exposure to TMZ at a low dose induced lymphopenia and might be responsible for a higher rate of viral infections.

4108 POSTER

Reduced intensity conditioning regimen and allogeneic stem cell transplantation from related or unrelated HLA identical donor in high risk neuroblastoma

A. Prete[1], R. Rondelli[1], F. Locatelli[2], E. Lanino[3], C. Favre[4], M. Rabusin[5], A. Pession[6], F. Fagioli[7]. [1]*Ospedale S. Orsola Malpighi, Oncology and Hematology Pediatric Department, Bologna, Italy;* [2]*IRCCS S. Matteo, Oncology and Hematology Pediatric Department, Pavia, Italy;* [3]*G. Gaslini Institute, Oncology and Hematology Pediatric Department, Genova, Italy;* [4]*Clinica Pediatrica, Oncology and Hematology Pediatric Department, Pisa, Italy;* [5]*IRCCS Burlo Garofaolo, Oncology and Hematology Pediatric Department, Trieste, Italy;* [6]*S. Orsola-Malpighi, Oncology and Hematology Pediatric Department, Bologna, Italy;* [7]*Ospedale S. Anna, Oncology and Hematology Pediatric Department, Torino, Italy*

Background: To evaluate the feasibility and efficacy of a reduced intensity conditioning regimen (RIC) followed by allogeneic stem cell transplantation (SCT) from related or unrelated HLA identical donor (MUD) in neuroblastoma (NB) poor responder to front line therapy or relapsed after a previous autologous stem cell transplantation.
Methods: 19 patients (pts), aged 3−17 years, affected by resistant (5) or relapsed (14) NB were enrolled and submitted to an SCT after a RIC consisting of Thiotepa 15 mg/kg and Melphalan 140 mg/sqm. The donor was an identical sibling in 11 cases or a MUD in 8. At time of transplant 14 pts were in any kind of remission of disease and 5 in progressive disease. Graft versus host disease (GVHD) prophylaxis consisting of Cyclosporin A $\pm$ Anti-lymphocytic serum and short term methotrexate in MUD setting. Stem cell sources were bone marrow in 15 cases and peripheral blood in 4.
Results: The reconstitution of bone marrow function was obtained in all the 19 pts after a median time of 12 and 17 days for PMN and PLT respectively in sibling setting, and 14 and 17 days in MUD setting. Acute GVHD of grade II-III occurred in 7 pts and a complete marrow donor chimerism was observed after 40 and 60 days in sibling and MUD setting respectively. After a median follow-up of 25 (6−41) months, 9 pts relapsed, 6 dead for progressive disease and 10 are alive and well. The median time of relapse from SCT was 9 (3−25) months. No pts dead for treatment related causes (TRM). The 3 years probability of overall survival (OS) and event free survival (EFS) of the entire cohort of pts were respectively 0.58 (0.13) and 0.30 (0.13), with a better SUR and EFS for pts who developed grade II-III acute GVHD (SUR 0.67 versus 0.44; EFS 0.30 versus 0.22), were in any kind of stable disease (SUR 0.62 versus 0.53; EFS 0.41 versus 0 p = 0.041), received a MFD graft (SUR 0.62 versus 0.50; EFS 0.32 versus 0.25).
Conclusions: Our experience show the feasibility and efficacy of a RIC with SCT from HLA MFD or MUD in the treatment of relapsed or refractory NB. In fact no patient suffered TRM. Moreover in a setting of pts who the 3 years probability of survival is nearly to zero, in our experience more than 50% are alive and well. The observation that the develop of acute GVHD is related to a better outcome may offer the evidence of graft-versus-tumour in NB.

4109 POSTER

Rodent parvovirus H1 induces lytic infection in human neuroblastoma cells and down-regulates N-myc expression in N-myc amplified neuroblastoma cell lines

J. Lacroix[1], J. Li[1], B. Leuchs[1], H.E. Deubzer[2], O. Witt[2], J. Rommelaere[1], J.R. Schlehofer[1]. [1]*German Cancer Research Center, FS Infection and Cancer, Heidelberg, Germany;* [2]*University Children's Hospital, Paediatric Hematology Oncology and Immunology, Heidelberg, Germanyi*

With about 15% of all deaths in pediatric oncology advanced localized and high risk neuroblastoma remains a main therapeutic issue. Thus, despite applying multimodal therapeutic concepts, new modalities for the treatment of neuroblastoma are urgently required. H1-PV is an oncolytic wildtype Parvovirus in rodents. So far, no relevant pathogenic effects have been observed in laboratory animal populations, widely infected with H1-PV. Additionally, no pathogenicity and low immunogenicity of H1-PV infection have been observed in humans. Here, we investigated, whether the oncolytic H1-PV is cytotoxic for neuroblastoma cells.
Neuroblastoma cell lines with different MYCN status as well as normal primary cells of different origin were infected with H1-PV. We determined infection efficacy, viral replication, lytic activity and cell viability and effects of H1-PV on N-myc expression in vitro.
Non-neoplastic infant cells (myocardial myocytes, glia cells, astrocytes and neuronal cells in short term culture) could be shown to be unaffected in viability and morphology by H1-PV. In contrast, all 11 neuroblastoma cell lines analyzed were infectable with H1-PV, and H1-PV actively replicated in neuroblastoma cells with virus titres increasing up to 10.000-fold within 48 to 96 hours after infection. Parvovirus H1 induced lytic infection in all 11 neuroblastoma cell lines after application of MOIs between 0.001 and 1 pfu/cell. The lytic effect of H1 was independent of MYCN oncogene amplification or differentiation status of the respective cell line. Moreover, H1-infection could be demonstrated to down-regulate the protein level of N-myc in N-myc amplified neuroblastoma cell lines.
The application of H1-PV appears to be a promising treatment option for neuroblastoma. The treatment efficiency is currently analyzed in a rat xenotransplant model.

4110 POSTER

Survivors after childhood malignant lymphoma (MLCSs): what do they know about their diagnosis and treatment?

S. Hess[1], H. Hamre[1], C. Kiserud[1], J.H. Loge[1], S.D. Fossâ[1]. [1]*Rikshospitalet – Radiumhospitalet Trust, Clinical Cancer Research, Oslo, Norway*

Background: MLCSs are at risk for long term effects, but need to have knowledge about their diagnosis, treatment and possible late effects in order to take responsibility for their own health.
Methods: 215 adult MLCSs were invited to participate, 145 (67%) responded. So far 115 MLCSs have completed physical examination, blood sampling, cardiopulmonary tests and responding to a questionnaire evaluating health problems. Before the clinical examination, they were interviewed about their awareness of their malignancy and treatment. Their responses were compared with medical record data.
Results: Sixty-two were males (54%), 53 females (46%). Median observation time was 21 years (range: 7−37 years). The median age at diagnosis was 13 years (2−18), the median age at survey was 34 years (19−55). 71 (62%) had Hodgkin lymphoma (HL), 44 (38%) had non-Hodgkin lymphoma (NHL). 108 (94%) reported their diagnosis correctly, 7 (6%) reported that they had cancer, but did not identify malignant lymphoma. 28 (26%) could not differentiate HL vs NHL.
103 patients (90%) had been treated with chemotherapy (CT), of whom 37 with CT only. 78 patients (76%) had undergone radiotherapy (RT), 12 with RT only. 66 patients (64%) had been treated with both CT and RT.
109 of 115 (95%) reported their treatment modalities correctly. Among the 103 treated by chemotherapy, 73 (71%) did not know the name of any cytostatic drug. Of the 78 who had received radiotherapy, 73 (94%) described the radiation site precisely. Only 13 (11%) had – on request – received a written summary of their disease and treatment, and 96 (84%) reported that they were not regularly followed as to long-term effects. 75 (65%) were not aware of the risks for long-term effects and consequences of their treatment.
Conclusion: MLCSs in Norway seem to have a sufficient level of knowledge about their diagnosis and treatment modality. But they have a low level of knowledge about consequences and long-term toxicity. In general they have received verbal, but not written information about their disease and treatment. Improved communication seems necessary between MLCSs and the responsible health care team, both at the end of oncological follow-up and during subsequent years.

4111 POSTER

Esthesioneuroblastoma in children and adolescents: experience on 11 cases with literature review

O. Oberlin[1], J.L. Habrand[2], F. Janot[3], L. Amoroso[1], D. Couanet[4], M. Elkababri[1]. [1]*Institut Gustave Roussy, Paediatrics, Villejuif, France;* [2]*Institut Gustave Roussy, Radiotherapy, Villejuif, France;* [3]*Institut Gustave Roussy, Surgery, Villejuif, France;* [4]*Institut Gustave Roussy, Radiology, Villejuif, France*

Background: Esthesioneuroblastoma (ENB) is an uncommon malignancy developing from the olfactory placode, in the superior nasal vault. Purpose of this study was to review the cases of paediatric ENB treated at the Pediatric Department of the Institute Gustave Roussy (IGR).
Material and Methods: Between 1982 and 2002, eleven children and adolescents with histologically proven olfactory neuroblastoma were treated at IGR. Therapy included chemotherapy, administered before surgery, and radiotherapy.
Results: 10 out of 11 patients received chemotherapy. Only one patient underwent surgery before radiation therapy and did not receive chemotherapy. All patients underwent radiotherapy. The response to chemotherapy could be assessed in 10 patients of whom 7 achieved complete or partial response. One patient achieved complete response by chemo- and radiation therapy alone. After an 8.8 years median follow-up (range, 3.9−16.4 y), 10 patients were survivors. Only one patient relapsed locally and at distant sites 9 months after the diagnosis, and died after few

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.

4112 POSTER

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

L. Moreno Martin Retortillo[1], F.J. Bautista Sirvent[1], S. Zacharoulis[1]. [1]*Royal Marsden Hospital, Children's Department, Sutton Surrey, United Kingdom*

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. Comparisions 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.

4113 POSTER

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

W. Wozniak[1], A. Chybicka[2], J. Kowalczyk[3], M. Wysocki[4], M. Korzon[5], M. Krawczuk-Rybak[6], M. Rychlowska-Pruszynska[1], K. Szamotulska[7], I. Lugowska[1]. [1]*Institute of Mother and Child, Department of Paediatric Oncological Surgery, Warsaw, Poland;* [2]*Wroclaw Medical University, Department of Pediatric Bone Marrow Transplantation Oncology and Hematology, Wroclaw, Poland;* [3]*Medical University of Lublin, Department of Pediatric Hematology and Oncology, Lublin, Poland;* [4]*Medical University of Bydgoszcz, Department of Pediatric Hematology and Oncology, Bydgoszcz, Poland;* [5]*Medical University of Gdansk, Clinic of Pediatrics Pediatric Gastroenterology and Oncology, Gdansk, Poland;* [6]*Medical University of Bialystok, Department of Pediatric Hematology and Oncology, Bialystok, Poland;* [7]*Institute of Mother and Child, Department of Epidemiology, Warsaw, Poland*

Background: This prospective, multicentre trial was designed to compare two protocols: high-dose methotrexate+doxorubicin (MTX/DOXO) vs cis-platin+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 chi^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 we 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-respondres-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.

4114 POSTER

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

Z.M. Hegyi[1], A.F. Semsei[2], E. Cságoly[2], K. Bácsi[1], D. Erdélyi[2], C.S. Szalai[2], G.T. Kovacs[1]. [1]*Semmelweis University, 2nd Department of Pediatrics, Budapest, Hungary;* [2]*Semmelweis University, Department of Genetics Cell- and Immunobiology, Budapest, Hungaryi*

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 methorexate 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 methorexate infusion; the highest serum GPT, GGT and bilirubine 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.

4115 POSTER

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

A.R. Filippi[1], P. Ciammella[1], E. Biasin[2], A. Botticella[1], A. Namysl-Kaletka[1], E. Vassallo[2], A. Corrias[3], F. Fagioli[2], U. Ricardi[1]. [1]*University of Torino – S. Giovanni Battista Hospital, Radiation Oncology, Torino, Italy;* [2]*University of Torino – Regina Margherita Hospital, Pediatric Oncology, Torino, Italy;* [3]*University of Torino – Regina Margherita Hospital, Endocrinology, Torino, Italy*

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.
Matherials 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