidism affected 10/47 evaluable patients (21.2%). Cumulative incidence of hypothyroidism was 17% at 5 years and 22% at 10 years.

Conclusions: Long-term survivors treated with TBI-based HSCT in childhood are at significant risk for developing endocrine late toxicity (with age, chemotherapy, status at HSCT and GvHD possibly playing a role), and should be strictly monitored during their follow-up in a multidisciplinary setting.

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POSTER

Fusion genes PAX3/7-FKHR as molecular markers of bone marrow micrometastasis in paediatric alveolar rhabdomyosarcoma

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Background: Alveolar rhabdomyosarcoma (aRMS) in children is an aggressive soft tissue tumour. Patients with metastatic aRMS have a very poor prognosis and recurrences are common in advanced localized disease. As known the majority of aRMS have the reciprocal chromosomal translocations t(2;13)(q35;q14) or t(1;13)(p36;q14). The molecular counterpart of these translocations is the generation of the fusion genes PAX3-FKHR and PAX7-FKHR, respectively. Molecular detection of disseminated tumour cells in bone marrow (DTCBM) could contribute to a better staging and treatment stratification in paediatric patients with aRMS.

Material and Methods: Seventeen children with advanced stages aRMS are enrolled in our study. Patients were treated according to the protocols CWS-96 and EpSSG RMS-2005. Sixty-three samples of bone marrow aspirations has been analyzed. Bone marrow samples were collected at diagnosis, after initial chemotherapy before surgery, after completion of therapy and at relapse if present. The presence of DTCBM was analyzed by real-time RT-PCR assay, based on the expression of fusion genes PAX3-FKHR and PAX7-FKHR.

Results: Chimeric transcripts PAX3/7-FKHR has been revealed in bone marrow of 8 patients, in 3 of which DTCBM have not been identified in morphology examination of bone marrow. In 3 patients after protocol therapy DTCBM have not been revealed that evidence on the efficiency of the treatment. These patients are still alive more than 2 years after initial diagnosis. Another 5 patients eventually developed tumour progression and died of the disease 12–14 months after initial diagnosis. It is necessary to emphasize that according to the results of RT-PCR study DTCBM have been revealed in 4 patients with III stage of disease confirmed by complex study. Therefore, these patients can be referred to a high risk group. In the present study of a cohort of children with advanced-stage aRMS, patients with bone marrow involvement had poorer survival than patients without DTCBM.

Conclusion: The detection of micrometastatic disease by real-time RT-PCR, based on the expression of fusion genes PAX3/7-FKHR, yields highly reproducible results. Molecular detection of DTCBM helps specify prognosis, risk group, schedules of therapy and provides its monitoring, allows reliably determine extent of achieved remission.

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POSTER

The extracellular domain of HER-2 as a potential marker for treatment monitoring in osteosarcoma

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Background: The aim of this prospective, diagnostic study was to estimate the predictive value of circulating levels of the extracellular domain of HER-2 (ECD/HER-2) in patients with osteosarcoma.

Methods: Thirty three newly-diagnosed primary osteosarcoma patients treated at the Department of Paediatric Oncological Surgery of the Institute of Mother and Child in Warsaw were included. Median aged 14 years range: 6–18 years. Staging at diagnosis: disease localised (18) and dissemination (15). Patients were treated with standard chemotherapy with ADM and cDDP and/or HD-MTX, and surgery of primary tumour +/- metastasectomy. Follow-up: median 25 months; range 16–38 months. ECD/HER-2 was measured (1) at time of diagnosis, (2) at the end of preoperative chemotherapy, (3) within 30 days after surgery and (4) at the end of treatment. Concentration of ECD/HER-2 was determined by HER-2/neu immunoassay. ECD/HER-2 status was analysed according to clinical and radiological data and percent of viable tumour cells remaining after preoperative chemotherapy.

Results: We analysed the levels of ECD/HER-2 in 33 samples at the time of diagnosis, in 30 samples at the end of preoperative chemotherapy, in 31 samples obtained within 30 days after surgery and in 30 samples at the end of treatment. The cut-off point for ECD/HER-2 levels was assessed as 5.5 ng/mL. The elevation of ECD/HER-2 over time was corresponding with disease progression ($P = 0.003$). The elevated ECD/HER-2 levels had 73% of patients with disease progression and 23% of patients without disease progression. Test sensitivity and specificity were 62% and 85%. The overall survival was lower with ECD/HER-2 levels >5.5 ng/mL compared to ECD/HER-2 levels ≤ 5.5 ng/mL: 54% vs 85% ($P = 0.077$). No relationship was found between ECD/HER-2 levels and patients age, disease dissemination at the time of diagnosis, tumour size, or histological response to preoperative treatment.

Conclusions: This pilot study has shown that elevated ECD/HER-2 concentrations over time may correspond with disease progression. Therefore ECD/HER-2 might be considered as a potential marker for monitoring patients with osteosarcoma.

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POSTER

Clofarabine: safety and efficacy profile for treatment of pediatric patients with refractory or relapsed acute leukemias

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Background: Despite the considerable progress in the treatment of acute lymphoblastic (ALL) or myeloblastic (AML) leukemia in pediatric patients (pts), the prognosis in case of primary refractory or relapsed disease remains poor. In view of new therapeutic agents, we evaluated the toxicity profile of clofarabine, a novel deoxyadenosine analog. The hybrid of cladribine and fludarabine has been developed to improve the efficacy and minimize the toxicity of its congeners, considering the heavy pretreatment of the population enrolled.

Patients and Methods: 10 pts; 5M and 5F, aged 3–15 years (median 9) with ALL (5) and AML (5), with refractory (4 AML, 1 ALL) or relapsed disease (1 AML, 4 ALL) received 1–3 cycles of clofarabine i.v. over 2 hours on 4 different dose levels between 30 and 52 mg/m²/day for 5 days (d), as a single agent (2 cycles), or associated with cytosine arabinoside, cyclophosphamide, etoposide and liposomal doxorubicin.

Results: A total of 18 cycles were administered. Three pts received 1 cycle, 6 pts 2 cycles and 1 pt 3 cycles. For every cycle the major toxicity was haematological with 100% of grade 2–3 of anemia, grade 4 of neutropenia and grade 2–4 thrombocytopenia with a median platelet transfusion necessity of 5/cycle. 3 pts remained transfusion-dependent for platelets. Seven out of 10 pts had grade 1–2 headache. Nausea/vomiting of grade 1–3 could be observed in 58% of the performed cycles, despite antiemetic prophylaxis with Ondansetron ± Dexamethazone and Clorfenamina. Nine out of 10 pts presented grade 1–4 hypertransaminasis. No other major SAE has been registered.

After the first cycle the response rate was 60% of complete remission (CR), 10% of partial remission and 30% of non response (NR). After the second cycle the CR rate was 86% (NR 14%). The only pt who effected a third cycle had NR. All CR have been achieved with Clofarabine associated to