A CONSENSUS AND STATE-OF-THE-ART WORKSHOP

MARROW ABLATIVE CHEMOTHERAPY WITH HEMATOPOIETIC CELL RESCUE FOR MALIGNANT BRAIN TUMORS OF CHILDHOOD AND ADOLESCENCE

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OUTCOME IN CEREBRAL GLIOMA TREATED WITH A PROGRAM INCLUDING HIGH-DOSE CHEMOTHERAPY AND STEM CELL RESCUE

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This study describes the motor, sensory and cognitive outcome of 4 patients with cerebral glioma (3 located supratentorially and 1 located subtentorially) that had been previously treated at the Milan National Institute of Tumors with a protocol described elsewhere during this meeting (Massimino *et al*). For each patient, the medical and oncological history as well as treatment-related information were reviewed. All the patients received an assessment protocol including an evaluation of the motor, sensory and cognitive outcome. The mean age of the patients at diagnosis was 8.7 years (range: 6-10.5), the mean age at our assessment was 10.5 years (range 6.8-13), the mean age at focal radiotherapy was 9.2 (range: 6-11.2). The outcome assessment was performed at a mean time from diagnosis of 1.8 years (range: 0.75-3 years). Three patients showed neurological problems (hemiparesis/cranial nerve palsies), but none of them was epileptic. Ocular and auditory late effects were found in 3 and 2 patients, respectively. On the cognitive evaluation the VIQ, the PIQ and the FIQ were in the normal range (99.3, 101.7 and 102.7, respectively). Three out of 4 patients were re-assessed with a mean follow–up time of 30 months. On the repeat assessment, the 3 IQs were lower than on the first assessment (VIQ: 105.5 vs. 110.5; PIQ: 92 vs. 104; FIQ: 99 vs. 108.5), but the difference was not significant, probably due to the small number of patients. The lower cognitive level appears in line with published studies on patients receiving cranio-spinal radiotherapy. The lower PIQ score also partially depends on the reported visual problems. A longer follow-up period is needed for a more precise outcome assessment.

ENDOCRINE SEQUELAE IN CHILDREN WITH BRAIN TUMOURS

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The progressively increasing number of long-term survivors of brain tumors after treatment has lead to increased attention to late effects which can be defined as "persistent, adverse changes, related to the disease, its treatment or both". Endocrine complications are the most common and include the hypothalamic-pituitary axis, gonadal function and thyroid gland. When the hypothalamic-pituitary axis falls within the fields of irradiation, isolated GH deficiency or multiple anterior pituitary hormone deficiency can occur, depending on the total dose, fraction size, number of fractions and duration of treatment. Age of the patient at the time of radiotherapy is an additional factor contributing to endocrine morbidity with younger children being more vulnerable. In tumours such as craniopharyngiomas, given the location of the disease and the local surgery, which often necessitates transection of the pituitary stalk, it is unsurprising that long-term post-operative hypothalamo-pituitary endocrine dysfunction is common. Diabetes insipidus is commonly seen in these scenarios as well as anterior pituitary dysfunctions. A primary role of intense chemotherapy treatment on endocrine dysfunctions remains to be fully established. However it is now recognized as having a directly negative impact on bone metabolism leading to osteoporosis and impaired responsiveness to growth factors. *Innovative* intervention strategies such as marrow ablative chemotherapy with hematopoietic cell rescue for malignant childhood and adolescent brain tumours will be discussed at the meeting. It is imperative that prospective multicentre surveillance programmes are in place to monitor and document any positive or negative impact on growth, thyroid and gonadal function.

THE ROLE OF HIGH-DOSE CHEMOTHERAPY IN THE TREATMENT OF CENTRAL NERVOUS SYSTEM (CNS) GERM-CELL TUMOURS (GCT)

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First line therapy in both secreting and not secreting germ-cell tumours includes PEB chemotherapy and radiotherapy (whole ventricular irradiation and/or craniospinal irradiation). High-dose chemotherapy (HD-CT) followed by autologous stem-cell rescue has not a defined role in the treatment of relapsed CNS germ-cell tumours. *Aim.* The purpose of this study is to define the role of high-dose chemotherapy in the treatment of germ-cell tumours, when standard treatment schedules don't provide a complete and durable response or when there are risk factors at the diagnosis. *Methods.* From January 1998 to December 2004, 40 patients affected by intracranial germ-cell tumours were treated at our institution according to the institutional protocols for secreting and non secreting germ-cell tumours. In detail, non-secreting germ-cell tumours received 4 PEB cycles followed by radiotherapy on the whole ventricular system (total dose of 30.6 Gy if complete response/no evidence of disease or 36 Gy if partial response). Secreting germ-cell tumours received 6 total PEB cycles, 4 pre- and 2 post-radiotherapy (craniospinal irradiation plus whole ventricular irradiation with a total dose of 45 Gy). Of these 40 patients, 5 patients (2/5 secreting and 3/5 non secreting germ-cell tumours) were treated with high-dose chemotherapy followed by autologous stem cells rescue because of resistant (1), recurrent (2) or high-risk disease (2). The patient with resistant disease had had progression during therapy (evidence of malignant neoplastic cells in the cerebro-spinal fluid after 2 PEB courses), the 2 patients with recurrent disease (1 non secreting and 1 secreting germ-cell tumours) had relapsed after 18 and 84 months respectively from the end of the first line therapy. The 2 high-risk patients presented with elevated (>1000) α-feto-protein/β-hcg levels in cerebro-spinal fluid at diagnosis. High-dose chemotherapy consisted in two courses of high-dose thiotepa (300 mg/sqm x 3 days) in 4/5 patients while 1 patient received only one course because of a severe pulmonary infection during the myelodepression phase. Each course of thiotepa was followed by autologous stem-cell rescue on day +3. *Results.* At January 2006, all the 5 patients treated with HD-CT are living. Four out of 5 pts have a negative follow-up with no evidence of disease documented by neuroimaging studies and CSF evaluation, while 1 patient is at her 3rd progression (49 months after the second HD-TT) and she is still doing chemotherapy (4th line therapy with taxol, oxaliplatin and gemcitabine). All the 5 patients are actually treated with substitutive therapy: 4/5 patients present panhypopitutitarism from the diagnosis (1 also presents osteomalacia and 1 has been evaluated for growth hormone deficiency but has not still started the substitutive therapy) and 1 patient is actually treated only with calcium and D-vitamin. *Discussion.* Primary CNS germ-cell tumours are rare, constituting less than 5% of all brain tumours. Due to their rarity and to the reduced relapse rates, only few studies have focused on the approach to the recurrent, progressive or high-risk disease. Literature reports how patients who experience relapse after chemo- and radiotherapy, or those who do not

respond to initial treatment, invariably die as a result of progressive disease. High-dose chemotherapy (HD-CT) has not an established role in the treatment of CNS germ-cell tumours. Trying to improve survival in patients with recurrent/resistant/high-risk CNS germ-cell tumour, we evaluated the use of HD-CT followed by autologous stem-cell rescue. According to our experience, HD-CT can be proposed in the treatment of CNS germ-cell tumours as a second-line therapy for resistant and recurrent disease or as a first line therapy for disease presenting with risk factors at diagnosis. The use of HD-CT in these particular high-risk patients seems to be associated with a better prognosis.

THE ROLE OF HD CHEMOTHERAPY (CT) IN THE TREATMENT OF THERAPY-RESISTENT CNS PNETs. HIT-REZ-97 RESULTS

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Though relapsed neuroectodermal brain tumors have historically a dismal prognosis, initial treatment results using HD chemotherapy with stem cell support were promising ten years ago. Therefore the German relapse study for medulloblastomas, HITREZ 97, contained a stratification for these patients, in order to balance therapy intensity and quality of limited life span. Seventy-two out of 110 study patients with relapsed PNET received continuous infusions of carboplatin/VPI6 for 96 hours. Good responders (>PR after 6 weeks) were supposed to get stem collection during two more conventional courses and then receive a high dose carboplatin/VPI6/thiotepa course with stem cell support (PBSC). All means of local therapy and intraventricular therapy (in case of metastatic disease) were applied in addition. Twenty-six patients received HD chemotherapy with PBSC ($3.6x10^6$ CD34/kg). Chemotherapy consisted of carboplatin (2000 mg/m^2), VPI6 (1000 mg/m^2) and thiotepa 600 mg/m^2. One of 26 received thiotepa (900 mg/m^2) and cyclophosphamide (4500 mg/m^2). Eleven patients received methotrexate (7) or VP16 (4) intraventricularly. Prior to HDCT there were 9 CR (34.6%), 12 PR (46.2%) 5 SD/PD (19.2%), whereas there were 12 patients in CR (46.2%) and 9 in PR (34.6%) after HD chemotherapy. Two patients died of infectious complications. After HD therapy 3 patients had an operation, 4 patients got irradiated and 4 patients got more chemotherapy. Today 3 patients are alive, 2 in CR, 1 in PR; 1 patient is LFU. Comparing good responders to conventional chemotherapy there is no significant difference in PFS/OS of patients receiving or not receiving HD chemotherapy. Toxicity (CTC° 3/4) of HDCT was impressive: oral/gastrointestinal mucositis (90%), infectious episodes (50%), liver toxicity (33%, 1 VOD), lung toxicity (27%, 4 ARDS), and 66.6% ototoxicity. The TRM was 7.7%. In summary, there was no difference of DFS and OS in patients with relapsed cerebral PNETs receiving chemotherapy +/- HDCT in this study. Whether there might be a role of HDCT in individual patients having systemic and local therapeutic options has be investigated.

RECURRENT GERM CELL TUMOURS OF THE CNS

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Although survival rates in patients with germinomas and non germinomatous germ cell tumours of the central nervous system are high, 10-20% (germinoma patients) to 30-40% (NGGCT patients) will experience relapse and require second line treatment. Reports on retrieval strategies are few. Treatment modalities at the time of recurrence will depend on the type of first line treatment, and in particular the use of radiation and the volumes and doses of radiation treatment. Pilot studies suggest that intensive and high dose chemotherapy may provide a chance of long term survival in a subset of patients. Optimal high dose chemotherapy regimens need to be developed in large cooperative studies.

HIGH DOSE CHEMOTHERAPY IN CHILDREN WITH INTRACRANIAL RHABDOID/TERATOID TUMOURS (AT/RT): REVIEW OF AN INSTITUTIONAL EXPERIENCE

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Between 2002 and 2006, 7 patients (age 0.1 to 15.7 years, with 6/7 aged < 4 year old) with rhabdoid tumour (AT/RT) of the CNS were seen in our institution. 2 infants did not receive any treatment. One patient with primary AT/RT of the spinal cord was treated with surgery followed by CSI and chemotherapy. All 4 remaining patients were treated with a protocol including sequential high dose chemotherapy and are reported herein. The primary location was supratentorial in one patient and infratentorial in 3 (2 cerebellar, one cerebello-pontine angle). One patient with infratentorial tumour had a metastatic deposit in the frontal lobe. All patients underwent surgery, which consisted of GTR in 2 patients, subtotal resection in 2. The patient with metastatic disease underwent resection of both primary and metastatic lesions. 3 patients were treated with a combination of etoposide-ciplatin-vincristine-cyclophosphamide and one according to the IRS III regimen. One patient with subtotal resection underwent focal radiation during the early phase of chemotherapy. All patients then proceed to sequential high dose chemotherapy with 3 courses of carboplatin and thiotepa followed by peripheral stem cell rescue. All were in complete remission at the end of the treatment. One patient received adjuvant IMRT to the tumour bed after completion of chemotherapy. With a median follow-up of 15 months since diagnosis (range 12-25 months) all 4 patients are alive in CCR. *Conclusions:* this experience adds to the preliminary evidence suggesting a benefit of aggressive treatment in a subset of patients with AT/RT. Interestingly, 2 out 4 children in this experience did not receive radiation.

HIGH-DOSE CHEMOTHERAPY AND HEMATOPOIETIC STEM CELL RESCUE IN PEDIATRIC BRAIN TUMORS: THE EXPERIENCE AT CHILDRENS HOSPITAL LOS ANGELES

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From 1992 to 2005, 63 patients aged 8 months to 18 years received high dose chemotherapy with hematopoietic stem cell rescue (HDC+HSCR). This therapeutic approach was used as consolidation of the initial therapy in 41 patients (including 24 PNET/medulloblastoma, 7 high grade gliomas, 6 ependimoma, 3 rhabdoid tumors and 1 choroid plexus carcinoma) and after relapse in 22 patients (including 16 PNET/medulloblastoma, 3 germinoma, 2 high grade gliomas and 1 choroid plexus carcinoma). Of the 42 patients treated with upfront HDC+HSCR, radiotherapy was part of initial therapy in 3 of the 31 patients aged <6 years at diagnosis and 9 of 11 aged <6 at diagnosis. Of the 22 patients transplanted after relapse, radiotherapy was part of the relapse therapy in 7 patients; of the remaining 15, 11 had received radiotherapy upfront and 4 never received radiotherapy. 3 year event free survival (EFS), and survival from transplant are in the following table:

	N	*EFS*	*survival*
All patients	63	46±7	74±6
ALL patients treated upfront	41	51±9	84 ±6
PNET/Mbl treated upfront	24	66±10	86±7
ALLpatients treated after relapse	22	34±13	39±15
PNET/Mbl treated after relapse	16	25±13	42 ±14

The results of HDC+HSCR were significantly better if it was performed upfront. In patients transplanted upfront, diagnosis

of PNET/medulloblastoma, localized disease, complete resection and being in CR before transplant were associated with significant better outcome. In contrast, the use of radiotherapy had no impact on EFS or survival. In patients transplanted after relapse, the best outcome was in the patients in CR before transplants and in those who received radiotherapy at time of transplant and in those. In conclusion the most successful use of HDC+HSCR is as upfront therapy in patients with PNET/ medulloblastoma: in this setting it may avoid the use of radiotherapy. In the other settings results are less impressive however itcan still salvage a quarter of patients with recurrent PNET/medulloblastoma and possibly more patients with recurrent germinoma.

CONDITIONING REGIMENS BEFORE AUTOTRANSPLANT IN BRAIN TUMORS

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Conditioning regimens for brain tumor are typically based on high-dose alkylators. The highly lipophilic alkylator thioTEPA is widely used for its ability of penetrating into the central nervous system, but melphalan, busulfan, BCNU, carboplatin and cyclophosphamide were also utilized; temozolomide is presently tested in clinical trials. Alkylators are given either alone or in combination with other drugs. The rationale for using single-drug conditioning regimens is to use the highest possible dose of one effective drug avoiding the combined toxicity of drug combination. In contrast, the rationale for combining multiple drugs is based on potential synergy (eg, a DNA damaging alkylators and drugs affecting DNA repair, ie thioTEPA + etoposide) or on minimizing toxicity (drugs with similar anticancer mechanisms but different toxicity, eg. double alkylator regimens: melphalan + cyclophosphamide, thioTEPA+ carboplatin and more recently, thioTEPA + temozolomide). Doses and characteristics of conditioning regimens also depend on whether they are designed for a single or multiple transplants. *Single transplant* conditionings usually use more aggressive doses and drug combinations. In contrast *multiple transplant* regimens are typically milder: before each transplant patients either receive the same or different drug (or drug combination). Examples of the latter are cyclophosphamide +carboplatin +etoposide alternated to cyclophosphamide +thiotepa. Post transplant morbility and mortality vary greatly in different reports. Mortality as high as 30% was reported in early studies; in more recent studies transplant-related mortality is 5% or less. So far no conditioning regimen was proven superior in brain tumors or in any other cancer in the context of autotransplantation. Studies using temozolomide are too recent to be evaluated.

COMPLICATIONS FROM HIGH-DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANT: THE IMPORTANCE OF SEQUENCE AND TIMING OF THERAPY

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Treatment with high-dose chemotherapy (HDC) and autologous stem cell transplant (ASCT) is not without unanticipated and untoward side effects, though the frequency of some is thought to be acceptably low. Between 2002 and 2006, 18 patients have undergone HDC and ASCT at the Dana-Farber Cancer Institute/ Children's Hospital Boston for both newly diagnosed and recurrent malignant brain tumors (1 medulloblastoma, 7 recurrent medulloblastoma, 7 PNET, 1 glioneuronal tumor, 2 germ cell tumor). For four patients with newly-diagnosed PNET, a treatment regimen utilizing two induction cycles of cyclophosphamide and vincristine, followed by craniospinal irradiation (3600 cGy CSI, 5480 cGy total to the primary site), and then a single consolidation chemotherapy cycle of carboplatin, thiotepa and etoposide one month post-RT was administered. The other 14 patients received radiation therapy and various chemotherapy regimens, appropriate to their tumor type and prior therapy history. Consolidation regimens were thiotepa-based for all except for two patients. Timing of HDC/ASCT also varied among these patients. For the four patients who received this specific treatment plan, all have no evidence of disease at this time with a median follow-up time of 2.7 years (range 2.5-4.0 years). Among them, two patients experienced transverse myelitis (TM) within 12-14 weeks of transplant. Both patients remain paraplegic and require assistance in ambulation. Esophageal stricture formation was seen in two patients 5-12 months post-transplant; one patient continues to receive intermittent esophageal dilatation. Veno-occlusive disease occurred early during transplant in two patients; both patients received defibrotide and both have resolved without long-term sequelae. All other patients in our cohort treated with HDC/ASCT, in both up-front or retrieval settings, did not experience these complications, suggesting that the specific sequence and timing intervals between treatment modalities, i.e. radiation therapy in relationship to chemotherapy and autologous transplant, is of critical importance and impacts the quality of survival.

A PILOT STUDY OF INTENSIVE CHEMOTHERAPY WITH PERIPHERAL STEM CELL SUPPORT FOR INFANTS WITH MALIGNANT BRAIN TUMORS

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Introduction. Therapy for infants and young children with brain tumors remains a challenge because of both the aggressive nature of the neoplasm and the need to avoid radiotherapy. CCG-99703 was designed as a pilot study intended to evaluate the feasibility and toxicity in the context of a group-wide study of administering repetitive cycles of high-dose chemotherapy with peripheral blood stem cell rescue in infants with malignant brain tumors. *Methods and Patients.* Between March 1998 and October 2004 children with malignant brain tumors between the ages of 6-36 months were eligible for enrollment. Following best surgery and staging, patients were treated with three cycles of cyclophosphamide, etoposide, vincristine and cisplatin (Induction) using the same regimen as regimen A of CCG-9921. During induction, peripheral blood stem cells were harvested. Patient's eligible for consolidation were those that completed induction, achieved a minimum collection of 15 x 106 kg-1 CD34+ cells, were re-staged with brain and spine MRIs and CSF cytology and deemed not to have progressed, and met clinical and laboratory criteria to start consolidation within six weeks of the last dose of Induction therapy. Consolidation consisted of three cycles of carboplatin (17 mg/kg IV infusion on Days 0 and 1) and thiotepa. The initial cohort of patients was treated with a thiotepa dose of 6 mg/kg/day on Days 0 and 1. Cohorts of at least 6 patients (range 11-19 patients) were evaluated at escalating dosages of thiotepa until a set number of patients experienced DLTs. The study was complete when the patient achieved adequate unsupported white blood cell counts and platelet counts after the third cycle of consolidation. Radiotherapy was not part of the treatment. *Results.* 92 patients enrolled in the study, with two ultimately not being eligible. The most common histologies included PNET (17), medulloblastoma (21), ATRT (10) and all grades of ependymoma (19). Eleven patients did not proceed to consolidation because of either death or progression during induction, parent-initiate withdraw from the study or failure to achieve adequate stem cell harvest. 74 eligible patients were treated with consolidation therapy. DLTs included death (2-fungal), VOD (2), grade IV neurologic (1), grade IV pulmonary (1), severe diarrhea (1), and failure to complete 3 cycles of consolidation within 100 days because of neutropenia or thrombocytopenia (2). For M0 MB patients, the 6-month EFS was 100% in totally resected patients and 78% in the subtotally resected group. The 3-year OS for the M0 MB patients was 76%, with a 67% EFS in this group. The Kaplan-Meier actuarial survival for other subset of patients is still evolving. *Discussion and Summary.* In the context of a group-

wide study initiated in the later 1990s there was both the successful ability to adequately harvest peripheral blood stem cells and deliver the treatment with acceptable toxicity. The EFS and OS in some groups of patients appears to be significantly better than therapy in trials that utilized dosages of chemotherapy that did not require peripheral blood stem cell rescue. The EFS and OS compares favorably to the results of other treatment trials using autologous bone marrow rescue or peripheral blood stem cell rescue. Additional time will be needed before the 5-year EFS and OS results will be available and final comparison and conclusions can be discussed.

NEUROSPHERES AND SIDE POPULATIONS FROM GLIOBLASTOMA MULTIFORME (GBM) CAN CONTAIN CELLS WITH STEM –LIKE PROPERTIES

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We have obtained neurospheres from adult patients with GBM and found that they can express glial and neuronal markers in vitro and generate tumors in the brain of CD1 nu/nu mice. Although these tumors were highly infiltrating, they did not completely recapitulate the features of the original GBM. Cells from two GBM were cloned and we found a positive relationship between the fraction of clone–originating cells and their proliferation *in vitro*. Adherent cells from the same GBM were grown in the absence of EGF and b-FGF: when injected into mouse brains they also caused large infiltrating gliomas, but later and less frequently than neurospheres ($p<0.02$ on Kaplan Meier analysis, log rank test). When adherent cells were shifted to EGF-bFGF medium they did not form neurospheres. Also, neurospheres obtained by growing U87 cells (a GBM established cell line) with EGF-bFGF caused tumors that were larger but phenotypically identical to those derived from U87 cells grown as a monolayer without EGF-bFGF. The side population (SP) phenotype can identify a subpopulation of stem cells that are only weakly stained by Hoechst 33342 and is conferred by the expression of the ABCG2-BCRP gene. The side population was recently identified also in tumor cells, including GBM. We have sorted by flow cytometry rat C6 GBM cells. SP C6 cells were 4-5% of the whole population. After sorting, SP and NON-SP C6 cells were kept in culture as neurospheres for one week during which their proliferation rate was checked by WST staining: NON-SP cells were proliferating faster than SP cells ($p<0.03$).Ten days after sorting ABCG2 was expressed in 30 % of SP cells and in 10% of NON-SP cells, as assessed by flow-cytometry. We then injected 1x10e5 SP or NON-SP into the brain of CD1 nu/nu mice (n=12). After 15 days all mice injected with SP cells died because of a very large malignant gliomas. Gliomas in mice injected with NON-SP cells were smaller and not lethal until day 21, when mice were sacrificed for histology. These data suggest that neurospheres grown in EGF-bFGF and SP cells may express critical genes for tumor initiation and be endowed with cancer stem-like properties. Expression profiling of these two GBM subpopulations could help the identification of these critical genes.

FEASIBILITY AND TOXICITY OF HDCT IN LOW WEIGHT CHILDREN (< 20 KG AT DIAGNOSIS): THE EXPERIENCE AT G. GASLINI CHILDREN'S HOSPITAL IN TREATMENT OF MALIGNANT BRAIN TUMOURS

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High dose chemotherapy (HDCT) has been demonstrated to improve the event free survival (EFS) for children suffering from various cancers including some types of central nervous system neoplasias. Collection of progenitor cells (PBPC) has become a routine medical procedure in pediatric oncology patients. However, experience regarding the feasibility and toxicity of these procedures in patients weighing less than 20 kg is still limited. We present our mono-institutional experience in 32 children treated at Gaslini children's Hospital in the period 1996-2006. Diagnosis were: medulloblastoma (15), PNET (6), AT/RT (3) and other CNS tumours (8). All patients were treated according to the infants HR-CNS tumors protocol. PBPC's collection was carried out after the 2nd and/or the 3rd cycle of the induction (Phase A), namely after high dose Etoposide (2.4 g/m^2) and after cyclophosphamide (4 g/m^2). In all cases but one the PBPC's amount necessary for tandem HDCT and for post RT rescue was yielded. The majority of the patients performed 1 collection per cycle and the harvest was fractionated and stored in 3 separated bags. G-CSF was administered subcutaneously at 10 µg/kg, in a tailored fashion starting at the ANC nadir. Central venous monolumen catheter and a peripheral access were used for the apheresis, no double lumen or arterial accesses have been inserted. PBPC collections were performed as outpatients, in absence of citrate toxicity, clotting events or haemodinamic troubles. The 2 courses of HDCT with PBSCs re-infusion were administered in 26 children and consisted of Carbo 1.5 g/m^2/etoposide 1.5 g/m^2 and thiotepa 900 mg/m^2/melphalan 120 mg/m^2, respectively. In last years, thanks to the Home Care Unit availability, patients were discharged after the 1st reinfusion, followed at home and re-admitted in case of complications as febrile neutropenia or >WHO grade 1 mucositis. The thiotepa/melphalan has been demonstrated more toxic, especially for oral and gut mucosa, all patients had fever, required total parenteral nutrition and, rarely, major analgesic drugs use. One child didn't show haematologic recovery and needed a 2nd PBPC reinfusion followed by prompt and stable take. No toxic deaths or life-threatening complications were observed.

In summary, PBPC collection is feasible and safe, in a outpatient setting, even in children weighing less than 20 kg. Tailored G-CSF administration minimized the risk of yield failures and allowed a significant reduction in costs compared with traditional mobilization from the day +1. The storage of a 3rd bag for post-RT rescue is useful and can avoid treatment interruption. The double HDCT cycle is feasible, the mucosal toxicity of the combination Thiotepa/Melfalan is remarkable but manageable with the BMT Unit facilities. A strict follow-up for mid and long term sequelae is necessary to monitor consequences of intensive chemotherapy and subsequent cranio-spinal irradiation.

FEASIBILITY AND EFFICACY OF TANDEM HIGH-DOSE CHEMOTHERAPY FOR CHILDREN WITH HIGH-RISK MEDULLOBLASTOMA AND SUPRATENTORIEL PRIMITIVE NEUROECTODERMAL TUMORS AT DIAGNOSIS

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Purpose of the study. To evaluate feasibility and efficacy of an intensified chemotherapy regimen for children with high risk medulloblastoma/PNET at diagnosis. *Methods.* Twenty-one children with disseminated medulloblastoma (n=18) or sPNET (n=3) aged 5 to 15 years were enrolled. They received as post operative induction chemotherapy two cycles of etoposide (500 mg /m^2) - carboplatine (800 mg/m^2), followed by two myeloablative courses with autologous stem-cell rescue. Twelve patients received two cycles of Melphalan (100 mg/m^2 per course) and 9 others two cycles of Thiotepa (600 mg/m^2 per course). Radiotherapy was planned to start around day 45 after second transplantation, ie before day 120 after diagnosis. 55 Gy were administered to the primary site and craniospinal irradiation (30 Gy to the brain and 36 Gy to the spinal cord) was only administered to children with medulloblastoma. *Results and statistical assessments.* Forty cycles of high-dose chemotherapy with stem cell rescue were administered. Toxicity was manageable and mainly digestive (vomiting, mucositis). The response rate observed after the 4 courses of chemotherapy was 80.5% at the level of metastases. Out of 9 patients with disseminated medulloblastoma who received Melphalan, 3 CR, 2 PR and 4 stable disease were observed. Among 8 patients who received Thiotepa, 3 achieved CR, 4 PR and one showed progression (p=NS). The median time lapse for beginning radiation therapy was 156 days

after diagnosis (range, 129-335). As of January 2006, with a median follow-up of 3.25 years, 15 patients were alive: 12 with NED (7 after tandem thiotepa and 5 after tandem melphalan) and 3 with progressive disease. The 3-year EFS was 52% and the 3-year OS was 70%. *Conclusions.* This pilot study indicates that intensifying sandwich chemotherapy is feasible and may improve survival of high-risk medulloblastoma/PNET.

AUTOLOGUS STEM CELL TRANSPLANTATION IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS WITH BAD PROGNOSIS CENTRAL NERVOUS TUMOR

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Fifteen patients with Central Nervous System tumors were submitted to Autologus Stem Cell transplantation (ASCT). The median age was 7 yrs (2,5 to 20yrs). The underlying diagnosis were: medulloblastoma(5) glioblastoma multifome(4), brain stem glioma (2) choroid plexus carcinoma (2) ependymoma(1) anaplastic astrocitoma (1). Of these patients 9 were in 1st or 2nd Partial Response, only one was in 2nd Complete Response at the moment of the ASCT. The regimen used was Carbplatin/etoposide/thiotepa or high dose cyclophosphamide in all patients. The results of the procedure was: 10 patients died of progressive disease. The median survival was 9 months(4-29); 1 patient died of toxicity (CNS bleeding during chemotherapy); 1 patient died due second neoplasia (AML) 3 years after ASCT in complete remission of the CNS tumor; 3 patients are alive without evidence of disease. In conclusion, a despite of the poor prognostic of those patients, whereas only one patient was in CR at the moment of the ASCT, 20% of them are long survival. The toxicity was acceptable. More patients are needed to confirm the role of ASCT in relapse patients with brain tumor.

BRAINSTEM PRIMITIVE NEUROECTODERMAL TUMORS (bsPNET): RESULTS OF TREATMENT WITH HEAD START PROTOCOLS

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Aim. To evaluate the response rate and survival with an intensified induction chemotherapy regimen (Head Start Protocols) followed by myeloablative chemotherapy with autologous hematopoietic cell rescue in young children with newly diagnosed brainstem primitive neuroectodermal tumors (bsPNET). Methods. Six children with biopsy-proven bsPNET were treated with intensive autologous hematopoietic cell rescue (HDCx+AuHCR). Five patients were enrolled on the Head Start I and Head Start II regimens, and one patient was treated as per Head Start II. After a maximal safe surgical resection of the tumor, patients on Head Start I (1991-1997) were treated with 5 cycles of induction chemotherapy that included vincristine, cisplatin, cyclophosphamide and etoposide. Following induction, eligible patients went on to receive a single cycle of HDCx+AuHCR. patients enrolled on Head Start II (1997-2002) with metastatic diseases at diagnosis (M1+) also received high dose IV methotrexate with leucovorin rescue as part of each induction chemotherapy cycle. *Results*. Among the six patients treated, two patients survice at least 30 months, yielding an EFS and OS of 17+15% and 33+19%, repsctively. The four remaining patients died of progressive disease. Conclusions. This approach provides a promising alternative for young patients with newly diagnosis bsPNET who in previous reports have had a uniformly fatal prognosis.

HIGH-DOSE CHEMOTHERAPY WITH AUTOLOGOUS STEM CELL RESCUE (HDCT) FOR CHILDREN WITH HIGH RISK AND RECURRENT MEDULLOBLASTOMA

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Over the last 10 years the Neuro-Oncology unit at The Hospital for Sick Children, Toronto, used HDCT in children with recurrent medulloblastoma who showed complete or very good partial response to salvage chemotherapy. Infants with high risk medulloblastoma (incompletely resected or metastatic) were also candidate for HDCT. Included in this report are 17 children (11 males and 6 females, aged 16 months – 14 year-old) with recurrent (11) or high risk medulloblastoma (6). 10/11 children with recurrent medulloblastoma had previous craniospinal radiotherapy. All high risk infants were younger than 3 years at diagnosis. All had metastatic disease at diagnosis (4 M1, 2 M2/3). Three types of HDCT regimes were used in the 17 children prior to stem cell rescue. Six patients received a combination of cyclophospamide and melphalan. Six infants received a carboplatin-thiotepa based regimen (+etoposide in 2 patients, sequential HDCT in 4). Five patients were treated with busulfan and thiotepa. There was no toxic death. Three of the 11 children treated for recurrent medulloblastoma are alive. Four of the six patients with high-risk medulloblastoma are alive, 3 NED (one had IMRT to the tumour bed) and one with residual disease after low dose CSI. Conclusions: the role of high dose chemotherapy in the recurrent setting is still unclear and needs to be revisited. Promising results are observed in high risk infants.

IS THERE A ROLE FOR MYELOABLATIVE CHEMOTHERAPY WITH AUTOLOGOUS HEMATOPOIETIC PROGENITOR CELL RESCUE IN THE MANAGEMENT OF MALIGNANT GLIOMAS OF CHILDHOOD?

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Conventional dose chemotherapy in addition to local field irradiation has had only a modest impact upon the outcome of children newly-diagnosed with malignant gliomas, and only in the sub-group of children able to undergo radical surgical resection of tumor. In the setting of recurrent disease, conventional dose chemotherapy has been purely palliative at best. Several studies have attempted to improve outcome for malignant gliomas by using increased drug doses and drug combinations, both with and without autologous hematopoietic progenitor cell rescue (AHPCR). Thiotepa (40-70 mg/m^2) or cyclophosphamide (up to 7 Gm) alone proved ineffective. Similarly, the use of AHPCR after CCNU, procarbazine and vincristine, iin order to decrease hematologic toxicity and therefore facilitate a decrease of intervals between cycles or administration of concurrent irradiation, had no favorable impact upon outcome. Results of trials using myeloablative chemotherapy followed by AHPCR in recurrent or newly diagnosed malignant gliomas have been poor in adults but somewhat more encouraging in children. Although neither myeloablative doses of the nitrosourea BCNU (>800 mg/m^2) or thiotepa (>600 mg/m^2) alone appear effective, multidrug myeloablative regimens have produced durable survival in a small proportion of patients with both recurrent malignant gliomas and newly diagnosed glioblastoma multiforme (GBM), albeit in the face of significant morbidity (lung and neurologic) and mortality in excess of 20% of patients in some early studies. The most important factor predictive of a favorable outcome following myeloablative chemotherapy is the extent of surgical resection. More recent approaches will be discussed, including: (a) the use of tandem myeloablative regimens (b) the incorporation of temozolomide into a 'backbone' regimen of thiotepa and carboplatin, and (c) the addition of post-'transplant' biological agents (eg. Cis-retinoic acid, metronomic dose temozolomide, Avastin, Tarceva).

ROLE OF HIGH DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL RESCUE IN CHILDREN WITH RECURRENT CNS MALIGNANCIES

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Purpose. To evaluate the efficacy and toxicities of high dose chemotherapy (HDCT) and autologous stem cell rescue (ASCR) in children with recurrent CNS malignancies. *Patients and Meth-*

ods. Records were reviewed for 27 patients with recurrent CNS malignancies who received HDCT and ASCR at St Jude Children's Research Hospital between 1989 and 2004. The HDCT regimens included: carboplatin and etoposide (n=6), busulfan and thiotepa (n=3); cyclophosphamide and thiotepa (n=7), cyclophosphamide and melphalan (n=3); cyclophosphamide and topotecan (n=5), busulfan and melphalan (n=2); cyclophosphamide only (n=1). *Results.* The median age at diagnosis was 4.3 years (range: 0.4-16.6) and at ASCR was 6.2 years (range: 1.1-18.5 years). The diagnoses included: medulloblastoma (n=12), PNET (n=3), pineoblastoma (n=2), atypical teratoid rhabdoid tumor (n=3), ependymoma (n=3), anaplastic astrocytoma (n=3) and glioblastoma multiforme (n=1). The 5-year progression free survival (PFS) was 16±8% with a 3- and 5-year overall survival (OS) of 36.7±10% and 26.7±11 %, respectively. The median time to progression post ASCR was 137 days (range: 26-265 days). The 5-year PFS for the 7 patients ≤3 years at diagnosis (41.7± 18%) was significantly better than for the 20 patients >3 years (5.3±25%, p=0.012). Similarly OS for patients ≤3 years at diagnosis was 62.5±27.1% compared to 15.8% in the older group (p=0.11). Among the 6 long-term survivors, (median age 2.2 years, range: 1.1-11.7 years), 5 were M0 and 1 was M3 at diagnosis; 5 received both radiotherapy (RT) (craniospinal: n=3, focal, n= 2) and HDCT as part of their salvage regimen. Four were ≤3 years at diagnosis and had received chemotherapy only as part of their frontline therapy. The two survivors > 3 years at diagnosis were both M0 at diagnosis; 1 developed a local recurrence, underwent a GTR and received RT and HDCT as part of his salvage therapy; the other had CSF positivity only at recurrence, did not clear his CSF post HDCT and went onto receive further therapy. Conclusions. HDCT with ASCR is not an effective salvage strategy in older patients with recurrent CNS malignancies. The significantly better outcome in the younger cohort is most likely related to the use of radiotherapy as part of the salvage strategy.

HIGH DOSE VP16-THIOTEPA (HD VP-TTP) WITH PBSC RESCUE IN RELAPSING INTRA CRANIAL NON GERMINOMATOUS GERM CELL TUMORS (ICNGGCT): THE SFCE RETROSPECTIVE EXPERIENCE

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The survival of ICNGGCT treated with combined treatment by chemotherapy followed by focal radiotherapy reaches 65%. At time of relapse, no current recommendations are validated. *Patients and Methods.* Sixteen ICNGGCT patients were treated at relapse with (+/-salvage standard chemotherapy,+/- radiotherapy +/- surgery) and HD VP-TTP (500 mg/m^2/d 1-3 and 300 mg/m^2/d 1-3 respectively). First line strategy included: 6 patients TGM-TC 88-90 protocol (5 to 6 cycles alternating chemotherapies and no radiation if CR); 7 patients TGM TC 92 protocol (3-4 cycles VP Carbo/VP Ifos and focal RT 55 gy); 3 patients SIOP GCT 96 protocol (4 courses of PEI and focal RT: 55 gy). Rescue treatment prior to HD VP-TTP included no 2nd line chemotherapy (4pts), CDDP (9) or CBDCA (2) containing regimen, 1 HD VP; Status before HD VP TTP was CR (5pts), PR (4), or Evolutive-unknown (7). *Results*. Response HD VP-TTP was CCR (5), CR (3), PR (3), SD (1), PD (3), and NE (1). Outcome of 5 CCR patients was NED for all (4 after further RT, 2 of which had not been irradiated previously in first line). Among 4 patients in PR before VP-TTP, 2 are NED (1 after surgery, 1 after RT) and 2 DOD. Among the 7 patients treated in PD, only one is NED after further RT. None of the patients treated with SIOP GCT 96 could be salvaged. The 8 year relapse free survival after relapse was 48%; 95% CI [26-70%] and the estimated OS was 55%. Toxicity was as expected after high dose therapy with FUO in all patients, no VOD or toxic death. *Conclusions.* Relapse of ICNGGCT can be salvaged by an individualized strategy containing high dose chemotherapy. Response to reinduction chemotherapy and to high dose chemotherapy is of crucial importance. However, the patients initially treated with CCDP may be more difficult to salvage than others indicating for these pts the need to find a reinduction chemotherapy with new drugs allowing to obtain a 2nd CR before HD CT.

HYPERFRACTIONATED ACCELERATED RADIOTHERAPY (HART) IN MILAN STRATEGY FOR THE TREATMENT OF METASTATIC MEDULLOBLASTOMA

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To improve prognosis of patients with metastatic medulloblastoma, we elected to test the efficacy and toxicity of an hyperfractionated accelerated radiotherapy regimen delivered after intensive postoperative sequential chemotherapy. Radiobiological rationale for HART selection was: reduction of overall treatment time (acceleration) to lessen the effect of cancer cell proliferation during radiotherapy thus ameliorating the probability of tumor control without increasing severity of radiation sequelae (hyperfractionation). Between January 1997 and May 2006, 24 consecutive patients (median age 10 years) received postoperative sequential high-dose MTX (8 g/sqm), VP16 (2.4 g/sqm), CTX (4 g/sqm), and CBDCA (0.8g/sqm) given as soon as possible after recovery from hematological toxicity of previous cycle. According to Chang staging system of metastatic spread, patients were classified as follow: M1=9 patients (5 with post-surgical residual disease in posterior fossa), M2=3 patients, M3=16 patients, and M4=1 patient. HART was delivered 3 weeks after the end of chemotherapy at a total dose of 39 Gy to the neuraxis (1.3 Gy/fraction, 2 fractions per day) with a boost to the posterior fossa up to 60 Gy (1.5 Gy/fraction, 2 fractions per day). Nine children younger than 10 years and in CR after chemotherapy, received a reduced dose to the neuraxis of 31.2 Gy. In case of persistent disseminated disease before HART, patients were consolidated with 2 courses of myeloablative chemotherapy and PBSC rescue: eleven out of 29 patients were consolidated so far. Twenty-seven out of 29 patients responded to postoperative chemotherapy, while 2 showed disease progression. 80% of the patients required transfusional support during chemotherapy and 3 developed a bacterial sepsis. One septic death occurred before radiotherapy. HART was completed as scheduled in all cases. Eight patients relapsed at a median time of 13 months (3 of them were staged as M1). At a median follow-up of 77 months, EFS, PFS, and OS at 3 years are 75.1%, 77.8%, and 78.4% respectively and at 5 years are 67.4%, 69.8% and 74.2% respectively. No severe clinical complications of HART were detected so far. However neurocognitive and growth development as well as endocrinological status of the present series are object of prospective evaluation. Hyperfractionated accelerated radiotherapy combined with intensive postoperative chemotherapy and with myeloablative chemotherapy and PBSC rescue in selected cases proved to be feasible without limiting major toxicity in children with metastatic medulloblastoma. Therapeutic results compare favorably with our and other series treated with conventional therapies.

FEASIBILITY AND EFFICACY OF TANDEM HIGH DOSE THIOTEPA WITH AUTOLOGOUS STEM CELL RESCUE IN PATIENTS WITH RECURRENT TUMORS

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Background. Survival using a single course of multi-drug high dose chemotherapy with ASCR has been poor in patients with measurable disease due to significant toxicity and early relapse. The purpose of the present study was to administer tandem courses of high dose thiotepa with ASCR to patients with recurrent tumors who were not eligible for a single course of high dose therapy due to measurable disease. *Methods.* Patients received thiotepa 200 mg/m^2/d for 3 days followed by ASCR.

A second course of high dose thiotepa was given 4-6 weeks later to patients who did not have progressive disease. *Results:* Sixty-one patients received 101 courses. Diagnoses included medulloblastoma (MB)/primitive neuroectodermal tumor (PNET) (n=26); glioma (n=5); ependymoma (n=5); central nervous system germ cell tumor (CNS GCT)(n=5); atypical teratoid rhabdoid tumor (n=1) and choroid plexus carcinoma (n=1). The remaining patients had primary tumors outside the central nervous system. The median interval between courses was 42 days (range 25-86 days). The median duration of hospitalization was 7 days (range 0-34 days) for the first course and 5 days (range 0-54 days) for the second course. Twenty-seven courses were administered completely in the outpatient setting. Toxic mortality was 2/101 courses (2%). Five of 26 patients with MB/PNET were alive at a median of 35 months compared with 21/26 patients who died at a median of 11.7 months. Four patients with CNS GCT are alive 68-103 months following ASCR. *Conclusions.* Sequential high dose thiotepa with ASCR is well tolerated even in heavily pre-treated patients. This therapy may lead to prolonged survival in patients with recurrent malignant brain tumors, particularly those with MB/PNET and CNS GCT.

PHASE I DOSE ESCALATION OF TEMOZOLOMIDE WITH THIOTEPA AND CARBOPLATIN AND AUTOLOGOUS STEM CELL REINFUSION (ASCR) IN PATIENTS WITH RECURRENT/REFRACTORY MALIGNANT BRAIN TUMORS WITH MINIMAL RESIDUAL DISEASE

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Background. The prognosis for most patients with recurrent malignant brain tumors is dismal. Treatment options are limited especially for patients who have already received irradiation. Temozolomide is an oral alkylating agent which is approved for use in patients with high grade glioma and has also been shown to have activity in patients with recurrent medulloblastoma. It's primary dose limiting toxicity is bone marrow suppression. In the present study temozolomide is given in a dose escalation fashion with fixed doses of high dose thiotepa and carboplatin with ASCR in the treatment of patients with recurrent or refractory malignant brain tumors. *Methods*. Treatment consisted of temozolomide bid on days -10 to -6 followed by thiotepa 300 mg/m^2/d and carboplatin AUC=7/d on days -5 to -3 with ASCR day 0. Filgrastim was given day +1 and continued until engraftment. *Results.* Twenty-seven patients (18M; 9F) ages 3-46 years were treated from 11/00 until 10/04. Diagnoses included high grade glioma (n=12); medulloblastoma/PNET (n=9); CNS germ cell tumor (n=4); and 1 each ependymoma and spinal cord peripheral PNET. Temozolomide doses ranged from 100 mg/m^2 bid (200 mg/m^2/day) to 200 mg/m^2 bid (400 mg/m^2/day) x 5 days. Toxicity included bacteremia (n=11) and C. difficile enteritis (n=6). There were no toxic deaths. Survival includes 4 patients with glioma (32-48 months); 3 patients with PNET/MB (43-67 months) and 3 patients with GCT (17-65 months). *Conclusions.* Increased doses of temozolomide are feasible when given with ASCR. The combination of temozolomide, thiotepa and carboplatin with ASCR may improve survival in patients with recurrent malignant brain tumors, particularly those with high grade glioma.

ATYPICAL TERATOID RHABDOID TUMOUR OF THE CENTRAL NERVOUS SYSTEM (CNS): FINAL RESULTS OF THE FIRST ITALIAN COOPERATIVE STUDY FOR VERY YOUNG CHILDREN

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The AT/RT of the CNS has been recently well characterized as a distinct clinicopathologic entity with an unusually poor prognosis and with the highest incidence in the first two years of life. It often arises in the posterior fossa (63-65%) and it has been frequently misdiagnosed as medulloblastoma, but its distinctive histologic, immunohistochemical, and cytogenetic features permit a ready diagnosis in most cases. AT/RT of the CNS is an usually fatal disease virtually unresponsive to chemotherapy (CT) and radiotherapy (RT) comparing to PNET/Mb. Rapid progression and frequent CNS dissemination is reported to be the rule. It is under evaluation if more recent up-front combined regimens including high dose CT are capable to prolonge survival and change the natural history and aggressive behavior of this tumor favouring prolonged survival and even cure. Factors such as tumor site and pattern of growth other than chemo and radiosensitivity, may play a role on survival influencing tumor removal. In literature there are few perspective series including a large number of cases with well defined clinical features, treated with uniform combined therapeutic approach. In this study we present the cases with diagnosis of AT/RT of the CNS registered in the Italian Cooperative Study for children ≥ 3 years of age and treated in the period 1995-2003 according to two different protocols strategies. *Patients and Methods.* Since 1995 all cases with CNS AT/RT registered in the Italian Cooperative Study for children < 3 years of age were prospectively followed, either for treatment according to the protocols adopted (SNC 9501, first generation protocol and HD sequential CT protocol in the second generation study) or for study purpose of cases that for various reasons couldn't be treated according to protocol therapy guidelines. The main goal of the study was to postpone or avoid CNS radiation in young children affected by malignant CNS tumors using intensive chemotherapy after initial surgery. The first CT regimen (1995-1998) consisted of: CDDP (120 mgr/m^2) and VP16 (450 mgr/m^2) for two courses, followed by the sequence AAB repeated 4 times for a total of one year, where A was: VCR (1.5 mgr/m^2), CTX (1.5 gr/m^2) MTX (5 gr/m^2) and B: CDDP (90 mgr/m^2) VP16 (450 mgr/m^2). The second generation study (after 1998), adopted a strategy based on intensive sequential CT and MAT. Only patients with residual tumour or metastasis or relapse were candidate to radiation therapy in both protocols. *Results.* From 1995 to 2003 29 patients with primary AT/RT of the CNS diagnosed in ten different italian institutions were registered in this study; 14 were females, 15 males; age ranged from 6 days to 36 months; 12 cases (42.8%) were less than 12 months at diagnosis; of them 6 were < 6 months. The tumour was located in the posterior fossa in 11 cases; in 17 patients location was supratentorial and in 4 of them was multifocal; leptomeningeal dissemination was present at diagnosis in 2 cases (6.8%). In 23 cases (79%) tumour was considered un-operable (7) or only a partial removal was possible (16 cases); a total or subtotal removal was possible in 6 cases. 5 cases received no treatment for parental refusal; 11 were treated with a standard baby protocol (SNC9501) and 13, in a more recent period, received HD sequential chemotherapy (10 according to a PNET like protocol, 2 according to extra SNC like protocols. Five years Progression free Survival was 18.2 for the standard regimen and 16.7 for the HD regimen while OS was of 18.2 and 22.2 respectively. Four cases became long term survivors, 2 treated with conventional chemotherapy, 2 with

HD chemotherapy. *Conclusions.* Long-term survival despite the introduction of a more intensive chemotherapy (HDCT) is still un-frequent in AT/RT (8%). More effective CT regimens and a multidisciplinary approach in order to optimize "local" control are necessary in order to modify the natural history of this disease.

TREATMENT, INCLUDING HDCT, OF MALIGNANT GLIOMAS IN VERY YOUNG CHILDREN: RESULTS OF THE FIRST COOPERATIVE COOPERATIVE STUDY IN ITALY

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An analysis of all cases of malignant gliomas histologically proven of children <3 years of age enrolled in the first Cooperative Italian Study for Infants Malignant Brain Tumors, has been conducted in order to evaluate main clinical features and results of treatment aiming eventually to identify peculiar features of this entity and role of chemotherapy. In the period 1995 – 2003, a total of 14 Malignant Gliomas were recruited, 7 males, 7 females; 7 (50%) were under 1 year of age; age ranged from 3 months to 36 months (median 18). Treatment strategy in all cases was to remove as much as tumor possible when feasible and use chemotherapy as up-front modality in order to avoid or delay irradiation. RT was planned at the end of CT on residual tumor or at progression during chemotherapy. Chemotherapy protocols used were Standard Infants 8 cases (5 Baby SFOP, 3 SNC 9501); Infants HR (including HD CT) in 6 cases; histology was GBL 6 cases (2 giant cell variant); AA 3 cases; An. Oligodendrogliomas 2, other 3 (1 M. Gliomas not otherwise classifiable and presenting astroblastic features, 2 malignant glio-epithelial tumors); site of involvement: hemispheres +/- basal nuclei infiltration: 11 cases (78.5%), Posterior Fossa (cerebello-pontine angle) 1, Spinal Cord 1; Suprasellar 1. Outcome: 6 (42.8%) patients are alive free of disease (ANED) at respectively 18, 52, 60, 60, 68, 110 months from diagnosis; only 1 of them received RT after 5 years from dx for relapse at + 42 months form discontinuation of CT; 1 died of MOF after HD CT; 6 are died of tumor progression; 1 patient died in CR of unrelated causes. Malignant Gliomas in infants tend to prevail at age <1 and in the supratentorial compartment. Cure is possible with chemotherapy only as front line therapy after surgery in a significant proportion of cases of malignant gliomas at very young age indicating a greater chemo-sensibility comparing with older ages; more intensive chemotherapy (HDCT) in our experience presents a trend in obtaining better results than conventional CT but a greater number of cases is needed to confirm this observation.

MYELOABLATIVE CT IN INFANT MALIGNAT BRAIN TUMORS

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High dose (HDCT) or Myeloablative CT (MAT) is currently a widely applied treatment for some types of brain tumors. Previous experience with conventional strategies for patients defined as being at high risk (i.e., metastatic presentation, post-surgery residual disease, unfavorable histology, resistant or relapsing disease after first line treatment) was, on the whole, unsatisfactory. This represents the background for the pioneering period in which MAT was mostly administered to patients with recurrent or refractory disease. The incidence of bone marrow involvement in these patients is very rare, thus making the peripheral blood stem cells (PBSCs) yield almost always safe, plentiful and successful. At the same time, chemotherapy combinations, including drugs bearing non severe, extra-hematological toxicity that were able to penetrate the brain barrier, especially the alkylating agents such as cyclophosphamide, thiotepa, melphalan and busulfan, were experimented, in some instances together with platinum derivatives. Afterwards, an increasing number of papers reporting the use of MAT as front-line consolidation were published. Encouraging results were also obtained in newly-diagnosed patients by administering one or more courses of MAT, not only as final consolidation for patients in complete remission (CR), but even in the context of induction treatment, namely following a few (3-4) standard-dose chemotherapy cycles or sequential intensive CT in responding patients (partial and very good partial remission). In this setting, MAT may be considered part of a *short enforced induction*, which allows for a decrease in the cumulative toxic effects thanks to several cycles of chemotherapy which are administered in order to reach complete remission (CR) prior to consolidation with MAT. In addition, early, high dose administration could also minimize the risk that chemo resistant cell clones might appear. The fundamental goal of MAT in brain tumors of the infant is to try to reduce or to avoid cranio-spinal irradiation. It is well known that not all brain tumor types benefit from MAT or are in need of an aggressive approach . There is increased evidence of the feasibility of MAT in CNS tumor patients, considering the low incidence of early toxicity and the possibility of collecting a great number of PBPCs (even for repeated high-dose cycles and for rescue in case of myelosuppression as a consequence of spinal irradiation). Nevertheless, the patient's characteristics (i.e., very young age and low weight), uphold the indications that PBPC collection and MAT must only be performed by well-trained specialists in accredited Centers. Finally, although the number of patients treated with MAT and reported in the international registries is constantly growing, complete agreement regarding histology, cut-off age, residual disease extent, and type of conditioning regimen is still lacking. In Medulloblastoma the introduction of sequential HDCT for relapsed patients or for patients with metastases is currently being investigated in the 2nd generation infant studies, and high response rates have been reported . Current and future studies should clarify whether these regimens can also increase the proportion of patients that may be cured without RT in the M0/T0 group as well as in the high risk group. The Italian AIEOP infant pilot study, which uses HDCT followed either by conformal RT on the residual tumor or by CSI in patients with metastases, shows that 5 year EFS in the first 20 study patients has increased drastically (70%). Treatment of supratentorial PNETs is controversial. HDCT is active but not sufficient because local control still depends on the amount of surgical removal and irradiation. PNETs of the pineal region are increasingly recognized as being more chemosensitive, although local control by delayed surgery or RT would appear to be necessary even after MAT . In the Italian Infant Study (AIEOP SNC 9501), 5 cases were treated with intensive CT and MAT. Two of them achieved CR and 3 achieved very good partial remission, but the only long term survivors were the 3 cases in whom CT was followed by conformal RT (2cases) or 2nd look + RT (1 case). AT/RT of the CNS is usually a fatal disease. Unlike medulloblastoma/PNETs, it is known to respond poorly to conventional, *medulloblastoma like CT* and to radiotherapy. Rapid progression and frequent CNS dissemination have been reported. More recently, combined therapeutic regimens, including intensive *sarcoma like CT* and HDCT have been used. However, whether this therapy, together with better control as achieved by repeat surgery and irradiation are capable of prolonging survival and changing the outcome is still under investigation.

ROLE OF MIELOABLATIVE CT (MAT) IN TREATMENT OF INFANTS MEDULLOBLASTOMA: THE EXPERIENCE OF THE FIRST ITALIAN COOPERATIVE STUDY

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One third of cases of medulloblastomas are < 3 years of age at diagnosis; metastatic status and young age are the most widely accepted un-favourable prognostic factors. One of the goals of MAT in infant MB is to try to improve survival while trying to reduce or avoid cranio-spinal irradiation. The Italian AIEOP infant cooperative study , based on un-satisfactory results of first study in patients with residual or metastatic disease (Protocol SNC9501, 1995-1998) using up-front conventional systemic CT and delayed or omitted irradiation in newly diagnosed infants medulloblastoma, adopted, since 1998, a pilot study, which uses upfront HD sequential CT including MAT followed by conformal RT on the residual tumour or by CSI in patients with metastases. This approach was adopted later also for cases M0/T0; in these cases irradiation was not planned at end of CT. Chemotherapy consisted of sequential induction chemotherapy: VCR1.5 mg/m^2/MTX8gr/m^2; HDVP16 2.4 gr/m^2; VCR 1.5 mg/m^2/CTX 4 g/m^2; VCR 1.5 mg/m^2/CARBO 800 mg/m^2 followed by 2 courses of MAT (CARBO 1.5 g/m^2/VP 161.5gr/m^2 and THIOTHEPA 900 mg/m^2/MPH 120 mg/m^2) with re-infusion of PBSCs. A total of 21 cases have been treated in the period 1998-2004; 14 were males, 7 females; age ranged from 12 to 39 months (median 25 months): median duration of follow-up was 33 months. 6 cases were M0/T0; 9 T+/M0, 7 T+/M0; histological variants were: Classic in 15 cases, Desmoplastic in 4, other in 2. Ten patients received irradiation and 9 of them are alive and NED at a median of 45 months from diagnosis; 1/10 died of secondary leukaemia diagnosed very early after end of treatment. Three patients went into progressive disease before end of CT and couldn't be irradiated; 8 (38%) are alive and NED without having received irradiation (3 T0/M0, 3 T+/M0, 2 T0/M+ at a median time of 50 months from diagnosis. OS and EFS were 88 and 82% respectively; no difference was observed between patients M0/T0 and patients harbouring metastasis or residual tumour; no significant difference was also observed between cases with classic and desmoplastic variants. No deaths for acute toxicity were reported in this group of patients. *Conclusions.* Up front HDCT was associated in this cohort of patients to a better long term control of the disease with an excellent EFS and OS comparing with the previous study. The majority of these patients were presenting high risk features so a greater number of cases is necessary in order to understand if this approach allows to avoid irradiation at end of CT in T0/M0 patients.

A RETROSPECTIVE STUDY OF HIGH DOSE CHEMOTHERAPY (HDC) WITH AUTOLOGOUS STEM CELL RESCUE (ASCR) IN CHILDREN AND ADULTS WITH SUPRATENTORIAL PRIMITIVE NEUROECTODERMAL TUMORS (S-PNET) - THE DUKE EXPERIENCE 1991-2004

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Purpose: We evaluated the usefulness of a treatment regimen that included high-dose chemotherapy (HDC) with autologous stem cell rescue (ASCR) in children and adults with newly diagnosed and recurrent S-PNET. *Patients and methods:* Between April 1991 and March 2004, patients at Duke University Medical Center with newly diagnosed or recurrent disease were initially treated with surgery and induction chemotherapy. Craniospinal irradiation (CSI) with focal boosts was given to the primary tumor and sites of metastatic disease to all newly diagnosed patients except infants. All patients received HDC using cyclophosphamide (CTX) – melphalan (MEL), busulfan (BU) –MEL, carboplatin (CBDCA) + VP-16 +/- Thiotepa (TT) regimens and ASCR after achieving minimal residual disease. *Results:* A total of 25 patients (newly diagnosed 20, recurrent 5) with a median age of 6 years (range, 0.5- 43) were treated according to this strategy. Eight patients had metastatic disease confined to the neuraxis at diagnosis (n=7) or recurrence (n=1). Five children developed a pineal tumor following a diagnosis of bilateral retinoblastoma. Nineteen of 25 patients (42%) had either complete or partial resection of tumor at diagnosis or relapse. Fourteen patients received radiotherapy (XRT) at median doses of 36.0 Gy (range, 36-46.2) and 59.4 Gy (range, 55.2-66) to the neuraxis and primary sites respectively. Two patients received focal XRT of 54 Gy. XRT was omitted in 4 infants due to their young age. Nineteen patients received HDC with CTX + MEL, 3 with BU + MEL, 2 with CBDCA + TT+ VP-16, and 1 with CBDCA + VP-16 followed by ASCR. Only 7 patients (all with newly diagnosed disease) are alive with no evidence of disease recurrence at a median of 92 months from HDC (range, 28- 157), including 1 patient with metastatic disease and 2 infants who did not receive any radiotherapy. Conclusions. HDC with ASCR as a component of treatment for patients with S-PNET was useful in a limited group of patients with newly diagnosed S-PNET.

SUPRATENTORIAL PNET: THE EMERGING ROLE OF HIGH DOSE CHEMOTHERAPY AND STEM CELL RESCUE

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Supratentorial PNETs (e.g. cerebral PNET and pineoblastoma) a re a distinct group of aggressive embryonal brain tumors that can occur in children and young adults. They have a high propensity for neuraxis dissemination. Although histologically similar to posterior fossa medulloblastoma, they are distinct in both molecular charcateristics and biologic behavior. Unlike patients with medulloblastoma, survival for patients with tumors with conventional chemotherapy and irradiation is between 30-60%. There is some evidence that high-dose chemotherapy plus stem cell rescue with or without radiotherapy has been useful in improving survival in a proportion of patients with newly diagnosed (cerebral PNET and pineoblastoma) and recurrent tumors (cerebral PNET only). The biology of these tumors is not as well characterized as medullobalstoma. Further studies are required to understand the molecular charateristics and refine management for patients with these tumors.

HIGH-DOSE CHEMOTHERAPY CONSISTING OF THIOTEPA AND MELPHALAN FOR YOUNG CHILDREN WITH MB AND CHILDREN WITH METASTATIC MB

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HDC consisting of thiotepa and melphalan was administered to young children (<3 years) and children (> 3 years) with M1/2/3 medulloblastoma with stem cell rescue after four courses of chemotherapy (cyclophosphamide, cisplatin, vincristine, etoposide). On the first day of each chemotherapy, TIT (methotrexate, cytarabine and dexamethason) was administered. Children (> 3 years) received a CSI of 18 Gy and a local irradiation of 50 Gy. Radiation therapy was started concomitantly with the 2nd course of chemotherapy. Radiotherapy was not delivered to young children. Among 13 (< 3 years) and 14 children (> 3 years), 6 and 12 children remain in CR, respectively (11-61 months, median: 34 months).

OVERVIEW OF CHILDREN'S ONCOLOGY GROUP (COG) BRAIN TUMOR PROTOCOLS EVALUATING HIGH DOSE CHEMOTHERAPY WITH AUTOLOGOUS HEMATOPOIETIC STEM CELL RESCUE (HSCT)

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The Children's Oncology Group (COG) and its legacy groups, Children's Cancer Group (CCG) and Pediatric Oncology Group (POG), have been exploring the efficacy of high dose chemotherapy with HSCT rescue. There have been six recent or current brain tumor trials associated with autografting. Earlier trials demonstrated feasibility of stem cell collection and dose-finding of chemotherapy in the high dose setting. In POG 9430, children with relapsed responsive medulloblastoma and germinoma treated with cyclophosphamide and melphalan followed by HSCT had a 34% 2-yr PFS. The phase I study, CCG 99703, demonstrated feasibility of thiotepa 20 mg/kg plus carboplatin 34 mg/kg given in three sequential autograft procedures in young children with brain tumors. This strategy has been incorporated into two new protocols, ACNS0333 for atypical teratoid rhabdoid tumor and ACNS0334 for medulloblastoma in infants and young children. ACNS0122 is studying children with high risk germ cell tumors. Those who have suboptimal response to primary therapy are consolidated with high dose etoposide/thiotepa followed by HSCT. ACNS0231, a randomized single vs. triple autograft trial for relapsed malignant glioma, was closed recently due to slow accrual, at least, in part, related to stringent enrollment criteria. Lastly, Pediatric Blood & Marrow Transplant Consortium protocol ONC032 is underway to assess temozolomide in combination with carboplatin and thiotepa for relapsed medulloblastoma plus other brain tumors. This concept will be considered for further development in COG, should it prove promising.

NOVEL BIOLOGIC AND ANTI-ANGIOGENIC THERAPY AS ADJUVANT TREATMENT AFTER HIGH-DOSE CHEMOTHERAPY AND STEM CELL RESCUE IN PEDIATRIC CENTRAL NERVOUS SYSTEM TUMORS

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While standard dose chemotherapy continues to play a pivotal role for the treatment of pediatric brain tumors, either alone or in conjunction with radiotherapy, a significant number of patients succumb to their disease. Those with relapse disease after initial therapy have a very poor long-term prognosis. Even with high-dose chemotherapy and stem cell rescue, a significant number of patients that achieve minimal residual disease will eventually progress. Biologic and anti-angiogenic therapies have recently been developed which target important signaling pathways within tumors, and/or their ability to induce neovascularization. The majority of these agents lack the classical toxicities of chemotherapy, such as myelosuppression or nausea/vomiting and may therefore be ideally suited as adjuvant therapy during or after high-dose chemotherapy with stem cell rescue. Understanding which biologic agents will be suited for combination approaches, and in which circumstances, will be the basis for this presentation.

PERIPHERAL BLOOD STEM CELL COLLECTION IN PEDIATRIC PATIENTS: FEASIBILITY OF LEUKAPHERESIS UNDER ANESTHESIA IN UNCOMPLIANT SMALL CHILDREN WITH SOLID TUMORS

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Leukapheresis requires patient's compliance and adequate vascular accesses. Since 1998, at the Istituto Nazionale Tumori of Milan, the placement of peripheral vascular accesses and leukapheresis have been performed at the same time under general anesthesia in selected uncompliant small children with solid tumors, undergoing programs including myeloablative chemotherapty and stem cell rescue. Peripheral venous cannulas were positioned for blood collection, while blood was returned through either peripheral cannulas or mono-lumen central catheters previously installed for chemotherapy. A continuous-flow cell separator was used for leukapheresis. In the study-period 1998-2003, 47 children underwent anesthesia. The patients' age ranged from 12.7 to 93 months (median 30.3) and their weight ranged from 7 to 20 kg (median 14.1). A total of 54 leukaphereses under narcosis was performed. In 89% of cases, the CD 34(+) cell target was achieved at a single harvest; the median number of CD 34(+) cells was $10.8x10^6$/kg/leukapheresis (range 1-117) and the median collection efficiency was 63.4% (range 25-100.6). Neither metabolic nor anesthesiological complications were recorded. In our setting, leukapheresis under anesthesia was feasible and safe in very low-weight children whose compliance is lacking due to age and disease.

SUPRATENTORIAL PRIMITIVE NEUROECTODERMAL TUMORS (S-PNET) IN CHILDREN: A PROSPECTIVE EXPERIENCE WITH ADJUVANT INTENSIVE CHEMOTHERAPY, HYPERFRACTIONATED ACCELERATED RADIOTHERAPY AND MYELOABLATIVE CHEMOTHERAPY

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Purpose. S-PNET are rare and have a grim prognosis, frequently taking an aggressive course with local relapse and metastatic spread. We report the results of a mono-institutional therapeutic trial. *Methods.* We enrolled 16 consecutive patients to pre-radiation chemotherapy (CT) with hdMTX, hdVP16, hdEDX, hdCBDCA, CSI hyperfractionated accelerated radiotherapy (HART) with focal boost, maintenance with VCR/CCNU or consolidation with hd-thiotepa, followed by autologous stem cell rescue. *Results.* Median age was 9 years; 7 were male, 9 female. Site of disease was pineal in 3, elsewhere in 13. Seven patients were NED after surgery. Of those ED, 2 had CNS spread. Of the 9 ED patients, 2 had CR and 2 PR after CT, 4 SD and 1 PD. Of the 7 ED patients before RT, 1 had CR, 4 PR, and 2 MR, thus obtaining a 44% CR+PR after CT and 71% after HART. Due to rapid progression in 2 of the first 5 patients, hd-thiotepa was systematically adopted after HART in the subsequent 11 patients. Five of 16 patients relapsed (3 locally, 1 locally with dissemination, 1 with dissemination) a mean of 6 months after starting CT, 2 developed second tumors and one pt died of pneumonia after HD-thiotepa; all relapsers died at a median of 13 months. Four-year PFS, EFS and OS were 67.5%, 46 %, and 57%, respectively. *Conclusions.* HART was the main tool in obtaining responses in S-PNET; introducing the myeloablative phase improved the prognosis (2/11 vs 3/5 relapses, $p<0.04$), but RT needs to be anticipated when not obtaining optimal response to pre-radiation CT.

SEQUENTIAL CHEMOTHERAPY, HIGH-DOSE THIOTEPA, CIRCULATING PROGENITOR CELL RESCUE, AND RADIOTHERAPY FOR CHILDHOOD HIGH-GRADE GLIOMA: A MONO-INSTITUTIONAL STUDY

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Background. Clinical behavior of childhood malignant gliomas is almost as aggressive as in adults, with resistance to therapy, rapid progression, and not uncommonly, dissemination. *Methods.* Our study protocol incorporated sequential chemotherapy and high-dose thiotepa in the preradiant phase, followed by focal radiotherapy and maintenance with vincristine and lomustine for a total duration of one year. The induction treatment consisted of two courses of cisplatin (40 mg/m^2) plus etoposide (150 mg/m^2) per 3 days and of vincristine (1.4 mg/m^2) plus cyclophosphamide (1.5 g/m^2) and high-dose methotrexate (8 g/m^2), followed by high-dose thiotepa (300 mg/m^2 per 3 doses), with reinfusion of peripheral blood progenitor cells (PBPCs), whose harvest was done after the first cisplatin/etoposide course. *Results.* From August 1996 to November 2005, 30 children, 17 females and 13 males, with a median age of 9 years were enrolled, 26 presenting with residual disease after surgery. Histologies were glioblastoma multiforme in 15, anaplastic astrocytoma in 10, anaplastic oligodendroglioma in 3, anaplastic ganglioglioma and anaplastic pilocytic astrocytoma in one each; sites of origin were supratentorial areas in 25, spine in 4, and posterior fossa in 1; five patients had multiple foci of disease consistent with a clinical diagnosis of gliomatosis. Of the 30 patients, 17 have have relapsed and 17 have died (15 after relapse for tumor progression, but one affected by Turcot syndrome who died for duodenal cancer relapse; one for intratumoral bleeding at 40 months after diagnosis, and one for pneumonia at 13 months after diagnosis); median time to progression for the whole series was 9 months. Nine patients relapsed locally, 1 marginally to the radiation field, 2 locally and with dissemination and 4 with tumor dissemination only, in one girl site of relapse was unknown. Overall survival and progression-free survival at 4 years were 40% and 44%, respectively; PFS for pts with glioblastoma was 20% and for pts with other malignant glioma 62.5% (p 0.03), being OS 52% and 27% (p 0.11), respectively. *Conclusions.* Sequential and high-dose chemotherapy can be afforded in front-line therapy of childhood malignant glioma without excessive morbidity and rather satisfying results in patients with grade 3 glioma.

NO SALVAGE FOR RELAPSING ALREADY IRRADIATED MEDULLOBLASTOMA IF RESCUED WITH HIGH-DOSE CHEMOTHERAPY ± RE-IRRADIATION

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Myeloablative chemotherapy is used as rescue treatment in several relapsed solid tumors. This strategy has been particularly attractive in the last two decades for treating relapsing embrional CNS tumors such as medulloblastoma. We describe our mono-institutional experience during the years 1997-2002. *Methods.* Each relapse had to be discussed with referral neurosurgeon and radiotherapist. Scheduled protocol included sequential chemotherapy with HDMTX, HDVP16, HDEDX, HDCBDCA (as for de novo metastatic medulloblastoma), and two myeloablative courses with HD-thiotepa; if the patients had been already treated with the above mentioned regimen at diagnosis, re-induction included CDDP/VP16 for 2/4 courses. Mobilization of hematopoietic precursors was performed after HDVP16 or HDEDX or the first CDDP/VP16 course. Before the myelo-ablative phase or at the rescue of the hemopoesis the possible re-irradiation was prescribed. Results. Seventeen patients have been treated in the five years mentioned: 13 males and 4 females (in the same time span we treated 75 newly diagnosed children affected by medulloblastoma). All patients had been already treated with craniospinal radiotherapy (19- 36 Gy) with posterior fossa or tumor bed boost and 16 also with chemotherapy: 15 were at first relapse, 1 at the second and 1 at the third. Progression-free survival for the 15 patients at first relapse had been 17-93 months, median 28. Relapsing sites in 15/17 were: leptomeningeal in 8, single spine nodule in 4, posterior fossa in 3. Three patients had been re-operated on posterior fossa with complete tumor excision, 11 received the sequential schedule as above described, 5 CDDP/VP16, and one only the myeloablative corse after surgery. Eleven patients received re-irradiation at some point of their re-treatment. Ten of 14 with evidence of tumor at the re-induction, had a partial or complete response after the re-induction phase, four progressed and two of them did not go forward to the myeloablative phase. No patients died for acute toxicity. Remission duration was 13-69 months with a median of 17 months. Further relapses in the 14/15 patients continuing the treatment included leptomeningeal dissemination in 8, posterior fossa and one single supratentorial site in 4 and 1 patient, respectively, single spine nodule in 1. Twelve of the 15 patients died for tumor progression, one for pneumonia at 13 months after relapse; one patient is alive after further treatment. The only long-term survival in continuous remission at 69 months after relapse, had a single spine metastasis that was excised and irradiated. Survival of the whole series after relapse was 11-69 months, with a median of 39 months. *Conclusions.* Second-line therapy with myelo-ablative schedules, despite the high number of responses obtained and the wide application of surgery and radiotherapy, did not obtain cure if not in exceptional cases. A second-line therapy for medulloblastoma that could pursue cure has to be still looked for.

FEASIBILITY AND EFFICACY OF SEQUENTIAL HIGH-DOSE CHEMOTHERAPY FOLLOWED BY STEM CELL TRANSPLANTATION IN CHILDREN WITH HIGH-RISK MEDULLOBLASTOMA OR SUPRA TENTORIEL PRIMITIVE NEUROECTODERMAL TUMORS

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Purpose. Prognosis of disseminated medulloblastomas (MB) and supratentorial primitive neuroectodermal brain tumours (sPNET) is poor and treatment remains a major challenge, especially in young children because of late toxicity of craniospinal irradiation. We developed a strategy after surgery, using sequential high-dose chemotherapy (HDC) followed by autologous stem cell transplantation (SCT) and radiotherapy with decreased doses for these patients. *Patients and Methods.* Thirty children were enrolled in this pilot study (Disseminated MB=19; sPNET=11). Median age at diagnosis was 34 months (range, 11 to 60). In absence of disease progression after two courses of carboplatin and etoposide, five sequential conventional and HDC followed by ASCT were performed, i.e. melphalan (100 mg/m^2), cisplatin (100 mg/m^2) twice and thiotepa (720 mg/m^2). In case of persisting residue, children with resectable tumour were operated. Treatment was then completed by age-adapted irradiation. *Results.* Treatment was well tolerated with limited toxicity. Among the 30 patients enrolled, the tumour response consisted of 17 complete responses, 6 partial responses and 7 progressive diseases. The 3-year event-free survival and overall survival are 35% (95% CI 20% to 54%) and 50% (95% CI 33% to 67%), respectively. *Conclusions.* Sequential HDC using tandem melphalan and thiotepa was well tolerated and appeared effective. However the number of patients was small and further multicentric study is required.

HIGH DOSE VP16-THIOTEPA (HD VP-TTP) WITH PBSC RESCUE IN RELAPSING INTRA CRANIAL GERMINOMAS (ICG): THE SFCE RETROSPECTIVE EXPERIENCE

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The survival of ICG treated with combined treatment by chemotherapy followed by focal radiotherapy reaches more than 85%. At time of relapse, no current recommendations are validated. *Patients and Methods*. Among 120 patients treated for ICG in France between 1990 and 2003, 14 relapsed and 7 were treated with further chemotherapy and HD VP-TTP (500 mg/m^2/d 1-3 and 300 mg/m^2/d 1-3 respectively). First line strategy included 2 cycles alternating VP-Carboplatin/VP-Ifosfamide followed by focal RT (40 Gy) (in SFOP TGM-TC 90 for 5 patients or GCT 96 arm B for 2 patients). Median delay from end of treatment to relapse was 2 years. Site of relapse was local (1), ventricular and/or regional (4) or spinal (2). Rescue treatment prior to HD VP-TTP included VP CDDP (7) +/- Ifosfamide (2). Status before HD VP TTP was CR (2pts), PR (5). *Results.* Response HD VP-TTP was CCR (2), CR (2), PR (1 in the patient with local relapse), SD (2). *Outcome:* the 4 CR patients are NED (2 after further RT). The PR patient received no further treatment, relapsed and is currently alive with disease. The 2 SD are NED (1 after CSI, and 1 had second relapse that could be salvaged and is currently in CR3 after further chemotherapy and CSI). The 8 year relapse free survival after relapse was 71%; 95%CI [36-92%] and the OS was 100%. Toxicity was as expected after high dose therapy with FUO in all patients, no VOD or toxic death. *Conclusions.* ICG remain chemosensitive at time of relapse, and 2 out of 7 could be salvaged with HDCT without further RT. But the role of HD therapy remains speculative. Among the 7 other patients who relapsed during the same period of time, 5 are alive in CR2 without HDCT.

A UKCCSG STUDY OF THE TREATMENT OF RELAPSED CNS PRIMITIVE NEUROECTODERMAL TUMOURS USING HIGH DOSE CHEMOTHERAPY

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Background. The outcome following a relapse of CNS primitive neuroectodermal tumour (PNET) remains extremely poor. The UKCCSG has developed a protocol based on myeloablative chemotherapy for this patient group. *Methods.* The strategy consists of an initial cytoreductive phase using 2-4 courses of cyclophosphamide (4 mg/m^2) in conjunction with local therapy (surgery or local radiotherapy) if possible. Harvest of peripheral blood stem cells (PBSC) takes place during this cytoreductive phase. If complete or near complete remission is achieved, the patient proceeds to treatment with 2 sequential courses of myeloablative chemotherapy followed by PBSC rescue and G-CSF support. The first course consists of thiotepa (300mg/m2/day for 3 days) and the second course consists of carboplatin dosed to a total AUC of 21. *Results.* Data is available on 46 patients who have completed the treatment so far; 36 trial patients and 10 pilot patients. Median age at registration was 11.4 years (2.3-17.6 years). 16 patients had had a local relapse and 22 a metastatic relapse (8 patients, data awaited). Stem cell collection was successful in 26 patients and failed in 4 patients in whom a bone marrow harvest was performed. Of 20 evaluable patients the response rate (CR/PR) to cyclophosphamide was 46.5%. With a combination of surgery and chemotherapy, at the end of cytoreductive therapy, 9 patients were in CR2 and 6 in PR. 14 patients received high dose thiotepa but only 8 went on to complete the high dose carboplatin. At a median follow up 4.5 years (range: 0 to 5.5 years) 33 patients have died (32 from disease progression and 1 toxic death). The 3 year overall survival is 24.8 % (95% CI: 12.4 to 39.3) and 3 year event free survival is 15.1% (95% CI: 6.2 to 27.7). At present 18% of patients are alive and disease free. *Conclusions.* This treatment prolongs survival following relapsed PNET but in respect of long term survival this strategy has had a disappointing impact. Comparison with other studies requires an understanding of the population base from which patients are reported. Future improvements in this approach to treatment include improved therapies in order to obtain remission and a better definition of prognostic factors including understanding of the molecular biology associated with relapsed PNETs.

OUTCOME IN METASTATIC MEDULLOBLASTOMA TREATED WITH A PROGRAM INCLUDING HIGH-DOSE CHEMOTHERAPY AND STEM CELL RESCUE

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This study describes the motor, sensory and cognitive outcome of 10 patients with metastatic medulloblastoma that had been previously treated at the Milan National Institute of Tumors with protocols described elsewhere in this meeting (Massimino M, et al). For each patient, the medical and oncological history as well as treatment-related information were reviewed. All the patients received an assessment protocol including an evaluation of the motor, sensory and cognitive outcome. The mean age of the patients at diagnosis was 5.4 years (range: 1.0-16), the mean age at our assessment was 6.6 years (range: 1.9-17) and age at radiotherapy was 6.1 years (range: 3-16.5). The mean time from diagnosis to the outcome assessment was 1.1 years (range: 0.2-4 years). Three (3) patients presented with pyramidal problems, 3 patients with cranial nerve disorders, and 8 patients with ataxia. No patient had ever suffered from epileptic fits. Ocular and auditory late effects were found in 3 and 4 patients, respectively. On the cognitive test, the VIQ, the PIQ and the FIQ were in the normal range (93.9, 87 and 90.3, respectively). The results of the cognitive assessment were compared with those obtained by a control group formed by patients with medulloblastoma who had not received high-dose chemotherapy, but the same chemotherapy and radiotherapy schedule. This group was formed by 17 patients with a mean age at diagnosis of 9.3 years (range: 4-18), mean age at assessment of 10.8 years (range: 4.8-20.6) and age at radiotherapy of 9.6 years (range: 5-19.2). On the functional evaluation – with the mean time from diagnosis to evaluation being 1.6 years – the mean VIQ, PIQ and FIQ scores were 98.3 (SD: 17.8), 91.1 (SD: 20.2) and 94.6 (SD: 20.4), respectively. The difference between the two groups was not significant. Other 6 patients with age at diagnosis ≤3 years (mean age: 1.9 years; range: 1-3 years; mean age at assessment: 3.3 years; range: 1.9-7 years) were studied. The assessment was performed at a mean time from diagnosis of 1.4 years and revealed an FIQ of 88 (SD: 10.9) with a greater impairment on the performance tasks. Four patients received radiotherapy. A comparison of the IQ level did not show any significant differences. The lower IQ does not seem to be different from previous findings on patients affected by medulloblastoma who did not undergo any stem cell transplantation. Although a long-term follow-up of cognitive skills is necessary, these preliminary results allow to assume that patients from the first group are not at higher risk of cognitive deterioration. In line with the literature, the cognitive outcome of younger patients is more unfavourable. At the first assessment, no radiotherapy-related differences were found.

OUTCOME IN CEREBRAL PNET TREATED WITH A PROGRAM INCLUDING HIGH-DOSE CHEMOTHERAPY AND STEM CELL RESCUE

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This study describes the motor, sensory and cognitive outcome of 5 patients with supratentorial PNET that had been previously treated at the Milan National Institute of Tumors with a protocol described elsewhere in this meeting (Massimino M, et al). For each patient, the medical and oncological history as well as treatment-related information were reviewed. All the patients received an assessment protocol including an evaluation of the motor, sensory and cognitive outcome. The mean age of the patients at diagnosis was 8.8 years (range: 2.8-15), the mean

age at our assessment was 10.3 years (range: 3.4-17), the mean age at radiotherapy (craniospinal + boost) was 9.3 years (range: 3.8-15.7). The outcome assessment was performed at a mean time from diagnosis of 1.5 years (range: 0.7-2 years). Three (3) patients had developed neurological problems (hemiparesis in 3 patients, cranial nerve disorders in 1 patient and epileptic fits in 3 patients). Ocular and auditory late effects were found in 1 and 2 patients, respectively. On the cognitive evaluation the VIQ, the PIQ and the FIQ were in the normal range (88, 82 and 86, respectively). Only 2 out of 5 patients were re-assessed with a mean time to follow –up of 30 months. On the repeat assessment, the 3 IQs were lower than on the first assessment (VIQ: 86 vs. 91.5; PIQ: 80 vs. 88; FIQ: 81.5 vs. 90). The PIQ and the FIQ were significantly different. The first assessment already revealed some impairments and the results of follow-ups, although reduced in number, point to a further deterioration. An analysis of these findings must necessary take into account the supratentorial site of the tumour. However, the therapy administered - including high-dose chemotherapy and stem cell rescue - does not seem to significantly affect the cognitive picture.

HIGH DOSE CHEMOTHERAPY WITH AUTOLOGOUS STEM CELL RESCUE FOLLOWED BY POSTERIOR FOSSA IRRADIATION AS SALVAGE THERAPY IN YOUNG CHILDREN WITH LOCALIZED RELAPSES OF MEDULLOBLASTOMA

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Purpose. To determine the outcome of children with high risk localized medulloblastoma treated with high dose chemotherapy (HDC) and posterior fossa irradiation. *Patients and Methods.* HDC consisted in busulfan 600 mg/m^2 and thiotepa 900 mg/m^2, followed by autologous stem cells transplantation (ASCT). PF radiotherapy was performed at 50-55 Gy, at day +70 after ASCT. Twenty-seven patients had a local relapse of an initially completely resected medulloblastoma. Eighteen patients had a local residue after surgery; 12 were enrolled in the salvage protocol at the time of local progression under conventional chemotherapy and 6 immediately after the operation. *Results.* Acute toxicity consisted mainly in hepatic veno-occlusive disease observed in 35% of patients and in bone marrow aplasia. Two toxic deaths (4%) from infections were reported. Delayed and transient radiologic abnormalities were observed in the radiation fields in 11 patients. Five-year overall survival after this salvage treatment (OS5y) in the 45 children treated was 71.5% (95% CI = 56.3-83). In the group treated for local relapse, OS5y was 76.5% (95% CI = 57.1-88.9). Patients with local residue had an OS5y of 100% when treated initially with HDC but only 50% (95 % CI = 25.4-74.6) when treated at progression (p=0.08). *Conclusions.* This strategy has a manageable immediate toxicity and offers a high overall survival rate in the setting of localized high risk medulloblastoma.

CONCEPTS OF HDCT AS A PART OF MULTIMODAL TREATMENT REGIMENS WITHIN THE PROSPECTIVE MULTICENTER TRIAL HIT 2000 OF GERMAN-SPEAKING COUNTRIES FOR CHILDREN AND ADOLESCENTS WITH MEDULLOBLASTOMA AND SUPRATENTORIAL PNET

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Background: Within the prospective multicenter trial HIT 2000 of German-speaking countries, the role of high-dose chemotherapy (HDCT) as part of primary treatment is evaluated as a component of multimodal treatment regimens in high-risk children with medulloblastoma or supratentorial PNET. *Methods:* According to histology, tumor localization, age and staging, children are stratified to different different single-arm treatment groups: 1) Children between 4-21 years with metastatic medulloblastoma and children with stPNET (any stage!) and a very good response (> 2/3) to an induction chemotherapy with cyclofosfamide, vincristin, HD-methotrexate, carboplatin etoposide, and intraventricular methotrexate, qualify optionally to a single HDCT with carboplatin, etoposide and thiotepa, and ASCT followed by radiotherapy dependent on the remission status. 2) Children younger than 4 years of age at diagnosis with metastatic medulloblastoma and an objective response to an induction chemotherapy receive a tandem HDCT consisting of carboplatin/etoposide and cyclofosfamide/thiotepa and ASCT, respectively. The induction regimen has been intensified since January 2006 (cisplatin, vincristin, HD-methotrexate, cyclofosfamide, etoposide, and intraventricular methotrexate). 3) Children < 4 years with supratentorial PNET (any stage) and objective response to an induction chemotherapy with carboplatin/etoposide receive a tandem HDCT consisting of carboplatin/etoposide and cyclofosfamide/thiotepa and ASCT, respectively. *Results.* Preliminary analyses show that children without a good response to induction chemotherapy may not benefit from HDCT. As treatment arms are still open, no interim results can be presented. Current strategies including HDCT can be explained for the different treatment arms. Only the data which have been leading to treatment modifications can be shown for discussion. *Conclusions.* The role of HDCT in primary treatment of medulloblastoma/PNET needs to be further determined. Effective induction regimens before HDCT seem to be required to achieve prolonged remissions.

SUPRATENTORIAL PEDIATRIC HIGH GRADE GLIOMAS: A SINGLE INSTITUTION EXPERIENCE

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Aim. Astrocytomas are the most common group of childhood brain tumors, accounting approximately for 40% of all brain neoplasms. WHO grading defines high grade glioma (HGG) the anaplastic astrocytoma (Grade III) and the glioblastoma (Grade IV). HGG continue to present a great therapeutic challenge for pediatric oncologists, meanwhile the prognosis is still poor. This study reports a single institution experience using conventional chemotherapy (CT) and high dose CT (HDCT) followed by autologous peripheral blood stem cell (PBSC) rescue and local radiotherapy (RT) in childhood supratentorial grade III-IV gliomas, aged 3 to 18 years. The aim of this study was to evaluate the rate of response and the overall survival. *Methods.* Seven patients, 4 males and 4 females, aged 7.7 to 16.6 (median: 12.2) years were treated for grade III-IV glioma. Two tumors were anaplastic astrocytomas (WHO III), 5 were glioblastoma (WHO IV). The extent of the surgical resection was subtotal in 2 patients and partial in 3; in 2 cases only a biopsy was possible. After surgical resection, patients underwent the mobilizing regimen with Cyclophosphamide (4 gr/m^2/day day 1) and Etoposide (200 mg/m^2/day days 2, 3, 4), followed by G-CSF 10 µg/Kg s.c. daily from day 7. Then 2 courses of CECaT regimen were employed (Cyclophosphamide 300 mg/m^2/day days 1, 2; Etoposide 100 mg/m^2/day days 1, 2, 3; Carboplatin 500 mg/m^2/day days 2, 3; Thiotepa 10 mg/m^2/day days 1, 2, 3; G-CSF 5 µg/Kg s.c. daily from day 6) with three-four week interval, according to patients' hematological status. HDCT (Thiotepa 300 mg/m^2 days -5,-4,-3 and Etoposide 500 mg/m^2 days -5,-4,-3) was then given as consolidative treatment 4 weeks after completion of chemotherapy. One month after the end of chemotherapy (usually 3-4 months after surgery) patients underwent loco-regional conventional radiotherapy (up to 54 Gy) with techniques depending on initial and residual tumor. *Results and Conclusions.* The chemotherapeutic cycle with Cyclophosphamide and Etoposide was indeed an effective regimen for mobilizing peripheral blood progenitor cell, and for keeping tumors under control: in 6 out of 7 patients PBSC could be collected within 2 days, in 1 case the aphaeresis was three

days long. The median number of collected CD34/kg was $9.56x10^6$. CE regimen achieved 2 partial responses (PR) and 5 stable disease (SD), without any progressive disease (PD). After conventional chemotherapy the patients underwent high-dose chemotherapy with Thiotepa and Etoposide followed by autologous stem cell rescue. The revaluation at the end of HDCT assessed in 5/7 patients revealed one CR, one PR and three SD. The major response rate at the end of therapy among the patients was 42.9% (1 complete response and 2 PR); 1 patient had stable disease during all therapy, and 3 got PD (1 during CECaT, 1 before HDCT delayed for Central Venous Catheter thrombosis and 1 during RT). No patient died of treatment related toxicity. At the moment one patient is alive in stable disease at 48 months from diagnosis; 2 years overall (OS) and progression free survival (PFS) were both 14.3% (SE 13.22%). The median time to progression and death is respectively 9,5 and 12 months. In conclusion, little progress has been made in increasing the survival rates of children with such neoplasm and the prognosis still remains poor. Our study demonstrated the feasibility of a chemo-radiotherapy regimen including HDCT but without no improvement in term of overall survival. This chemotherapeutic approach in fact is able to give some responses that cannot however be maintained over time.

NEUROPSYCHOLOGICAL AND QUALITY OF LIFE LATE EFFECTS ARISING FROM THE TREATMENT OF PEDIATRIC BRAIN

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The long-term neuropsychological and psychosocial effects of cranial irradiation for brain tumors has been well documented over recent years with the most salient risk factors being young age at irradiation, wider volume of radiotherapy and higher total dosage. Radiation therapy for children receiving craniospinal radiation for such tumors as medulloblastoma and PNET are associated with long-term sequelae including deficits within the domains of intelligence, attention-concentration, memory, and psycho-motor processing speed. These deficits often reflect decreased white matter volume and increased abnormalities characterized by calcification, lacunar cysts and atrophy, particularly in the frontal cortex. Furthermore, cranial irradiation may also lead to diminished height, neuroendocrine dysfunction, and hearing loss. Those receiving surgery-only, or focal irradiation, are at less risk for developing cognitive deficits or emotional/behavioral problems; however, research has identified a mild to moderate degree of late effects that warrant thorough follow-up for each survivor. Furthermore, additional studies have begun to document the late effects of intrathecal chemotherapy, which appear to impact aspects of right hemispheric abilities, as well as the prolonged use of high dose steroids upon variable emotional and behavioral functioning. Location of the tumor is also an important predictor of outcome. For example, since germinomas are readily curable with radiotherapy, along with the older average age at diagnosis, the degree of late effects that may negatively impact the neuropsychological function and quality of life of long term survivors remains unclear. Current studies are being developed to test the hypothesis whether the reduction of radiation dose and volume, or the addition of pre-radiotherapy chemotherapy will permit response-based reductions in radiotherapy fields and doses, which may translate into meaningful improvements in functional outcome with preservation of excellent long-term disease control. Additionally, children undergoing treatment for midline tumors such as craniopharyngioma can experience a decrease in overall quality of life; however, the most significant impact appears to be within the domain of internalizing social-emotional and behavioral functioning, such as social problems, and symptoms of anxiety and sadness, as well as the effects of any physical impairment and attentional difficulties on daily functioning. Health care providers should be aware of potential predictors such as, retrochiasmatic location, shunt insertion surgery, etc. for increased behavioral problems or diminished physical capacity, to enhance the patient and family adaptation to the medical condition which may include memory and executive functioning deficits, obesity, endocrine disorders and emotional lability. Consequently, future studies with these populations should include baseline neuropsychological assessments of patients prior to treatment, or shortly after the conclusion of treatment, followed by bi-annual evaluations that include testing instruments which move beyond a singular measure of intelligence and provide data on a range of domains such as attention-concentration, memory and executive function, quality of life, and social-emotional and behavioral functioning in order to clarify the late effects arising from the treatment of pediatric brain tumors. Additionally, research is currently underway to investigate the potential benefit from the use of either stimulant medication to enhance attention and processing speed, or individual cognitive remediation to assist the students with tutoring to improve their academic functioning.

ENDOCRINE EVALUATION AND THERAPY IN PAEDIATRIC PATIENTS WITH PRIMARY BRAIN TUMOURS TREATED WITH RADIOTHERAPY (RT) PLUS HIGH-DOSE CHEMOTHERAPY AND AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

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High dose chemotherapy (HDCT) followed by autologous stem cell rescue and radiotherapy have remarkably improved survival rates in certain groups of children affected by malignant brain tumours. The purpose of this study was to evaluate the endocrinological deficits occurred in this particular subset of children. From 1996 to 2006, 41 patients (19 females; 22 males; age ranging from 7 months to 17 years) were treated with HDCT for CNS tumours: 14 had malignant gliomas (HGG), 15 medulloblastomas (MBL) (5 metastatic, 10 recurrent), 6 supratentorial PNET (s-PNET) and 6 recurrent/resistant germ-cell tumors (GCT). After standard CT, HDCT with thiotepa and autologous hematopoietic stem cell transplantation was given before (22) or after (19) tumor tailored RT. All but 4 patients (younger than three years) were irradiated on the tumour bed (dose range: 30-60 Gy) with additional craniospinal irradiation in 22 patients (dose range: 20-39 Gy). All patients were submitted to endocrinological evaluation at baseline and every 6 months. We observed panhypopitutitarism in 5 patients (5 GCT), isolated GH deficit in 12 patients (3 HGG, 7 MBL, 2 s-PNET), reduction of mineralized bone mass in 9 patients (4 HGG, 3 MBL, 1 s-PNET, 1 GCT), precocious puberty in 2 patients (2 MBL) and primary hypothyroidism in 5 patients (1 HGG, 3 MBL, 1 s-PNET). All these deficits were corrected with an adequate endocrine therapy including GH medication. The latter therapy determined not only growth recovery but also an improvement of lean body mass, bone mineral density and quality of life. Of particular interest, in 5 out of 12 patients an amelioration in neuropsychological performances was also observed.

BRAIN MAGNETIC RESONANCE IMAGING (MRI) FINDINGS AFTER HIGH-DOSE CHEMOTHERAPY AND RADIOTHERAPY (RT) FOR CHILDHOOD CNS TUMORS: A DEVELOPING WORLD

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The RT-related jatrogenic Magnetic Resonance Imaging (MRI) changes are known, while a possible synergistic effect of HDCT and RT is under-estimated. The authors reviewed their experience on imaging studies following RT and high-dose CT and autologous stem cell rescue (HDCT/ASCR) in 35 children. Diagnosis was as follows: 18 high grade gliomas, 11 medulloblastomas, 6 PNETs. There were 14 males and 21 females; median age at diagnosis 7,1 yrs (range 1,4-20,8 yrs). Conditioning regimen consisted of thiotepa (900 mg/m2); carboplatin (1 g/m2) was added in 5 pts. Among medulloblastoma/PNETs, the treat-

ment plan included 2 HD-thiotepa courses in 13 cases, and 3 courses in 2 cases. Irradiation was given pre HDCT in 18 cases or post in 17 cases. Children with gliomas received local RT at a median dose of 60 Gy, while medulloblastoma/PNETs had median 39 Gy craniospinal hyperfractionated-accelerated RT (range 20,8-39 Gy) plus posterior fossa boost (60 Gy). Median follow-up is 22 mos from diagnosis. Twelve children (34%) (5/18 high grade gliomas; 7/17 medulloblastoma/PNETs) had abnormal brain MRI findings, after median 7 mos from RT (range 2-21 mos). The particular pattern of lesions was rapresented by multiple pseudonodular, irregular-shaped, millimeter-sized, T1-weigthted disomogeneously enhancing foci; the T2-weighted images demonstrated surrounding edema. The lesions gradually decreased in size over several months, often living a colliquative central nucleus. In 4 medulloblastoma/PNET pts we observed subdural fluid leaks too, with hyperintense T2-weighted and isointense T1-weighted signal. Typically, meningeal enhancement and thickening over the leaks were observed. The low compressive effect meant a subacute origin of the effusions, rather than an acute event. The higher incidence of pathological MRI in medulloblastoma/PNET pts could be explained by the use of craniospinal irradiation (vs tumor bed only) and a higher number of lumbar punctures (which can be the cause of intracranial hypotension and subdural effusions). Multiple enhancing cerebral lesions on brain MRI early post HDCT/ASCR are frequently seen and may be a consequence of the treatment, to be distinguished from metastatic disease.

ATYPICAL TERATOID/RHABDOID TUMOR THERAPY ON INFANTS AND YOUNG CHILDREN

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Atypical Teratoid/Rhabdoid Tumor (ATRT) is an exceedingly aggressive Central Nervous system (CNS) malignancy. Though there are reports of occasional long-term survival with conventional therapies report, the outlook for infants and young children with this disease remains bleak. We describe the use of dose intensive chemotherapy in the treatment of infants and young children with ATRT. Ten patients with ATRT were enrolled on COG 99703 from July 1998 through February 2003. This was a pilot study to 1) determine the maximum tolerated thiotepa dose administered with fixed dose carboplatin followed by peripheral blood stem cell rescue for 3 cycles following 3 cycles of combination cisplatin, cyclophosphamide, etoposide and vincristine induction therapy and 2) to determine the response rate and disease free survival in these patients (with the caveat that radiation was not mandated). Ten children with ATRT, median age 19 months (range 2.5-33 months) were enrolled on COG 99703, 2 were male. Five patients had cerebellar primary lesions, five had supratentorial lesions, nine had localized disease, and one patient had positive CSF cytology. At diagnosis, 4 patients underwent gross total resection, 2 patients had a near total resection, 2 had subtotal resections and 2 patients had biopsy only. Seven patients developed disease recurrence at a median of 5.8 months after diagnosis (range 2.5-12 months). Four patients had cranial radiation (RT), three had recurrent disease and 2 of these patients had RT prior to disease recurrence. Five patients are alive at a median of 42 months from diagnosis (range 30-75 months), 3 had RT. Two patients with recurrent disease are alive, 24 and 35 months post disease recurrence. The results of this pilot study are encouraging. Further investigation of this therapy in infants and young children with ATRT is warranted.

LONG-TERM NEURO-COGNITIVE AND AUDITORY SEQUELAE AFTER HD CHEMOTHERAPY IN CHILDREN WITH BRAIN TUMOR DIAGNOSED <6 YEARS OF AGE

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We evaluated neuro-cognitive and auditory sequalae in 17 children diagnosed with brain tumors (14 PNET/medulloblastoma, 3 HGG and 1 ependymoma) when aged <6 year. All children received high dose (HD)thiotepa and carboplatin in one or multiple cycles. Eleven children received HD chemotherapy before disease progression (median age at transplant 2.5 year): five of them had radiotherapy either at the time of transplant [1 focal and 1 craniospinal (CS)+boost] or after they relapsed after transplant (2 focal, 1 CS +boost). Of these 11 children, only one had severely abnormal hearing tests. In contrast, neuro-cognitive tests were severely abnormal (IQ <1st percentile) in 4 and borderline (IQ 1-14th percentile) in 2. Five children had IQ in the normal range, however 4 of them had abnormalities in specific tests for working memory, verbal and non verbal memory and processing speed Additional 6 patients had HD chemotherapy after relapse (median age at transplant 5.5 years): 2 had CS radiation as part of the initial therapy and 3 focal radiotherapy at time of transplant. Of these 6 children 2 had severe hearing impairment. As intellective functions, a child was autistic; in the others, IQ was severely abnormal in 2 , borderline in 1 and normal in 2. One of the children with normal IQ had abnormal processing speed. While severe hearing loss was only found in children who received CS radiotherapy, the etiology of severe mental retardation was unclear. Severe mental retardation was more frequent in children treated with CS radiotherapy (3 of 4 children who received CS were severely retarded), but occurred also in children who received focal (1 in 6) or no radiotherapy (2 in 7). In conclusion: HD chemotherapy alone does not seem associated to significant hearing loss. In contrast, residual intellectual impairment can be detected even in children who never received radiotherapy. Large prospective studies are necessary to define the role of the different disease- and therapy- related variables (ie tumor location, surgery, use of one or multiple cycles of ID therapy, etc) on the pathogenesis of the neuro-cognitive impairment in children surviving brain tumors. Specific tests for memory and processing speed are likely to be more informative than IQ testing alone.