was 4-years old at diagnosis and received all 3 induction cycles with mg/m2 dosing, developed serious nephrotoxicity during cycle #1 followed by SOS during cycle #3. The HS 4 trial was amended and reopened after external, independent Data Safety Monitoring Board review to dose all chemotherapy drugs in children <6 years old with mg/kg dosing instead of BSA. None of 75 patients enrolled since the amendment developed SOS during induction. These data suggest using caution while dosing young children <6 years of age with intensive induction chemotherapy by BSA.

DDEL-03. LONG-TERM INTRAVENTRICULAR THERAPY ALTERNATING ETOPOSIDE AND LIPOSOMAL CYTARABINE: EXPERIENCE IN 75 CHILDREN AND ADOLESCENTS WITH MALIGNANT BRAIN TUMORS

Natalia Stepien[1], Andreas Peyrl[1], Amedeo Azizi[1], Johannes Gojo[1], Lisa Mayr[1], Dominik Reisinger[1], Christine Haberler[2], Thomas Czech[3], and Irene Slavc[1]; [1]Medical University of Vienna, Department of Pediatrics and Adolescent Medicine, Vienna, Austria, [2]Medical University of Vienna, Institute of Neurology, Vienna, Austria, [3]Medical University of Vienna, Department of Neurosurgery, Vienna, Austria

BACKGROUND: Malignant brain tumors of childhood carry a high risk for leptomeningeal dissemination and tumor cells floating in the CSF are often not amenable to systemic and/or antiangiogenic chemotherapy. We report on our experience with an intraventricular therapy consisting of alternating cycles of liposomal cytarabine and etoposide. PATIENTS AND METHODS: Between 2004 and 2017, 75 patients aged 0.6 to 22 years (median 11) with various malignant brain tumors received intraventricular etoposide 0.25mg (<1year) - 0.5mg on five consecutive days alternating with liposomal cytarabine at a dose of 25mg (<3 years) - 50mg via an Ommaya reservoir. RESULTS: 5533 doses of etoposide (5–277/patient, median 141) corresponding to 1–56 five-day-cycles/patient alternating with 534 doses of liposomal cytarabine (1–21/patient, median 11) were administered. Treatment was given over a period of 1 – 146 months (median 73.5). Toxicities did occur but were infrequent and mostly mild. Since all patients received some sort of concurrent anti-cancer therapy, the efficacy of intrathecal therapy cannot be assessed independently. However, 29/75 patients are still alive, and none of the patients had tumor cells in the CSF at their last evaluation. CONCLUSION: In conclusion, alternating intraventricular liposomal cytarabine and etoposide produced responses and proved to be an important adjunct for patients receiving drugs with a low penetrance into the CSF. Since production of liposomal cytarabine was discontinued in 2017 it remains to be determined whether substitution of the slow release formulation by aqueous cytarabine on days 1, 4, 8, and 11 may produce similar results.

DDEL-04. ENGINEERED NANOCARRIERS TO ENHANCE DRUG DELIVERY ACROSS THE BLOOD-BRAIN BARRIER

Joelle P. Straehla[1,2], Cynthia Hajal[3], Hannah Safford[2], Giovanni Offeddu[4], Jeffrey Wyckoff[2], Roger D Kamm[3,4], and Paula T Hammond[2,5]; [1]Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA, USA, [2]Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, MA, USA, [3]Mechanical Engineering, Massachusetts Institute of Technology, Cambridge, MA, USA, [4]Biologic Engineering, Massachusetts Institute of Technology, Cambridge, MA, USA, [5]Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA, USA

Pediatric central nervous system tumors are the leading cause of cancer death in children. Promising therapeutics have been identified, but the ability to deliver an effective concentration to the tumor without causing excessive systemic toxicity remains a challenge. To address this, we leveraged a tunable nanocarrier platform to design a brain-penetrant nanocarrier with preferential uptake into tumor cells over healthy brain cells. First, we used the layer-by-layer technique to iteratively coat liposomes with nanometers-thick layers of oppositely charged polyelectrolytes. To investigate the influence of surface chemistry on cellular trafficking, a panel of layered liposomes was tested for interactions with cancer cell lines, identifying poly-L-aspartic acid and hyaluronic acid as the highest-performing formulations across brain tumor lines. To facilitate nanocarrier transit across the blood-brain barrier (BBB), we developed a click chemistry platform to functionalize the nanocarrier with BBB shuttle ligands. To investigate trafficking *in vitro*, we utilized a microfluidic brain microvascular model comprising endothelial cells, astrocytes, pericytes, and glioma cells that self-assemble into a perfusable vascular network. We found that nanocarrier size influenced vascular transport, and the addition of BBB shuttle ligands improved transport in the presence of a glioma spheroid. To investigate *in vivo* nanocarrier trafficking, we performed intravital imaging through a cranial window in anesthetized mice. After intravenous administration, nanocarrier transit across intact brain capillaries was visualized using two photon microscopy, and vessel permeability was quantified over time. Ongoing studies in mice bearing patient-derived xenograft medulloblastoma and glioma tumors are being conducted to further characterize trafficking across tumor-associated vasculature.

DDEL-05. BLOOD-BRAIN BARRIER DISRUPTION AND ENHANCED RADIOSENSITIZERS EXTRAVASATION UPON FOCUSED ULTRASOUND FOR TREATMENT OF DIFFUSE INTRINSIC PONTINE GLIOMA

Elvin 't Hart[1], Marc Derieppe[1], Maaike Bruin[2], Helena Besse[3], Rianne Haumann[4], Eelco Hoving[1], Alwin Huitema[3,2], Mario Ries[3], and Dannis van Vuurden[1]; [1]Princess Máxima Center for Pediatric Oncology, Utrecht, Netherlands, [2]The Netherlands Cancer Institute, Amsterdam, Netherlands, [3]University Medical Center Utrecht, Utrecht, Netherlands, [4]Amsterdam University Medical Center Location VU Medical Center, Amsterdam, Netherlands

Poor prognosis of diffuse midline glioma, including diffuse intrinsic pontine glioma (DIPG), reflects the low efficacy of current treatment strategies, mainly due to (1) a largely intact blood-brain barrier (BBB) and (2) the proficiency of tumour tissues to upregulate multiple DNA repair genes, resulting into radio-resistance. *In vitro* studies showed therapeutic benefit by combining radiotherapy and radiosensitizers, while pre-clinical and clinical studies evidenced safe and transient opening of the BBB using microbubble mediated focused ultrasound (FUS). Previously, we demonstrated the enhanced extravasation of olaparib, a poly(ADP-ribose) polymerase (PARP) inhibitor in the mouse pons. Local drug delivery was applied using an in-house built X-ray image-guided FUS system with a 1 MHz mono-element transducer delivering a tone-burst pulse with a mechanical index of 0.4. Tissue/blood drug concentrations were analysed by LC-MS/MS, 30 minutes after intraperitoneal injection of 10 mg/kg olaparib. The FUS system allowed for precise treatment of the pons, proven by local extravasation of Evans Blue-conjugated albumin. A significant 5.1 fold median increase was observed in absolute concentrations in the pons after FUS intervention compared to the control and a 4.9 fold increase of the median tissue-blood ratio ($*p<0.05$). No significant differences were detected in brain regions outside the ultrasound focus and other organs, confirming the local intervention. With this, the 299 nM equivalent olaparib concentration found in the pons will facilitate PARP inhibition in future murine patient-derived xenograft tumour models, thus leading to a greater therapeutic effect when in combination with radiotherapy treatment of DIPG.

DDEL-06. DRUG INTERACTION BETWEEN EVEROLIMUS AND CANNABIDIOL IN PEDIATRIC PATIENTS WITH SUBEPENDYMAL GIANT CELL ASTROCYTOMAS: A SINGLE INSTITUTION EXPERIENCE

Ashley Sabus[1], Shelby Winzent[2,1], Molly Hemenway[2,1], Jean Mulcahy Levy[2,1], and Nicholas Foreman[2,3]; [1]Children's Hospital Colorado, Aurora, CO, USA, [2]University of Colorado, Denver, CO, USA, [3]Children's Hospital Colorado, Denver, CO, USA

Tuberous sclerosis complex (TSC) is an autosomal recessive genetic disorder associated with clinical manifestations including subependymal giant cell astrocytomas (SEGA) and seizures. The combination of everolimus and Epidiolex, a purified form of cannabidiol, has become an increasingly common treatment regimen in this population. Everolimus is primarily metabolized via CYP3A4, which may be inhibited by cannabidiol. We seek to describe our institution's experience with this drug interaction. METHODS: Investigators conducted a retrospective review of neuro-oncology patients with TSC and SEGA who were treated concurrently with everolimus and cannabidiol. Data collected included demographics, body surface area, everolimus dose, everolimus troughs, date of cannabidiol initiation, documented symptoms, liver and renal function tests, and reason for discontinuing therapy. RESULTS: Three patients (ages 11–17 years) met inclusion criteria. All patients were stable on everolimus doses ranging from 6.5 to 9.5 mg/m^2/day and achieving trough goals of 5–10 ng/mL. Two to four weeks after initiating cannabidiol, everolimus trough concentrations rose 200–860% above goal. One patient reported new-onset involuntary movements, but no other toxicities were noted. Cannabidiol was discontinued in all cases due to caregiver concerns regarding drug interactions. All patients were able to achieve goal trough concentrations on previously stable doses of everolimus after discontinuing cannabidiol. CONCLUSIONS: Cannabidiol appears to modulate everolimus metabolism leading to significantly elevated serum concentrations. Additional research is required to determine the need for empiric dose adjustments upon cannabidiol initiation. Patient counseling, frequent trough monitoring, and surveillance for adverse effects are crucial for optimizing outcomes in patients prescribed this regimen.

DDEL-07. A PHASE I STUDY EXAMINING THE FEASIBILITY OF INTERMITTENT CONVECTION-ENHANCED DELIVERY (CED) OF MTX110 FOR THE TREATMENT OF CHILDREN WITH NEWLY DIAGNOSED DIFFUSE MIDLINE GLIOMAS

Stergios Zacharoulis[1], Luca Szalontay[1], Dominic Higgins[1], Zachary Englander[1], ZhenZhen Jin[1], James Garvin[1], Rebecca Zylber[1], Eileen Stark[1], Alexis Maddocks[1], Chankrit Sethi[1], Peter Canoll[1], Steve Dammnett[2], Craig Cook[2],