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NEURO-ONCOLOGY

2013 WFNO-SNO Abstracts

PEDIATRICS CLINICAL RESEARCH

PC-001. DISSEMINATED PNET WITH AN UNUSUAL PRESENTATION AND COURSE

Reuben Antony, Michael Zagardo, Meena Gujrati, and Julian Lin; OSF/St.Francis Medical Center/Children's Hospital of Illinois, Peoria IL, USA

Supratentorial primitive neuroectodermal tumors while histologically similar to medulloblastoma is less curable. Gross total resection and therefore early recognition is crucial to a favorable outcome. We report our experience with a 4 year old girl whose clinical course and radiology were atypical. The patient was referred to our center for management of a seizure disorder manifesting as episodic choking, spitting, drooling and vomiting. MRI showed cortical thickening (right perisylvian fissure; right frontal operculum; insula) patchy/gyriform enhancement of the right sylvian fissure resembling angiomatous dysplasia and clusters of dysplastic meningeal vessels. There was no mass effect, midline shift, ventriculomegaly and MRV/MRA were normal. The radiological differential diagnoses offered were polymicrogyria, focal cortical dysplasia, neuronal migrational disorders, neurofibromatosis and Sturge-Webber syndrome. She had no neurological deficits and seizures were controlled with Topiramate/Levetiracetam. Brain CT 3 months later showed focal dystrophic calcification in the right perisylvian region superimposed on the cortical dysplasia again suggestive of a phakomatosis. ASA was commenced to reduce risk of stroke. MRI performed two months later showed progression of leptomeningeal enhancement involving the suprasellar cistern/perimesencephalic cistern, left sylvian fissure, ventral brainstem and cerebellar vermis. There was tumefactive material in the right pre-pontine cistern and right ventricular effacement. Spinal cord MRI done at this time showed diffuse subarachnoid spread. Throughout this period apart from episodic facial pain the patient had no neurological, speech, ocular, cerebellar or major cognitive deficits. A biopsy was performed and histopathology was consistent with supratentorial PNET. CSF was negative for malignant cells. Due to the extent /inoperability of the tumor, minimal possibility of cure/high likelihood of severe treatment related side-effects parents opted for supportive care rather than curative treatment. The patient passed away a few months later. A high index of suspicion and low threshold to biopsy is recommended for early diagnosis of these tumors.

PC-002. ROSETTE FORMING GLIONEURONAL TUMORS (RGNT) - DIFFERENT OUTCOMES IN TWO PATIENTS WITH DIFFUSE TUMORS

Reuben Antony[1], Mohamad Al-Rahawan[1], Michael Zagardo[1], Meena Gujrati[1], Julian Lin[1], and Alberto Broniscer[2]; [1]OSF/St.Francis Medical Center/Children's Hospital of Illinois, Peoria, IL, USA; [2]St.Jude Children's Research Hospital, Memphis,TN, USA

Rosette-forming glioneuronal tumor was first described by Komori et al as a low grade glioneuronal posterior fossa tumor having a neurocytic component with synaptophysin(+) neurocytic rosettes and an astrocytic component with GFAP/S-100(+) spindle cells, Rosenthal fibers, granular bodies, glomeruloid capillaries and microcalcifications. About 60 cases, some outside the posterior fossa have since been reported mostly in adults. RGNT are generally slow growing with low risk of progression/recurrence even after subtotal resection. Few RGNT in children have been reported and to our knowledge none involving the spinal cord. Herein we describe two children with histologically similar RGNTs who had significantly differing outcomes. Patient (1) 14 yrs/male, presented with a syncopal attack, multifocal lesion involving the third ventricle, fourth ventricle, septum pellucidum, corpus callosum and spinal cord involvement from C6 to T3. Diffuse coating of tumor within the ventricular space was observed during subtotal resection. Pathology - Low Grade Glioneuronal Tumor with neurocytic rosettes with focal areas on the surface having ependymoma/subependymoma features. CSF was negative for malignant cells. With no further treatment patient has been clinically stable for 4 years and on MRI residual tumor masses have decreased slightly in size and enhancement. Patient (2) 5 yrs/female, presented with constipation, scoliosis and lower extremity weakness. MRI revealed an enhancing tumor from T6 to T10 levels with associated syrinx and leptomeningeal involvement of the cerebellar folia. Spinal cord tumor was sub-totally resected. Pathology -Typical RGNT with Synaptophysin/GFAP positive neurocytic rosettes and glial component with Rosenthal fibers and eosinophilic granular bodies. Low Ki-67 index and no mitotic figures. In spite of subsequent treatment with VCR/Carbo/Temozolomide, Irradiation (CSI 43.2 Gy/Boost to tumor sites to 54 Gy), Irinotecan/Bevacizumab, TPCV, Vinorelbine her tumor progressed and she expired 6 years after diagnosis. Our experience with these two patients with histologically similar RGNTs highlights the need for further molecular characterization of these tumors.

PC-003. ANALYSIS OF THE Wnt5b SIGNALING PATHWAY TO IDENTIFY NOVEL THERAPEUTICS FOR ATYPICAL TERATOID RHABDOID TUMORS

Ratan Bhardwaj[1,2], Chris Hampton[2], Victor Ozols[1,2], and Madhavi Chakravadhanula[1]; [1]Phoenix Children's Hospital, Phoenix, AZ, USA; [2]Translational Genomics Institute, Phoenix, AZ, USA

Atypical Teratoid Rhabdoid Tumors (ATRTs) are aggressive tumor types in the field of pediatric neuro-oncology that need new therapeutic strategies since they are associated with significantly worse overall prognosis than other pediatric tumors. A characteristic feature of ATRTs is usually an aberration of SMARCB1/INI1/hSNF5 gene. The Smarcb1 protein is a component of the mammalian SWI/SNF complex and functions in chromatin remodeling in an ATP dependent manner, although its role in malignancies is unclear. Wnt proteins are a family of 19 secreted glycoproteins and act as ligands that have crucial roles in the regulation of diverse cellular processes. Perturbation of the activities of Wnt ligands can result in defects in embryonic development and diseased states such as cancer. Wnt signaling typically has been subdivided as being canonical (involving nuclear β-catenin) or non-canonical. Our preliminary results from Nanostring™ sequencing analysis indicate that the Wnt5B ligand specifically is significantly overexpressed in patient derived ATRT tumor samples and pre-characterized ATRT cell lines compared to normal brain cortex. This result was validated further by qRT-PCR analysis in the pre-characterized ATRT cell lines compared to normal brain cortex. We performed qRT-PCR and Western blotting analyses to study the gene and protein expression levels of Wnt pathway genes. Next, Wnt5B knockout studies were performed using Wnt5B siRNA on ATRT cells followed by qRT-PCR and Western blotting analyses. The results from these studies indicate that Wnt5B ligand affects expression of genes in both canonical and non-canonical Wnt pathways in ATRT cells. Since it is important to explore therapeutic options for ATRT, we performed drug assays with some known Wnt pathway inhibitors on ATRT cells. The results indicate that pyrvinium which targets casein kinase1α can be tested as a potential therapeutic either individually or synergistically with other therapeutic options for these tumors.

PC-004. WEEKLY VINBLASTINE IN CHEMOTHERAPY NAIVE CHILDREN AND ADOLESCENT WITH UNRESECTABLE OR PROGRESSIVE LOW GRADE GLIOMA: A CANADIAN COOPERATIVE STUDY

Eric Bouffet[1], Cynthia Hawkins[1], Katrin Scheinemann[2], Shayna Zelcer[3], Donna Johnston[4], Lucie Lafay-Cousin[5], Valerie Larouche[6], Nada Jabado[7], Anne Sophie Carret[8], Juliette Hukin[9], David Eisenstat[10], Gregory Pond[2], Ken Poskitt[9], Beverley Wilson[11], Ute Bartels[1], and Uri Tabori[1]; [1]The Hospital for Sick Children, Toronto, ON, Canada; [2]Hamilton Health Sciences, Hamilton, ON, Canada; [3]Children Hospital of Western Ontario, London, ON, Canada; [4]Children Hospital of Western Ontario, Ottawa, ON, Canada; [5]Alberta Children's Hospital, Calgary, AB, Canada; [6]Centre Hospitalier Laval, Quebec, Canada; [7]McGill Children's Hospital, Montreal, QC, Canada; [8]Hopital Sainte Justine, Montreal, QC, Canada; [9]BC Children's Hospital, Vancouver, BC, Canada; [10]CancerCare Manitoba, Winnipeg. MB, Canada; [11]Stollery Hospital, Edmonton, AB, Canada

BACKGROUND: Vinblastine has shown promising activity in a phase II study in children with recurrent/refractory low grade glioma. The aim of this study was to assess the activity of vinblastine in chemotherapy naïve children. METHODS: Patients < 18 years old with unresectable or progressive low grade glioma were eligible if they had not received any previous treatment with chemotherapy or radiation. Vinblastine was administered weekly at a dose of 6 mg/m^2 over a period of 70 weeks. Patients who showed progression or on 2 consecutive imaging studies or evidence of clinical progression were off study. RESULTS: 54 patients (24 female) were enrolled between 2007 and 2010. Mean age at inclusion was 8.4 years. 27 had chiasmatic/hypothalamic tumours, 6 had evidence of dissemination. 13 had neurofibromatosis type

1. Histology was Pilocytic astrocytoma (25), Pilomyxoid astrocytoma (4), low grade astrocytoma variant (7), gangliogliomas (1). 17 patients had no histological diagnosis. Treatment was well tolerated. However, only 14 patients received the full dose for the duration of the study. The most common toxicity was haematological with 40 patients who experienced grade 3+ neutropenia. There were only 6 episodes of febrile neutropenia and 3 RBC tranfusions. No patient died of treatment related toxicity. Best response to chemotherapy was assessed centrally by an independent radiologist: There were 1 CR, 3 MR, 10 PR, 28 SD, 12 PD, for a response rate of 24.5%. Progression free survival at 2 years was 72.1% (CI: 58.1-82.2). On patient with disseminated disease died of uncontrolled progression despite multiple lines of treatment. CONCLUSIONS: Weekly vinblastine is well tolerated in paediatric patients with low grade glioma. Although the response rate appears inferior to other common LGG regimens, the progression free survival at 2 years favourably compares to most currently used regimens. Supported by a grant from the Ontario Institute Cancer Research

PC-005. PHASE I TRIAL OF DASATINIB, LENALIDOMIDE, AND TEMOZOLOMIDE IN CHILDREN WITH RELAPSED OR REFRACTORY CENTRAL NERVOUS SYSTEM (CNS) TUMORS

Girish Dhall, Kelley Haley, Jonathan Finlay, Teresa Rushing, Richard Sposto, and Robert Seeger; Children's Hospital Los Angeles, Los Angeles, CA, USA

BACKGROUND: Dasatinib is a tyrosine kinase inhibitor that inhibits SRC kinases, EGFR, PDGFR-β, c-KIT, and BCR-ABL, and has antiangiogenic and immunomodulatory functions. Lenalidomide is an immunomodulatory agent that inhibits angiogenesis and various pro-inflammatory cytokines and chemokines. Temozolomide is a chemotherapeutic agent with activity against a variety of pediatric CNS tumors and when administered in metronomic doses, exerts an anti-angiogenic effect. METHODS: We performed a phase I trial of this combination using a modified 3 + 3 phase I dose escalation design with a continuous 21-day schedule q 28 days to determine the maximum tolerated dose (MTD) and toxicity in children with recurrent/refractory CNS tumors. The starting dose level (DL 1) of dasatinib was 65 mg/m^2 BID, lenalidomide 70 mg/m^2 daily, and temozolomide 75 mg/m^2 daily, from which dasatinib or lenalidomide would be escalated or de-escalated in alternate patients.. Blood was collected during cycle 1 (days 1, 8, 22 and 29) for NK/T cell subsets (flow cytometry), plasma cytokines and chemokines (cytometric bead arrays), and gene expression related to immune system and angiogenesis. RESULTS: 13 of 15 enrolled patients (2 high grade glioma, 2 ependymoma, 3 medulloblastoma, 1 AT/RT, 4 DIPG, 1 pilocytic astrocytoma, 1 glioneuronal tumor, 1 sPNET) were evaluable for toxicity and response. Dose limiting toxicity (DLT) occurred in 2 patients at DL 1 (somnolence and neutropenia), 2 at DL 0A (dasatinib 55mg/m2) (hypokalemia and thrombocytopenia), and 1 of 6 patients at DL 0B (lenalidomide 40mg/m2) (thrombocytopenia). 5/15 patients died of progressive disease, 10 are alive with disease and 1 patient had a partial response. CONCLUSIONS: DL 0B (dasatinib 65 mg/m^2 BID, lenalidomide 40 mg/m^2 daily, and temozolomide 75 mg/m^2 daily) is the MTD and recommended phase 2 dose of this combination. Analysis of biologic studies is ongoing.

PC-006. PILOMYXOID ASTROCYTOMA: IMPACT OF PRE-EMPTIVE CHEMOTHERAPY

James Garvin[1,3], Karishma Rupani[2,4], Eileen Stark[1], Richard Anderson[2], and Neil Feldstein[2]; [1]Department of Pediatrics, Columbia University Medical Center, New York, NY, USA; [2]Department of Neurological Surgery, Columbia University Medical Center, New York, NY, USA; [3]Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, New York, NY, USA; [4]School of Medicine, Royal College of Surgeons in Ireland, Dublin, Ireland

Pilomyxoid astrocytoma (PMA; WHO Grade II) is a variant of pilocytic astrocytoma (PA), occurring at earlier age, usually in the hypothalamic/suprasellar region, and with unique histologic features and tendency for locally aggressive growth, dissemination, and inferior outcome. Accordingly, we have advocated pre-emptive chemotherapy at diagnosis of PMA. Between 2002 and 2012, 10 children were seen with PMA: 5 males, 5 females, ages 15 months to 6 years. One patient had antecedent PA. Tumor locations were suprasellar (4), hypothalamus (2), thalamus, third ventricle, temporal lobe, and medulla (1 each). One patient had leptomeningeal dissemination at diagnosis. Two patients had gross total resection, 6 subtotal resection, and 2 biopsy. Tumors had typical histologic features of PMA, without co-existing PA; some expressed OLIG2 and PDGFRα. Chemotherapy was vincristine + carboplatin (5) or vincristine + carboplatin + temozolomide (5). All patients are surviving, at 3 months to 11 years (median 5 years). Five patients had disease progression, at 2 months to 6.8 years (median 4.5 years), and received additional chemotherapy with thioguanine + procarbazine + CCNU + vincristine. One patient had further disease progression and received cisplatin + etoposide and ultimately craniospinal irradiation. Pre-emptive chemotherapy appears to improve outcome in PMA, but multiple courses may be required. Further investigation of gene expression in PMA could lead to more effective targeted therapy.

PC-007. HERBY: A PHASE II COMPARATIVE STUDY OF BEVACIZUMAB-BASED THERAPY IN CHILDREN WITH HIGH-GRADE GLIOMA

Jacques Grill[1], Darren Hargrave[2], Maura Massimino[3], Tim Jaspan[4], Pascale Varlet[5], Chris Jones[6], Paul Morgan[7], Marie Cecile Le Deley[1], Amedeo Azizi[8], Adela Cañete[9], Eric Bouffet[10], Frank Saran[11], Jeanette Bachir[11], Lida Bubuteishvili-Pacaud[11], Raphael Rousseau[12], and Gilles Vassal[1]; [1]Institut Gustave Roussy, Villejuif, France; [2]Great Ormond Street Hospital, London, UK; [3]Fondazione IRCCS, Istituto Nazionale Tumori, Milan, Italy; [4]University Hospital, Nottingham, UK; [5]Sainte-Anne Hospital, Paris, France; [6]Institute of Cancer Research, Sutton, UK; [7]Nottingham University Hospitals, Nottingham, UK; [8]Universitäts Klinik für Kinder und Jugendheilkunde, Vienna, Austria; [9]H.U. LA FE, Valencia, Spain; [10]Hospital for Sick Children, Toronto, ON, Canada; [11]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [12]Genentech Inc., South San Francisco, CA, USA

PURPOSE: Despite therapeutic advances, pediatric high-grade glioma (HGG) outcomes remain poor. The phase I study (Glade-Bender et al., J Clin Oncol 2008) indicated that bevacizumab (Bv) is well tolerated in children with refractory solid tumors and supported further studies in children. METHODS: 120 evaluable patients (main cohort) aged ≥3-18 years with newly diagnosed histologically confirmed WHO grade III or IV HGG are randomized to standard therapy ± Bv. Treatment consists of 6 weeks of concomitant temozolomide (TMZ) and radiotherapy, followed by 4-week TMZ treatment break and 48 weeks of adjuvant TMZ + Bv every other week. Primary endpoint is event-free survival (EFS). Evaluation is based on Response Assessment in Neuro-Oncology (RANO) criteria. Secondary endpoints are overall survival (OS), safety, feasibility, and tolerability. All Bv patients will have PK sampling at cycles 1-4 of the adjuvant phase. Health-related quality of life, neurocognitive functions, MGMT methylation status, and functional tumor changes based on MR diffusion, perfusion imaging, spectroscopy, and correlation of biomarkers with clinical activity and adverse events are explored. In addition, a young patient cohort of 10 patients aged ≥ 6 months and < 3 years with recurrent or progressive localized or metastatic WHO grade III or IV HGG will be evaluated, and will receive TMZ and Bv for 12 cycles without radiotherapy. The exploratory objective is to assess safety, pharmacokinetics, and benefit of Bv (assessed by PFS). All children will be followed for ≥3 years. Endpoints for both cohorts will be analyzed after the 120 patients have been followed for 1 year. Multimodal imaging will aid development of new criteria for pediatric neuro-oncological treatment response. An updated OS and safety analysis will be performed 3 years after randomization of the last patient. The first patient was randomized in October 2011; study completion is expected in 2016.

PC-008. PEDIATRIC SPINAL CORD ASTROCYTOMAS: A SINGLE INSTITUTION EXPERIENCE

Shveta Gupta, Nathan Robinson, Nitika Dhir, Kenneth Wong, Shengmei Zhou, Jonathan Finlay, and Girish Dhall; Childrens Hospital of Los Angeles, Los Angeles, CA, USA

BACKGROUND: Spinal cord astrocytomas are a relatively rare group of neoplasms accounting for <5% of all CNS tumors. There is little information on therapy and outcome of astrocytomas in this location. METHODS: We conducted a retrospective review of consecutive children with spinal cord astrocytomas evaluated at Children's Hospital Los Angeles between 2001 and 2012. Medical records were reviewed and clinical data was abstracted. RESULTS: We identified 16 children with spinal cord astrocytoma, including 8 (50%) with low grade astrocytoma (LGA, 3 grade I, 5 grade II) and 8 (50%) with high grade astrocytoma (HGA, all grade III). Location was cervical in 11 (69%) patients. All 16 patients underwent surgical resection. Gross total resection (GTR) was achieved in 5 (31%) patients. Eight of 8 HGA and 3 of 8 LGA received adjuvant irradiation, with or without chemotherapy. All HGA patients and 7 of 8 LGA patients suffered subsequent radiographic recurrence/progression. Median time to progression was 9 months (range 3-80) after GTR and 6 months (range 3-48) after subtotal resection. Recurrence was

distant in 6 (38%) patients, of which 4 (50%) were HGA and 2 (25%) were LGA. Three patients with LGA who received irradiation had subsequent radiologic progression at a median of 8 months. With a median follow-up time of 39 months (range 12-80), all LGA patients are alive; 5 with stable disease and 3 with no evidence of disease. Three of 8 patients with HGA are alive with evidence of disease. Median overall survival for patients with HGA was 14 months. CONCLUSION: Spinal cord astrocytomas represent a distinct group of diseases with a high rate of recurrence post therapy and a high rate of dissemination. The role of adjuvant therapy is unclear. Further investigation is required to better define optimal treatment of both high and low-grade spinal cord astrocytomas.

PC-009. CLINICAL SIGNIFICANCE AND LIMITATIONS OF REPEAT RESECTION FOR PEDIATRIC MALIGNANT NEUROEPITHELIAL TUMORS

Toshihiro Kumabe[1,2], Tomohiro Kawaguchi[1], Ryuta Saito[1], Masayuki Kanamori[1], Yoji Yamashita[1], Yukihiko Sonoda[1], and Teiji Tominaga[1]; [1]Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan; [2]Kitasato University, Sagamihara, Kanagawa, Japan

OBJECTIVE: Maximized tumor resection and minimized surgical morbidity are extremely important in the treatment of children with malignant neuroepithelial tumors. However, the indications for repeat surgery for these tumors remain unclear. The present study investigated the clinical significance and limitations of repeat resection for these tumors. METHODS: This study included 61 consecutive pediatric patients with malignant neuroepithelial tumor, histologically diagnosed as World Health Organization (WHO) grades III and IV. All patients were initially treated between January 1997 and March 2011 and followed up for more than 2 years. The number of surgeries, presence of leptomeningeal dissemination, survival, WHO grade of the tumor, and Eastern Cooperative Oncology Group (ECOG) performance status (PS) before and after surgery were retrospectively reviewed. RESULTS: Repeat resections were performed for 21 (34.4%) patients. ECOG PS was not aggravated by surgery, even after multiple operations. The 5-year survival rates of patients who received single and repeat surgery were 58.6% and 38.7%, respectively ($p = 0.12$). The time interval between initial surgery and leptomeningeal dissemination detection was 331 $+/-108$ days in the single surgery group and 549 $+/-122$ days in the repeat surgery group ($p = 0.19$). The median survival time after leptomeningeal dissemination was 580 days in the single surgery group and 890 days in the repeat surgery group ($p = 0.74$). CONCLUSIONS: Repeat resection with minimized surgical morbidity is an effective method to achieve better local control of pediatric malignant neuroepithelial tumors. Leptomeningeal dissemination was a leading cause of death, but repeat surgery did not increase the frequency of this complication.

PC-010. IMMUNOHISTOCHEMICAL EVALUATION FOR THE PATHOGENESIS OF INTRACRANIAL GERM CELL TUMORS: EXPRESSION OF PLURIPOTENCY AND CELL DIFFERENTIATION MARKERS

Tadashi Miyagawa; Chiba University Graduate School of Medicine, Chiba, Chiba, Japan

INTRODUCTION: Primary intracranial germ cell tumors (iGCT) are rare neoplasms that occur in children and adolescents. This study examined both the pathogenesis and the origin of these tumors, as it has been hypothesized that they originate from a totipotent primordial germ cell. MATERIALS AND METHODS: We applied recent knowledge from gonadal germ cell tumors and analyzed expression of a wide panel of stem cell-related proteins(C-KIT, OCT-3/4 (POU5F1), NANOG, SOX2, CD30 and PLAP). Expression shown by immunohistochemistry was analyzed in 12 children and young adults with iGCT, contributing to a careful description of these unusual tumors and adding to the understanding of pathogenesis. RESULTS: Immunohistochemistry showed 5/5 positive in Oct3/4, 5/5?in NANOG, 9/9 in C-KIT and 1/5 in SOX2. All cases that showed positive staining in Oct3/4 or NANOG indicated that the tumors contained germinoma or embryonal carcinoma component. Immunohistochemistry revealed that stem cell related proteins were highly expressed in iGCT, and many similarities were detected with their gonadal equivalents, including a close similarity with primordial germ cells. CONCLUSION: The expression of genes associated with embryonic stem cell pluripotency in CNS germ cell tumors strongly suggests that these tumors are derived from cells that retain, at least partially, an embryonic stem cell-like phenotype, which is a hallmark of primordial germ cells. In addition, these data can be applied to stratify iGCT for treatment strategy in order to provide good survival rate and good functional outcome.

PC-011. EFFECTS OF TREATMENT MODALITY ON HEALTH RELATED QUALITY OF LIFE (HRQOL) IN LONG-TERM SURVIVORS OF PEDIATRIC LOW GRADE GLIOMA (LGG)

Chika Nwachukwu, Ryan Youland, and Nadia Laack; Mayo Clinic, Rochester, MN, USA

PURPOSE/OBJECTIVE: Although multimodality treatment is leading to longer survival of pediatric patients with LGG; little is known on the long-term effects of these treatments on HRQOL. The study aims were to evaluate HRQOL in long-term adult survivors of pediatric LGG using adult HRQOL instruments and assess the impact of various treatment factors on HRQOL. METHODS: The Mayo Clinic Tumor Registry Database identified 313 patients <21 years at diagnosis, with a minimum 3 year follow-up and were at least 18 years old at time of contact. Patients were sent the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC-QLQ-C30), which was supplemented by the EORTC QLQ-BN20 specifically developed and validated for patients with brain tumors. RESULTS: The median follow-up for 121 out of 313 patients who completed the survey was 21.9 years. 77% of patients had a gross total resection (GTR), 19% had a subtotal resection (STR) and 4% had biopsy only. 80% of patients were observed post-operatively, 17% received radiation therapy (RT), 1 patient received chemotherapy and 2 received chemotherapy and RT. Based on the QLQ-C30, GTR treated patients compared to STR reported better cognitive function ($p = 0.027$). RT treated patients reported lower physical ($P = 0.003$), role function ($P = 0.004$) and more constipation problems ($p= 0.002$). Based on QLQ-BN20, brain-specific symptoms, patients treated with STR ($P = 0.006$) or RT ($p < 0.001$) reported more bladder control problems. RT patients reported more problems with visual disturbance ($p = 0.001$), motor dysfunction ($p = 0.017$) and weak legs ($p = 0.003$). CONCLUSION: With a median follow-up of over 20 years from diagnosis, GTR is associated with better self-reported cognitive functioning. RT is associated with a poorer self-reported physical and role functioning and some brain specific symptoms. Further study is necessary to evaluate whether supportive therapy or other interventions can ameliorate these symptoms or improve HRQOL in this population.

PC-012. IRINOTECAN WITH CARBOPLATIN- AN ALTERNATIVE THERAPEUTIC OPTION FOR CHILDREN WITH HIGH GRADE GLIOMAS (HGG) - ONE INSTITUTION EXPERIENCE

Iwona Filipek[1], Monika Drogosiewicz[1], Marta Perek- Polnik[1], Ewa Swieszkowska[1], Bozenna Dembowska-Baginska[1], Elzbieta Jurkiewicz[2], and Danuta Perek[1]; [1]The Childrens' Memorial Health Institute, Oncology Department, Warsaw, Poland; [2]The Childrens' Memorial Health Institute, Radiology Department, Warsaw, Poland

Since responses to irinotecan in HGG have been reported we have introduced a combination of irinotecan and carboplatin at first as a second line/salvage treatment in patients with disease relapse/progression then as preirradiation chemotherapy in patients with measurable residual tumors. AIM: To assess response and toxicity of irinotecan and carboplatin regimen for HGG in children. PATIENTS AND METHODS: 20 pts were assessable for response. Two were diagnosed with anaplastic oligoastrocytoma, 2 anaplastic oligodendroglioma, 3 anaplastic astrocytoma and 13- glioblastoma. 7 pts received this regimen as a second/third line treatment and 13 after tumor resection, prior to radiotherapy. Chemotherapy protocol consisted of 5 day courses of irinotecan 50 mg/m^2 in 1 hour infusion and carboplatin 250 mg/m^2 on day 1st given every 3 weeks. Response to chemotherapy was evaluated using RANO criteria, toxicity was assessed according to CTC. RESULTS: 20 pts received from 1 to 14 courses (median 4) of chemotherapy. Out of 7 pts with disease progression/relapse, previously treated with chemotherapy and radiotherapy 1 showed CR, 3 pts- SD and 3 had progressive disease. Of 13 pts naïve to chemotherapy 1 pt achieved CR, 8 pts obtained PR, SD was observed in 1 pt and 3 had PD. 1 pt who showed PR on irinotecan/carboplatin regimen in first line treatment, achieved CR in second line treatment. Myelosuppression and gastrointestinal toxicities were the most common and manageable. CONCLUSION: Irinotecan with carboplatin regimen shows activity against high grade glioma in children and has acceptable toxicity. Supported by The National Centre for Research and Development

PC-013. PEDIATRIC MULTIDISCIPLINARY NEURO-ONCOLOGY PROGRAM TRANSLATES INTO IMPROVEMENT OF SURVIVAL RATES OF CHILDREN WITH CENTRAL NERVOUS SYSTEM (CNS) TUMORS - POLISH EXPERIENCE

Danuta Perek[1], Bozenna Dembowska-Baginska[1], Monika Drogosiewicz[1], Marta Perek- Polnik[1], Wieslawa Grajkowska[2], Marcin Roszkowski[3], Grazyna Sobol[4], Katarzyna Musiol[4], Jacek Wachowiak[5], Bogna Kazmierczak[5], Jaroslaw Peregud - Pogorzelski[6], Wojciech Młynarski[7], Beata Zalewska- Szewczyk[7], Mariusz Wysocki[8], Ewa Niedzielska[9], Jerzy Kowalczyk [10], Hanna Wiśniewska - Slusarz[10], Walentyna Balwierz[11], Ewa Zaleska - Czepko[11], and Anna Szołkiewicz[12]; [1]The Children's Memorial Health Institute, Oncology, Warsaw, Poland; [2]The Children's Memorial Health Institute, Patology, Warsaw, Poland; [3]The Children's Memorial Health Institute, Neurosurgery, Warsaw, Poland; [4]Medical University of Silesia, Oncology, Hematology and Chemotherapy, Katowice, Poland; [5]Medical University of Poznan, Pediatrics, Oncology and Hematology, Poznan, Poland; [6]Pomeranian Medical University, Pediatrics, Hemtology and Oncology, Szczecin, Poland; [7]Medical University of Lodz, Pediatrics and Oncohematology, Lodz, Poland; [8]Medical University of Bydgoszcz, pediatrics, hematology an Oncology, Bydgoszcz, Poland; [9]Medical University of Wroclaw, Pediatrics, Hematology, Oncology and Bone Marrow Transplantation, Wroclaw, Poland; [10]Medical University of Lublin, Oncology and Hematology, Lublin, Poland; [11]Jagiellonian University, pediatric Oncology and Hematology, Cracow, Poland; [12]Medical University of GdanskPediatric, Hematology, Oncology and Endocrinology, Gdansk, Poland

INTRODUCTION: Before the introduction of the National Pediatric Neuro-Oncology Program the majority of children with CNS tumors in Poland were treated by adult neurosurgeons and radiotherapists. Unified chemotherapy protocols for CNS tumors were not available. Epidemiological data, treatment results were scarce. In 1996 Pediatric National Neuro-Oncology Program was developed. It was committed to improving survival and deliver research based care. AIM: We present our experience in developing the program and results of 17 years of its functioning. METHODS: Retrospective analysis of children with CNS tumors from our center treated before 1996 was performed to serve as a reference (it was the only pediatric center treating children with CNS tumors), treatment protocols for specific tumors (adapted from SIOP or own) were prepared and implemented in 10 pediatric oncology centers. In each center multidisciplinary team (pediatric oncologist, radiologist, neurosurgeon, pathologist, radiotherapist) were established. All tumors had to be reviewed by pathology board, interdisciplinary consultations were available for all CNS tumor patients. National computer data collection of CNS tumors was initiated. Studies on the role of imaging techniques (MRI spectroscopy, DWI,PWI) and on molecular biology of CNS tumors are being conducted. Program supported by the Ministry of Health and The National Centre for Research and Development. RESULTS: Since 2002 1735 patients with CNS tumors were registered. LGG were the most common- 42.8%, followed by MB/PNET-17.1%, HGG-.8%, brain stem-7.3%, Ependymoma 6.6%, GCT-3.4%. Interdisciplinary approach and unified treatment protocols resulted in the improvement of survival of all CNS tumors as compared to historical results. 5 yrs OS for LGG – 96,1 %, MB/PNET- 64 vs 52%, HGG-29,7 vs 24.4%, Anaplastic Ependymoma-82,7 vs 32%, GCT-89 vs 87%, NGCT-55%, CPC-54%, ATRT-26,9%, brain stem 23,7 vs 14%. These results are superior to those obtained before 1996. This program has also instituted cooperation with its national participants.

PC-014. TREATMENT RESULTS OF METASTATIC MEDULLOBLASTOMA (M2 AND M3 ACCORDING TO CHANG CLASSIFICATION) IN CHILDREN OVER 3 YEARS OF AGE - EXPERIENCE FROM ONE INSTITUTION

Danuta Perek[1], Marta Perek-Polnik[1], Bozenna Dembowska-Baginska[1], Monika Drogosiewicz[1], Wieslawa Grajkowska[1], Maria Lastowska[1], Marzanna Chojnacka[2], Iwona Filipek[1], Magdalena Tarasinska[1], and Marcin Roszkowski[1]; [1]The Children's Memorial Health Institute, Warsaw, Poland; [2]The Maria Skłodowska-Curie Institute of Oncology, Warsaw, Poland

AIM: Analysis of treatment results of patients with M2 and M3 Medulloblastoma treated according to Polish Pediatric Neurooncology Group protocol. MATERIAL AND METHOD: Between 1999 and 2009 153 Medulloblastoma patients older than 3 years were treated in the Children's Memorial Health Institute. 59 presented with metastases visible on MRI were treated according to high risk protocol (4 courses of preirradiation chemotherapy, craniospinal irradiation of 35 Gy, tumor bed boost up to 55Gy and individual boost to the remains of metastases followed by 8 courses of maintenance chemotherapy). Analysis included: age and gender stage of disease, location of metastases, pathological subtypes, molecular subtypes in the M2&3 group, survival according to pathological and molecular subtype and location of metastases. The results were evaluated and compared in 2 groups M0&1 and M2&3. RESULTS: 5years OS was 87% in M0&1 group and 62% in M2&3 ($p = 0,005$), 5years PFS was 80% and 59% respectively ($p = 0,003$). There was no correlation between age and gender and disease stage (mean age 9,4 in both groups, 105 boys, 65 M0&1, 40 M2&3; 48 girls 29 M0&1, 19 M2&3), metastases were localized in brain in 7 pts, spine 35 and in 17 pts in both. There was a higher proportion of LCA subtype in the metastatic group (3,8% v/s 16,9, $p = 0,007$). 5years OS was 64,3% in classic Medulloblastoma and 29,1% in anaplastic, PFS was 62% and 0 respectively. 5years OS was 71,4% in pts with brain, 67,7% in pts with spine and 47,5% in pts with metastases in both sites. CONCLUSIONS: The strategy of conventional chemotherapy administered both before and after individualized irradiation is an option of treatment that offers long time remission to approximately 60% of M2&3 patients, but is ineffective in patients with LCA Medulloblastoma. Supported by The National Centre for Research and Development.

PC-015. MEDULLOBLASTOMA IN THE OPERATIVE THEATER: ARE THEY PLAYING ACCORDING TO THEIR SUBTYPES?

Sebastien Perreault[1,2], Kevin Chao[1], Vijay Ramaswamy[3], David Shih[3], Marc Remke[3], Betty Luu[3], Simone Schubert[1], Paul Fisher[1], Sonia Partap[1], Hannes Vogel[1], Michael Taylor[3], Liliana Goumnerova[4], and Yoon-Jae Cho[1]; [1]Stanford, Palo Alto, CA, USA; [2]CHU Sainte-Justine, Montreal, QC, Canada; [3]SickKids, Toronto, ON, Canada; [4]Boston Children's Hospital, Boston, MA, USA

Medulloblastomas are subtyped into four distinct molecular subgroups. Little is known about the in vivo characteristics of medulloblastoma according to their subtypes. We sought to investigate the intra-operative aspects of medulloblastomas based on their subtypes. We conducted a historical cohort study of children diagnosed with medulloblastoma from January 1998 to January 2013. Patients with available operative report and tissue were included in the study. Molecular subtyping was conducted using a nanoString-based assay and tumors were classified into four subgroups according to their molecular profile: WNT, SHH, Group 3 and Group 4. Operative reports were reviewed by an independent neurosurgeon. Location, invasion and vascularity were correlated to their molecular subtype. A total of 41 medulloblastoma patients were evaluated in our discovery cohort. Four (9.8%) were classified as WNT, 11 (26.8%) as SHH, 11 (26.8%) as Group 3 and 15 (36.6%) as Group 4. Location at time of surgery was significantly different between tumor subtypes ($p < 0.001$); Group 3/4 commonly involved the fourth ventricle (92%), SHH tumors involved the cerebellum (72.7%) whereas WNT tumors were located at the cerebellopontine angle (CPA) (75%). Tumor invasion was also significantly different ($p = 0.001$); only one SHH tumor (9.1%) invaded the braistem floor/CPA compared to 76.7% for the other subgroups. Interestingly, all WNT tumors were more likely to be described as highly vascular, hemorrhagic and often friable compared to other subgroups. These findings were validated in two independent, non-overlapping medulloblastoma cohorts. In conclusion, how medulloblastoma handle in the operative theater offers valuable information and in the case of WNT pathway medulloblastoma points to specific biology that results in a highly hemorrhagic phenotype. In addition, appreciation of tumor location and invasion at time of surgery could be use to predict medulloblastoma subgroups and offer insight into the cell of origin of each molecular subgroup.

PC-016. GLIOBLASTOMA MULTIFORME WITH PRIMITIVE NEURO-ECTODERMAL-LIKE COMPONENTS (GBM-PNET): CLINICAL COURSE AND MANAGEMENT OF THREE PEDIATRIC CASES

Nathan Robison[1], Girish Dhall[1], Robert Brown[1], Timothy Cloughesy[2], Tom Belle Davidson[2], Mark Krieger[1], Mitchel Berger[3], Kenneth Wong[1], Arie Perry[3], Floyd Gilles[1], and Jonathan Lester Finlay[1]; [1]Children's Hospital Los Angeles, Los Angeles, CA, USA; [2]University of California-Los Angeles, Los Angeles, CA, USA; [3]University of California-San Francisco, San Francisco, CA, USA

PURPOSE: Glioblastoma (GBM) with primitive neuro-ectodermal (PNET)-like components (GBM-PNET), has been described as a rare entity in adults. We report our experience with 3 pediatric cases. METHOD: Retrospective medical record review. RESULTS: Case 1: 12-year-old girl with right frontal GBM underwent gross-total resection (GTR) and focal irradiation (RT) with subsequent temozolomide and isotretinoin. Less than 6 months later, she developed a spinal cord tumor; biopsy showed GBM-PNET. She underwent craniospinal irradiation (CS) with focal boost, with concurrent carboplatin and oral etoposide; post-radiation therapy

included two cycles of cyclophosphamide followed by three cycles of thiotepa and carboplatin with autologous hematopoietic stem-cell rescue. She achieved complete remission for 13 months before developing recurrent disease. Case 2: 17-year-old girl with left frontal low-grade oligo-astrocytoma (OA, 1p/19q intact) underwent surgical resection followed by temozolomide. First local progression was resected and pathology again showed low-grade OA. Subsequent GTR of a second local recurrence revealed GBM-PNET. Patient underwent CSI with boost, with concurrent vincristine and carboplatin, followed by maintenance chemotherapy, and remains in continuing complete remission (CCR) at 8 months. Case 3: 3-year-old girl with left temporal anaplastic OA (1p/19q intact) underwent surgical followed by intensive chemotherapy. Progressive local tumor was resected eighteen months later. She was treated with irinotecan, temozolomide and bevacizumab, followed by maintenance therapy with temozolomide, isotretinoin and vorinostat. Subsequent GTR of a second local recurrence revealed GBM-PNET. Patient received focal RT with vincristine and carboplatin, followed by lomustine maintenance therapy. She remains in CCR at 14 months. CONCLUSION: These three cases of pediatric GBM-PNET share similar features: all occurred in the setting of prior glial tumors (oligoastrocytoma or GBM), and none occurred within a prior irradiation field. Our experience suggests a possible role for combination chemoradiotherapy. Further investigation of this disease is needed.

PC-017. NON-GERMINOMATOUS GERM CELL TUMORS OF THE CENTRAL NERVOUS SYSTEM IN CHILDREN: A SINGLE INSTITUTION EXPERIENCE

Nathan Robison, Nitika Dhir, Jyotsana Khemani, Kenneth Wong, Shveta Gupta, Barbara Britt, John Grimm, Jonathan Finlay, and Girish Dhall; Children's Hospital Los Angeles, Los Angeles, CA, USA

BACKGROUND: Non-germinomatous germ cell tumors (NGGCT) of the central nervous system in children are relatively rare. Risk stratification and management remain controversial. OBJECTIVE: To describe significant characteristics of NGGCT in a single institutional cohort. METHODS: Patients with NGGCT evaluated at Children's Hospital Los Angeles between 1993 and 2011 were identified. Clinical and histologic data were abstracted from the medical record. RESULTS: We identified 23 patients with NGGCT. Median age at diagnosis was 13 years (range 4-28); 16 (70%) were male. Histologic findings were available for 15 patients: 12 had a yolk sac tumor component, including 5 with pure yolk sac tumor; 7 had a choriocarcinoma component, including 2 with pure choriocarninoma; 8 had teratomatous component; 1 patient had pure embryonal carcinoma. Extreme elevation of tumor markers (alpha-fetoprotein >1000 ng/mL or human chorionic gonadotropin >1000 IU/L in serum or cerebrospinal fluid) was observed in 7 patients. Detailed treatment information was available for 21 patients, all of whom received 3-6 cycles of platinum-based induction chemotherapy. End-induction radiologic complete response was observed in 10 patients (48%), and tumor marker normalization in 17 (80%). Fourteen patients (67%) underwent consolidation chemotherapy with autologous stem cell rescue; 14 (67%) patients received RT, including craniospinal (7, 33%), whole ventricular (6,28%) and local only (1, 5%). With a median follow-up time of 32 months, 10 patients have relapsed. Recurrences were local only (4), ventricular only (2), local and extra-ventricular (2), local and ventricular (1), and spinal (1). Neither histologic features nor degree of tumor marker elevation were associated with increased risk of relapse; however, extreme tumor marker elevation at presentation was associated with increased risk of death due to disease ($P = 0.008$). CONCLUSIONS: NGGCT represent a heterogeneous entity. Extreme tumor marker elevation at presentation was associated with poorer prognosis.

PC-018. FEASIBILITY, RISK PROFILE AND DIAGNOSTIC YIELD OF STEREOTACTIC BIOPSY IN THE PEDIATRIC POPULATION

Maximilian I. Ruge[1], Tobias Blau[2], Vanessa Hafkemeyer[1], Christina Hamisch[1,3], Katharina Klinger[1], and Thorsten Simon[4]; [1]Department of Stereotaxy and Functional Neurosurgery, Centre of Neurosurgery, University of Cologne, Cologne, Germany; [2]Department of Neuropathology, University of Cologne, Cologne, Germany; [3]Department of General Neurosurgery, Centre of Neurosurgery, University of Cologne, Cologne, Germany; [4]Department of Pediatric Hematology and Oncology, University of Cologne, Cologne, Germany

OBJECTIVE: While stereotactic biopsies (SB) are widely accepted as routine diagnostic tool for unclear cerebral pathologies in adult patients, there is still a certain reluctance to apply this technique for the pediatric population. Probable reasons might be the localization of pathologies predominantly in highly eloquent regions (posterior fossa/midline structures) and/or a perceived elevation of other peri-operative risks. Here we present feasibility, risk profile and diagnostic yield of SB in one of the largest reported pediatric populations. METHODS: All pediatric patients (age < 21) who underwent SB in our institution (1994–2013) were analyzed in detail retrospectively regarding success of performing the SB, diagnostic yield, and procedural complications. These parameters were correlated with localization (lobar vs. midline) and amount of biopsy material (1 vs. ≥ 2 probes). RESULTS: 133 patients (median age 11.0 ± 5.1 range 1-20) underwent 148 SB's located lobar (41) and midline (97). Tissue was obtained in all cases (90.6% ≥ 2 probes) and was diagnostic in 93.2%. In 3.4% a second SB procedure was successful. Mortality was zero and procedural morbidity was transient and low (5.4%). These parameters were not influenced by localization or amount of biopsy material. CONCLUSION: In the pediatric population SB can be performed safely and with a high diagnostic yield in specialized institutions. Under the aspect of providing tissue for advanced histo-pathological- immunological and molecular information to tailor more individualized treatment this well established technique deserves to be considered more often in the pediatric population.

PC-019. MDACC EXPERIENCE WITH CLINICAL AND MOLECULAR HETEROGENEITY IN PEDIATRIC PILOCYTIC ASTROCYTOMA

Zsila Sadighi[1], Benjamin Ellezam[2], Michele Guindani[3], and Joann Ater[3]; [1]St. Jude Children's Research Hospital, Memphis, TN, USA; [2]Sainte-Justine Hospital-Universite de Montreal, Montreal, QC, Canada; [3]MD Anderson Cancer Center, Houston, TX, USA

BACKGROUND: Pilocytic astrocytoma (PA), the most common glioma in the pediatric population, has clinical and molecular heterogeneity. We present the clinical and molecular experience at MD Anderson Cancer Center (MDACC) of 118 pediatric patients. METHODS: We conducted an IRB approved retrospective review of patients ≤ 18 years old with PA at MDACC over the past 17 years. Medical records were reviewed for clinical information of 118 patients. 112 cases with available formalin-fixed paraffin-embedded tissue were retrieved from the pathology archives to confirm diagnosis. 42 had representative blocks for molecular testing of BRAF fusion, $BRAF^{V600E}$ mutation, KRAS, NRAS, and IDH178. Statistical analysis correlated clinical and molecular data to location, survival, and age. RESULTS: Of 118 patients with PA, 19 had a clinical diagnosis of NF1, 1.34:1 male to female ratio, and were diagnosed at median age 12 years seen between 1995 and 2012. Of 42 available patients, 55% were BRAF fusion positive. Only 3 of 37 patients tested positive for $BRAF^{V600E}$ mutation. Mosaic plots relating molecular markers to tumor location found BRAF fusion, NRAS, and clinical diagnosis of NF1 to be higher in cerebellar, brainstem, and supratentorial locations, respectively. There was no significant relationship to survival with BRAF fusion in this cohort, nor in patients selected with NF1 and extracerebellar tumor location. Patients with ≥ 2 molecular variations had worse progression-free survival (PFS) ($p = 0.0139$). Presence of KRAS also demonstrated worse PFS ($p = 0.0476$). BRAF fusion did not vary significantly with age in this pediatric cohort. CONCLUSION: The experience at MDACC in pediatric PA shows clinical and molecular heterogeneity. BRAF fusion is more common than $BRAF^{V600E}$ mutation, although did not correlate to survival. Molecular alterations correlate to location. BRAF fusion is higher in cerebellar and NRAS in brainstem PAs. KRAS may imply worse PFS. PAs with multiple alterations have worse outcome.

PC-020. THE METASTASIS THEORY OF MEDULLOBLASTOMA

Yuzaburo Shimizu, Hajime Arai, Masakazu Miyajima, Kazuaki Shimoji, and Akihide Kondo; Juntendo University, Tokyo, Japan

BACKGROUND: Medulloblastoma is a malignant pediatric brain tumor, arises in the cerebellum and easy to disseminate through the cerebrospinal fluid into the leptomeningeal space. However, it is hard to say that the mechanisms of metastasis through the cerebrospinal fluid are clearly discussed. Recent studies on the molecular biology of medulloblastoma classified four subgroups. And they reported that tumors in one group are easy to disseminate if compared to the other groups. Then, we studied if the tumors in this group start dissemination in the early phase of tumor origin in this study. METHODS: We measured the size of tumors in forth ventricle supposed that the tumor occurred and reviewed the presence of metastasis in the patients who had surgical interventions in our institution from 2009 to 2012. RESULTS: The size of tumors in fourth ventricle with the evidence of

metastatic lesions are relatively small in compared with the tumors without dissemination. CONCLUSION: The tumor having a character easy to disseminate may start drop tumor cells in their early phase of tumor origin.

PC-021. LATE CAUSES OF DEATH IN SURVIVORS OF CHILDHOOD MEDULLOBLASTOMA

Eric Shinohara[1], Stephanie Perkins[2], and Todd DeWees[2]; [1]Vanderbilt University, Nashville, TN, USA; [2]Washington University, Saint Louis, MO, USA

BACKGROUND: With improvements in multi-modality therapy, many children diagnosed with medulloblastoma become long-term survivors. However, data are limited on the risk of late mortality and subsequent malignancy in these patients. METHODS: Using the Surveillance, Epidemiology, and End Results database, we evaluated the causes of mortality in 5-year survivors of medulloblastoma diagnosed prior to the age of 20 years. Standardized mortality ratios (SMRs) were calculated to compare number of deaths observed to the expected number for the cohort. Cumulative incidence of subsequent malignant neoplasms (SMNs) and standardized incidence ratios (SIRs) of observed to expected SMNs were calculated. RESULTS: 455 patients diagnosed between 1973–2003 were included in the study. Overall survival at 35 years was 54.6% compared to an expected overall survival of 96.2% for a cohort of this age ($p < 0.001$). These patients experienced a 24-fold increased risk of death compared to their peers (SMR = 24.0, 95% CI = 19.3–29.4). The most common cause of death was recurrent tumor (59.1%), while death from a subsequent malignancy accounted for 11.8% of deaths. There was a 10-fold increased risk of subsequent malignancy compared to their peers (SIR = 10.4, 95% CI = 6.9–15.0). Cumulative incidence of subsequent malignancy at 30 years was 11.0%. The most common subsequent malignancy was a secondary brain tumor; however, these patients also experienced an increased risk of colorectal cancer, thyroid cancer and leukemia. CONCLUSIONS: 5-year survivors of pediatric medulloblastoma experience a high risk of late mortality. This is predominately due to recurrent disease and subsequent malignancies. The recognition of these risks is important in order to provide appropriate follow-up care for this patient population.

PC-022. ATYPICAL TERATOID RHABDOID TUMOR (ATRT): IMPROVED LONG-TERM SURVIVAL WITH AN INTENSIVE MULTIMODAL THERAPY AND DELAYED RADIOTHERAPY. THE MEDICAL UNIVERSITY OF VIENNA EXPERIENCE 1992-2012

Irene Slavc, Monika Chocholous, Ulrike Leiss, Christine Haberler, Andreas Peyrl, Amedeo A. Azizi, Karin Dieckmann, Adelheid Woehrer, Christian Dorfer, and Thomas Czech; Medical University of Vienna, Vienna, Austria

BACKGROUND: Atypical teratoid rhabdoid tumors (ATRTs) are recently defined highly aggressive embryonal CNS tumors with a poor prognosis and no definitive guidelines for treatment. We report on the importance of a disease specific therapy on outcome and propose a new treatment strategy. PROCEDURE: From 1992 to 2012, 9 of 22 patients with ATRT were treated uniformly according to an intensive multimodal regimen (MUV-ATRT) consisting of three 9-week courses of a dose dense regimen including doxorubicin, cyclophosphamide, vincristine, ifosfamide, cisplatin, etoposide and methotrexate augmented with intrathecal therapy, followed by high-dose chemotherapy (HDCT) and completed with local radiotherapy. A tenth patient was started on the protocol but had to be switched to craniospinal irradiation due to low bone marrow tolerance. Most of the remaining patients were originally misdiagnosed and treated according to various protocols in use for their respective diagnoses at the time. RESULTS: As of May 2013, all 10 patients started on the MUV-ATRT protocol are alive for a median of 63 months (range: 14 to 195), 8 in first CCR and 2 after relapses. In contrast, only 2 of 12 patients treated according to other protocols are long-term survivors. 5-year overall survival and event-free survival for the 10 MUV-ATRT intention-to-treat patients was 100% and $79 \pm 13\%$ and for the 12 patients treated differently both (OS and EFS) were $25 \pm 13\%$. CONCLUSION: The proposed MUV-ATRT regimen is well tolerated and appears to be efficacious in preventing early relapses also in young children with M1-M3 stage disease allowing to postpone radiotherapy until after HDCT.

PC-023. C19MC AMPLIFIED TUMOURS: A NEW HISTO-GENETIC AND DIAGNOSTIC ENTITY

Tara Spence[1,2], Daniel Picard[1], Mark Barszczyk[1,2], Seung-Ki Kim[3], Young-Shin Ra[4], Jason Fangusaro[5], Helen Toledano[6], Hideo Nakamura[7], Lucy Lafay-Cousin[8], Xing Fan[9], Karin M. Muraszko[9], Ho-Keung Ng[10], Eric Bouffet[11], William Halliday[2,12], Mary Shago[12], Cynthia E. Hawkins[1,2], and Annie Huang[1,2]; [1]Arthur and Sonia Labatt Brain Tumour Research Center, The Hospital for Sick Children, Toronto, ON, Canada; [2]Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada; [3]Department of Neurosurgery, Seoul National University Children's Hospital, Seoul, Republic of Korea; [4]Department of Neurosurgery, Asan Medical Center, Seoul, Republic of Korea; [5]Division of Pediatric Hematology/Oncology and Stem Cell Transplantation, Children's Memorial Hospital, Chicago, IL, USA; [6]Oncology Department, Schneider Hospital, Petach Tikva, Israel; [7]Department of Neurosurgery, Kumamoto University, Kumamoto, Japan; [8]Department of Pediatric Oncology, Alberta Children's Hospital, Calgary, AB, Canada; [9]Department of Neurosurgery, University of Michigan Medical School, Ann Arbor, MI, USA; [10]Department of Anatomical and Cellular Pathology, Chinese University of Hong Kong,, Hong Kong, China; [11]Division of Haematology and Oncology, The Hospital for Sick Children, Toronto, ON, Canada; [12]The Department of Paediatric Laboratory Medicine, The Hospital for Sick Children, Toronto, ON, Canada

Central Nervous System Primitive Neuro-ectodermal Tumours (CNS-PNETs) are highly aggressive tumours with poorly defined histopathology and genetics that present a significant diagnostic and therapeutic challenge. The current WHO diagnostic scheme for these tumours encompasses various histological sub-types, however, to date the biological relationship and clinical significance of these subtypes is unclear. In recent work, our lab has discovered amplification of a novel oncogenic miRNA cluster on chr19q13.42 (C19MC) that identified a highly aggressive subgroup of CNS-PNET arising in the cerebral hemispheres of young children. In order to assess the utility of the C19MC amplicon as a diagnostic and prognostic marker, we investigated the prevalence of C19MC in a wide histologic spectra of intrinsic CNS tumour arising within the brain and spine. We investigated the status of the C19MC amplicon using FISH on tumour tissue microarrays in 500 pediatric brain and spinal tumours, including; CNS-PNET, medulloblastoma, ependymoma, choroid plexus tumours, and malignant gliomas. We identified C19MC amplification in 3% (15/500) of tumours, most prevalently in infants (<4yrs) and arising in the cerebrum (10/15). However, a portion (5/15) arose in various CNS locations, such as posterior fossa, brain stem, spine, and ventricles. Strikingly C19MC amplified tumours originating at different CNS locations and with variable reported histology exhibited the same gene expression profiles in microarray analyses, which was distinguished by a highly primitive-neural lineage signature. All tumours expressed synaptophysin/nestin and BAF47/INI1, with variable GFAP expression, and 9/15 tumours displayed a "variant" rosette-forming histology that has been described for C19MC amplified tumours. Notably, C19MC amplification was also found in a spectrum of tumours with other formal histologic diagnoses; ependymoblastoma, medulloblastoma, anaplastic ependymoma and medulloepithelioma. Our collective findings indicate common histo-genetic and cellular origins for all C19MC amplified tumours, and we propose screening for C19MC amplification in CNS tumours arising in infants.

PC-024. 2 CASES OF EPENDYMOMA WITH EXTRACRANIAL EXTENSION

Mario Suzuki, Akihide Kondo, Masakazu Miyajima, and Hajime Arai; Juntendo University, School of Medicine, Tokyo, Japan

INTRODUCTION: Ependymoma is an uncommon group of glial tumors and represent 10% of the intractanial tumors in childhood. They typically arise within ependymal cell lining of the ventricular system, and occasionally occur within the brain parenchyma, but rarely extend to extracranium. We reviewed 2 cases having extracranial extensions in terminal stages of ependymoma in this study. CASES: Case 1: 13-year-old boy with ependymoma arose from 4th ventricle was received several surgical interventions and radiotherapy. However the tumor came back 5 years after last radiotherapy and he had fallen into coma. A little while later, his mandibula swelled up gradually. The patient died 6 years after first surgery, and autopsy revealed the tumor spread to his mandibula and oral cavity. Case 2: 14-year-old boy. Four years after his first surgery, he had respiratory failure caused by brainstem invasion and been assisted with a respirator to live. The patient died 2 years later, and autopsy revealed?that the tumor extended to his right orbit. DISCUSSION: Recurrence and extension of ependymomas are generally developed around primary lesion. It is rare that tumor extend to extracranial organ. We had 2 boy suffered from ependymoma been kept on respirators. Their autopsy revealed that tumors spread to extracranial organs. We report our cases with studies of tumor extensions.

PC-025. CENVECTION ENHANCED DELIVERY (CED) OF CARMUSTIN IN CHILDREN WITH DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG)

Sophie Veldhuijzen van Zanten, Marc Jansen, Dannis van Vuurden, Esther Hulleman, Sander Idema, David Noske, Nicole Wolf, Harry Hendrikse, Peter Vandertop, and Gert Jan Kaspers; VU University Medical Center, Amsterdam, The Netherlands

INTRODUCTION: DIPG patients have a dismal prognosis with a median overall survival of only nine months. Typically, surgical resection is not possible, radiotherapy has only temporary effect and systemic chemotherapeutics fail. Convection Enhanced Delivery (CED) provides high local drug concentrations and equal drug distribution directly at the tumor site through microcatheters via a pressure gradient. In a murine CED-model, we injected DIPG with carmustine, a highly-active nitrosourea compound, and found a significantly prolonged survival with no severe toxicity. Based on these preclinical data, and on studies in adults showing the safety of the procedure, we developed a clinical study in children with DIPG. METHOD: Patients will be included after initial or subsequent (systemic) therapy, at time of progression or recurrence. Catheters will be placed based on iPlan Flow software simulations (BrainLAB AG, Germany). Two cohorts of three patients will receive escalating concentrations of carmustine up to 50% of the maximum tolerated dose in adults. Infusion-volume and infusion-rate will be determined based on tumor volume (with a maximum 7 ml). Co-infusion of gadolinium enables observation of distribution by MRI. Maximum infusion-duration will be 41 hours, during which a patient will be awake and observed intensively. Primary endpoints of this study are safety and feasibility. CONCLUSION: Preclinical data has shown carmustine-CED to be safe and effective in DIPG mouse models. With this clinical study we intend to show safety and feasibility of carmustine administration via CED in patients with DIPG. This technique improves treatment options, and hopefully the dismal prognosis of patients in the future. ACKNOWLEDGEMENT: Financially supported by the Semmy Foundation (Stichting Semmy).

PC-026. CRANIOSPINAL IRRADIATION WITH CONCURRENT METRONOMIC TEMOZOLOMIDE FOR THE TREATMENT OF PRIMARY METASTATIC HIGH-GRADE OR DIFFUSE INTRINSIC PONTINE GLIOMAS IN CHILDREN: EXPERIENCES FROM THE GERMAN MULTICENTER HIT-HGG 2007 TRIAL

Klaus Müller[1], Annika Schlamann[1], Monika Warmuth-Metz[2], Torsten Pietsch[3], Sophie Pietschmann[1], Rolf-Dieter Kortmann[1], Christof M. Kramm[4], and André O. von Bueren[4]; [1]Department of Radiation Oncology, University Medical Center Leipzig, Leipzig, Germany; [2]Department of Neuroradiology, University Medical Center Würzburg, Würzburg, Germany; [3]Institute of Neuropathology, University of Bonn Medical Center, Bonn, Germany; [4]Department of Pediatrics and Adolescent Medicine, Division of Pediatric Hematology and Oncology, University Medical Center Goettingen, Goettingen, Germany

BACKGROUND: Primary metastatic pediatric high-grade glioma (HGG) and diffuse intrinsic pontine glioma (DIPG) are extremely rare and associated with an unfavorable prognosis. Combining craniospinal irradiation with concurrent metronomic temozolomide may be beneficial in terms of treatment efficacy. However, little is known about the feasibility, toxicity, and efficacy of this treatment approach. PATIENTS AND METHODS: Within the German multicenter trial HIT-HGG 2007 (EudraCT 2007-000128-42) we identified six children, at time of analysis (December 2012), with primary metastatic HGG ($n = 4$) or DIPG ($n = 2$) who were treated with craniospinal irradiation ($\pm$ focal boost) - instead of local radiotherapy based on an individual therapy recommendation - and concurrent metronomic temozolomide (75mg/m^2/day). We assessed outcome (progression-free and overall survival) by the Kaplan-Meier method and treatment-related toxicity by the Common Terminology Criteria for Adverse Events v3.0. All patients received craniospinal irradiation (5x 35.2 Gy, 1x 36 Gy). Five of them additionally received a local boost. Simultaneously to radiotherapy metronomic temozolomide (5×75 mg/m^2/day, 1x 60 mg/m^2/day) was administered. One patient additionally received nimotuzumab weekly. RESULTS: As expected the key toxicity was hematotoxicity (grade 3 or grade 4 toxicities were reported for all patients) leading to a temozolomide treatment discontinuation/interruption during craniospinal irradiation in four of six patients. No major unexpected other toxicities or treatment-related deaths were reported. The median follow-up was 10.0 months (range, 6.5-18.7 months), the median progression-free survival was 4.0 ± 0.8 months (range, 2.4 - 10.7 months), and the median overall survival was 7.6 ± 3.5 months (range, 4.0 - 17.6 months). CONCLUSIONS: Combining craniospinal irradiation with concurrent metronomic temozolomide is feasible in disseminated HGG and DIPG and toxicities acceptable thus far. This approach should be considered for metastatic HGG and DIPG. Further, ideally large internationally prospective studies are needed to define the efficacy and toxicity of this approach.

PC-027. A MULTI-INSTITUTIONAL EXPERIENCE IN PEDIATRIC HIGH GRADE GLIOMA

Steve Walston[1], Terence Williams[1], Daniel Hamstra[2], Kevin Oh[3], and Christopher Pelloski[1]; [1]Ohio State University, James Comprehensive Cancer Center, Department of Radiation Oncology, Columbus, OH, USA; [2]University of Michigan, Department of Radiation Oncology, Ann Arbor, MI, USA; [3]Massachusetts General Hospital, Department of Radiation Oncology, Boston, MA, USA

BACKGROUND: While pediatric high grade gliomas (HGG) have more favorable prognosis compared with the adult population, outcomes remain poor and the optimal management remains incompletely defined. METHODS: We conducted a multi-institutional retrospective study of 51 patients with HGG (Grade III-IV, excluding brain stem location) treated from 1984-2008 at the Ohio State University or University of Michigan. Various clinical, pathologic, and treatment factors were analyzed for their associations to these outcomes. Log-rank and stepwise Cox proportional hazard modeling were used to analyze time to progression (TTP) and overall survival (OS). RESULTS: At a median follow up of 19 months, median TTP and OS for the entire cohort were 8 months and 31 months, respectively. Tumor distribution was 45.1% (23/51) grade III tumors and 54.9% (28/51) grade IV tumors. On univariate analysis, pre-treatment factors predicting decreased TTP were non-cerebrum location and grade IV histology ($p < 0.05$). Pre-treatment factors significant for their adverse association with OS were non-seizure presentation, nerve deficit, grade IV histology, and non-cerebrum location ($p < 0.05$). Treatment factors determined to have a negative effect on TTP were subtotal resection (incomplete resection or biopsy) and not receiving temozolomide ($p < 0.04$); while those negatively impacting OS were subtotal resection and not receiving adjuvant chemotherapy ($p < 0.03$). In multivariate analysis, factors determined to be significant for decreased TTP were: grade IV histology, subtotal resection, not receiving temozolomide, and not receiving chemotherapy concurrently with radiation ($p < 0.05$). In a multivariate analysis for overall survival both subtotal resection and grade IV histology remained significant ($p < 0.04$). CONCLUSIONS: Similar to the adult population, gross total resection and tumor grade are closely associated with TTP and OS in pediatric HGG. Additionally, we concluded that patients who received temozolomide and those treated with concurrent radiation and chemotherapy had improved TTP, but we cannot exclude the possibility that other unanalyzed or confounding factors exist.

PC-028. VERY LONG-TERM SURVIVAL OF PAEDIATRIC LOW GRADE GLIOMA PATIENTS; POSSIBLE ROLE OF BRAF-KIAA1549 FUSION

Nataliya Zhukova[1,2], Jason Pole[2], Matthew Mistry[3,4], Iris Fried[5], Ute Bartels[1], Annie Huang[1,4], Normand Lapperiere[6], Peter Dirks[7,4], Katrin Scheinemann[8], Jason An[9], Noa Alon[10], Paul Nathan[1], Mark Greenberg[1,2], Eric Bouffet[1], David Malkin[1,10], Cynthia Hawkins[11,4], and Uri Tabori[1,4]; [1]The Hospital for Sick Children, Division of Haematology/Oncology, Toronto, ON, Canada; [2]Pediatric Oncology Group of Ontario, Toronto, ON, Canada; [3]University of Toronto, Institute of Medical Science, Toronto, ON, Canada; [4]The Hospital for Sick Children, The Labatt Brain Tumour Research Centre, Toronto, ON, Canada; [5]Hadassah Medical Centre, Jerusalem, Israel; [6]Princess Margaret Hospital,Radiation Medicine Program, Toronto, ON, Canada; [7]The Hospital for Sick Children, Division of Neurosurgery, Toronto, ON, Canada; [8]Division of Haematology/Oncology, McMaster Children's Hospital, Hamilton, ON, Canada; [9]University of Alberta, Faculty of Medicine Undergraduate Program, Edmonton, AB, Canada; [10]Program in Genetics and Genome Biology, The Hospital for Sick Children Research Institute, Toronto, ON, Canada; [11]The Hospital for Sick Children, Division of Pathology, Toronto, ON, Canada

BACKGROUND: Paediatric Low Grade Gliomas (PLGG) are the most frequent paediatric CNS malignancy marked by excellent 5 year overall survival (OS) (80-90%). Existing data is focused on short-term outcomes due to lack of follow up in adulthood. Several groups have recently reported association of BRAF-KIAA1549 fusion with favorable outcome in PLGG. However its role in a very long-term outcome (over 10 years post-diagnosis) is unclear. METHODS: We performed a population based study of all patients treated for PLGG in Southern Ontario since 1985. Comprehensive demographic, clinical, treatment and pathological data was collected. Long term outcome was gathered from the Pediatric Oncology Group of Ontario (POGONIS), OCR (Ontario Cancer Registry) and ICES (Institute for Clinical Evaluative Sciences) databases. BRAF-fusion was determined by fluorescent in situ

hybridization (FISH). RESULTS: Out of 808 PLGG patients 56 (6.9%) died; median time of death was 3.7 years post-diagnosis (3 months - 21.5 years). OS was 96.1 +/−1% at 5 years and 93.1 +/−1% at 15 years for the whole cohort. 41 patient (13%) died before age 18 (n = 307) and only 15 (3%) died in their adulthood (n = 503) ($p = 0.4 \times 10^{-8}$). 28% died of tumor progression, 9% of side effects, 11% developed second malignancy, transformation to HGG caused death in 34% of cases. All 28 PLGG patients transformed to HGG before age 18. OS at 10 and 15 years post-diagnosis of patients with BRAF-fusion data available (n = 175) was 89.9 +/−4.5% for patients with BRAF-fusion positive tumors, while survival for BRAF-fusion negative ones continued to drop to 63.7 +/−8.02% by 15 years (p = 0.0048). Moreover, of the deceased patients only 3 had the BRAF fusion, and only 1 died of tumor progression. CONCLUSIONS: Long term outcome for children with PLGG is excellent. BRAF-fusion is a positive predictor of long-term survival. These observations suggest that BRAF-fused PLGG should be managed conservatively. Further investigations are ongoing.