RARE-20. A RARE CASE OF A PRIMARY CENTRAL NERVOUS SYSTEM NEUROENDOCRINE CARCINOMA AND SUCCESSFULL THERAPY IN A FIVE-YEAR-OLD CHILD

Natalia Stepien, Christine Haberler, Maria-Theresa Schmook, Johannes Gojo, Amedeo A Azizi, Thomas Czech, Irene Slavc, and Andreas Peyrl; Medical University of Vienna, Vienna, Austria

Neuroendocrine tumors (NETs) are rare neoplasms predominantly arising in the GI-tract or the lungs of adults. To date, only ten cases of primary CNS NETs have been reported with just three of them describing a neuroendocrine carcinoma (NEC) in patients aged 34–77 years and none occurring in a child. We report on a previously healthy 5-year-old boy, who presented with headaches, nausea and vomiting and was diagnosed with a left cerebellar solid mass with a cystic component, radiologically suggestive of a pilocytic astrocytoma. After gross-total resection, histological analysis revealed an epithelial tumor growing in a nest-like pattern with a very high mitotic frequency, staining positive for CK8, CK18 and CK19. Chromogranin A and synaptophysin expression indicated a neuroendocrine differentiation. Molecular analysis of the tumor tissue revealed a KRAS- splice-site mutation (c451-3C>T). After extensive search for an extracranial primary, including Ga-68 DOTANOC-PET-CT, the diagnosis of a primary CNS NEC was made, and proton irradiation was performed. However, the patient developed an in-field recurrence just five weeks after the end of radiotherapy. The tumor was re-resected en-bloc, showing vital tumor tissue, demonstrating its aggressiveness. Chemotherapy consisting of etoposide, cisplatin and ifosfamide was initiated. After two cycles chemotherapy was continued with etoposide and carboplatin for another four cycles. The patient remains disease free one year after the end of relapse-treatment, supporting the beneficial effect of platinum- and etoposide-based chemotherapy for this tumor entity. Physical exam revealed a sagittal synostosis with a mild dolichocephaly. Interestingly, the KRAS-mutation was discovered to be a maternal germline mutation, previously described as likely benign. However, alterations of the RAS/MAPK pathway have been described in NECs and in craniosynostosis cases. It remains to be elucidated whether the KRAS-mutation is merely a variant of uncertain significance or might have been implicated in the development of this exceptional tumor.

RARE-21. A RARE CASE OF PEDIATRIC SPINDLE CELL ONCOCYTOMA WITH EML4-ALK FUSION

George Michaiel, Debra Hawes, Samuel Guzman, Ashley Margol, Jaclyn Biegel, and Jianling Ji; Children's Hospital Los Angeles, Los Angeles, CA, USA

A 12 year-old male presented with a 2-month history of intermittent headaches, nausea, and vomiting. Magnetic resonance imaging (MRI) of the brain revealed a 2.2 x 3.5 x 2.6 cm lobulated, sellar/suprasellar mass, mildly T1/T2 hyperintense, with mild homogeneous enhancement and diffusion restriction. He underwent transsphenoidal and right craniotomies for gross total resection of the mass. Pathology demonstrated a hypercellular neoplasm with spindled to ovoid tumor cells arranged in fascicles and tight whirls, consistent with a spindle cell oncocytoma. OncoKids, a DNA- and RNA-based next generation sequencing panel, demonstrated an in-frame EML4 exon 2-ALK exon 19 fusion with a total of 179,872 supporting reads. The EML4-ALK fusion gene is predicted to encode a chimeric tyrosine kinase that facilitates multimerization and autophosphorylation of ALK, and activates its downstream targets, such as RAS/ERK, PI3K/AKT, and JAK/STAT pathways. This fusion is found in approximately 5% of patients with non-small cell lung cancer, a subset of inflammatory myofibroblastic tumors, as well as single cases of pulmonary atypical carcinoid, cholangiocarcinoma, and high-grade glioma. However, it has not been previously described in oncocytoma. Chromosomal microarray analysis demonstrated two interstitial non-contiguous deletions in 2p, and an interstitial deletion in 18q that does not include any known cancer-related genes. The deleted segment in 2p23.3p23.2 includes DNMT3A, which mediates DNA methylation and functions in modification of gene expression. DNMT3A mutations are frequent in hematological malignancies, however their role in oncocytoma is currently unknown. The proximal breakpoint of the deletion in 2p23.3p23.2 is in close proximity to but does not reside within ALK. Spindle cell oncocytoma is rarely reported in the pediatric population, with only one case described in the literature. This is the first case report of an oncocytoma with an EML4-ALK fusion. Additional studies are warranted to confirm its functional effect.

RARE-22. THERAPEUTIC TARGETING OF PURINE METABOLISM IN DIPG

Ian Mersich[1,2], and Biplab Dasgupta[1]; [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, [2]University of Cincinnati Cancer and Cell Biology Graduate Program, Cincinnati, OH, USA

Diffuse intrinsic pontine glioma is a universally lethal disease primarily impacting pediatric patients. There are currently no targeted therapies increasing overall for patients with these tumors; therefore, our lab set out to elucidate metabolic dependencies in DIPG patient-derived cell lines with the ultimate goal of identifying novel therapeutic targets. Through untargeted metabolomics and gene expression analyses, we have identified the purine metabolism gene ATIC to be important for DIPG tumor cell survival and proliferation. Anti-folate drugs such as methotrexate target de novo purine biosynthesis and are used to treat other pediatric cancers; however, we have identified a small molecule inhibitor of ATIC that may offer clinical benefits over other inhibitors of this pathway. In vitro cell viability experiments have demonstrated DIPG cell lines are much more sensitive to the ATIC inhibitor relative to normal neural stem cells and glial cell lines. Furthermore, we have started in vivo studies on pre-clinical mouse models of DIPG with promising results. Treatment with the ATIC inhibitor has significantly increased overall survival relative to control and vehicle treated mice. The dosage we started at was well tolerated in these mice so we are following up on this in vivo work through dose-escalation studies as well as combination treatment strategies. Mechanistically, the ATIC inhibitor works differently than anti-folate compounds such as methotrexate; therefore we are also elucidating why cancer cells are much more sensitive to this compound.

RARE-23. DIFFUSE LEPTOMENINGEAL GLIONEURONAL TUMOR: A CASE SERIES

Ashley Aaroe[1], Alexander Ou[1], Susan McGovern[2], Arnold Paulino[2], Jason Johnson[3], Jason Huse[4,5], Gregory Fuller[6,7], John de Groot[1], Andrew Walter[8], and Wafik Zaky[9]; [1]Department of Neuro-Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [2]Department of Radiation Oncology, Division of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [3]Department of Neuroradiology, Division of Diagnostic Imaging, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [4]Departments of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [5]Department of Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [6]Department of Anatomic Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [7]Department of Neuroradiology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [8]Division of Pediatric Hematology/Oncology, Department of Pediatrics, Nemours/Alfred I. duPont Hospital for Children, Wilmington, DE, USA, [9]Department of Pediatrics, Division of Pediatrics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Introduction: Diffuse leptomeningeal glioneuronal tumor (DLGNT) is a rare diagnosis first incorporated into the WHO Classification of Tumors of the Central Nervous System in 2016. Though historically considered indolent, emerging evidence suggests that the biological behavior of these tumors may be further classified by molecular features of prognostic significance. Methods: A retrospective review was conducted in accordance with IRB approval of patients with the histologic diagnosis of DLGNT. Demographic, clinical, and molecular data where abstracted from the medical record when available. Results: 10 patients were identified (M = 8, F = 2). Median age at diagnosis was 6 years (range 0.3–21 years), and the most common symptoms at diagnosis were related to obstructive hydrocephalus, for which 3 patients required CSF diversion. MRI findings included diffuse leptomeningeal thickening, nodularity, or coating of the subarachnoid or ependymal surfaces. Histologically, these tumors expressed variable features of neuronal and/or glial differentiation. Four patients (40%) were treated with radiation therapy (all craniospinal), which was upfront for 2 patients. Chemotherapy regimens used included temozolomide, carboplatin and vincristine and vinblastine. NTRK or BRAF-targeted therapy were used upon progression. At follow-up, 6/10 had stable disease (4/6 of whom were on second line therapy), 1 had partial response, 1 passed away from sepsis and 2 were lost to follow-up. The median progression-free survival for the four patients who developed disease progression was 26 months (range 12–34 months). Next generation sequencing of the tumor tissue performed using a high-multiplex PCR-based NGS panel detected BRAF-KIAA1549 (4 patients) and NTRK (1 patient) fusions. Conclusions: DLGNT are rare tumors with scarce data about imaging characteristic and standard of care treatment. Our case series reinforces current literature that although these tumors appear low-grade, they can be clinically aggressive. Further study is needed regarding molecular diagnosis and profiling treatment strategies.

RARE-24. IDENTIFYING INDIVIDUALS WITH PRIMARY CENTRAL NERVOUS SYSTEM TUMORS AT RISK FOR HEREDITARY CANCER SYNDROMES USING THE UTAH POPULATION DATABASE

Nicholas Whipple[1,2], Wendy Kohlmann[3,4], Samuel Cheshier[2,5], Zhe Yu[3], Karen Curtin[3,6], and Joshua Schiffman[3,7]; [1]Division of Pediatric Hematology-Oncology, Department of Pediatrics, University of Utah, Salt Lake City, UT, USA, [2]Primary Children's Hospital, Salt Lake City, UT, USA, [3]Huntsman Cancer Institute, Salt Lake City, UT, USA, [4]University of Utah, Salt Lake City, UT, USA, [5]Division of Pediatric Neurosurgery, Department of Neurosurgery, University of Utah, Salt Lake City, UT, USA, [6]Division of Epidemiology, Department of Internal Medicine, University of Utah, Salt

Lake City, UT, USA, [7]Department of Pediatrics, University of Utah, Salt Lake City, UT, USA

Background: CNS tumors are the most common solid tumors and the deadliest cancers in children. Approximately 10% of children with a CNS tumor harbor a hereditary cancer syndrome (HCS), but many will not be tested for a HCS. The Utah Population Database (UPDB) contains comprehensive cancer registry data for Utah families and can determine multigenerational cancer pedigrees across an archive of 5.8 million individuals. We hypothesize that the UPDB can identify children and families with HCSs not previously identified. Methods: We queried the UPDB for individuals ages 0–39 diagnosed with a primary CNS tumor (malignant and benign) between 1966–2017 and generated cancer pedigrees of 3 generations or more for probands, extending to at least third-degree relatives. Specialized software calculated a familial standardized incidence ratio (FSIR) to determine families with excess clustering of CNS tumors. Clinical cancer genetics experts reviewed pedigrees to confirm patterns of HCS. Results: We identified 4,634 CNS tumors in 4,550 individuals, of whom 2,233 (49%) reside in high-quality pedigrees containing ≥2 grandparents, at least 1 from both maternal and paternal sides. To identify families with excess clustering of CNS tumors, we selected pedigrees with an FSIR $P<0.05$ and ≥2 affected patients, resulting in 161 high-risk families with a mean of 170 (median 96) relatives per pedigree of 3–6 generations. Among these 161 families, there were 2,017 unique relatives (first-third degree) of CNS probands with 2,355 tumors (any site), for a per pedigree average of 14.7 tumors in 12.5 relatives. Review of the 10 highest risk pedigrees indicated that 4 meet HCS criteria, including Li-Fraumeni (n=2), von Hippel-Lindau (n=1), and rhabdoid tumor predisposition (n=1). Conclusion: The UPDB can produce multigenerational cancer pedigrees that identify individuals and families at risk of harboring a HCS who warrant germline testing. These findings should encourage clinicians to perform thorough family history screening.

RARE-25. DISSECTING THE CONTEMPORARY EPIDEMIOLOGY OF PRIMARY AND SECONDARY BRAIN TUMORS IN INFANCY THROUGH CHILDHOOD

Nayan Lamba[1] and Bryan Iorgulescu[2,3]; [1]Massachusetts General Hospital, Boston, MA, USA, [2]Dana-Farber Cancer Institute, Boston, MA, USA, [3]Brigham and Women's Hospital, Boston, MA, USA

Introduction: Herein we utilize national registry data to evaluate the epidemiology of primary and secondary pediatric brain tumors according to the WHO2016 classification. Methods: Pediatric patients (age≤14) presenting between 2004–2017 with a brain tumor were identified by ICD-O-3 and brain metastasis (2010–2017) coding from the National Cancer Database (comprising >70% of newly-diagnosed cancers in the U.S.), and categorized by NICHD age stages: infant (<1yr; n=1,686), toddler (1-2yrs; n=1,732), early- (2-5yrs; n=6,712), middle- (6-11yrs; n=9,175), and late- (12-14yrs; n=5,042) childhood. Patients' age, sex, race/ethnicity, and overall survival, and tumor location and size were evaluated by WHO2016 tumor type. Results: 24,347 pediatric brain tumor patients were identified. Overall, other astrocytic tumors (24% of females, 20% of males), diffuse astrocytic/oligodendroglial gliomas (23% of females, 21% of males – 64% of which were midline), embryonal (13% of females, 19% of males), and sellar region tumors (12% of females, 8% of males) predominated. Embryonal tumors prevailed in infancy (24%) and toddlerhood (24%), declining to 9% in late childhood; only 40% were female. Ependymal tumors peaked at 15% in toddlerhood (6% overall), whereas choroid plexus tumors peaked at 11% in infancy (1.9% overall). A minority of brain tumors were of neuronal & mixed neuronal-glial (6.1%), germ cell (3.8%), cranial nerve (3.2%), mesenchymal non-meningothelial (2.4%), meningioma (1.6%), pineal (1.1%), hematological/histiocytic (0.5%), and other glioma (0.2%) types. Brain metastases were rare (1.5% overall; from 4.0% in infancy to 0.8% in late childhood; and only 41% were female) – 61% came from adrenal neuroblastoma, 16% from sarcomas, and 6% from malignant rhabdoid tumors/extracranial AT/RT. Conclusions: Pediatric brain metastases overwhelmingly originate from adrenal neuroblastoma. Although, overall, diffuse astrocytic/oligodendroglial, other astrocytic, embryonal, and sellar region tumors predominate among pediatric brain tumors, together they only comprise 70% of cases and their distribution varies substantially by patients' age and sex.

TRANSLATIONAL/EARLY PHASE CLINICAL TRIALS

EPCT-01. A NOVEL PEPTIDE VACCINE DIRECTED TO CMV PP65 FOR TREATMENT OF RECURRENT MALIGNANT GLIOMA AND MEDULLOBLASTOMA IN CHILDREN AND YOUNG ADULTS: PRELIMINARY RESULTS OF A PHASE I TRIAL

Eric Thompson[1], Daniel Landi[1], Gerald Archer[1], Eric Lipp[1], Ashley Walter[1], Bridget Archambault[1], Bea Balajonda[1], Charlene Flahiff[1], Denise Jaggers[1], James Herndon[1], Evan Buckley[1], Kristin Schroeder[1], Dina Randazzo[1], Annick Desjardins[1], Margaret Johnson[1], Katherine Peters[1], Mustafa Khasraw[1], Michael Malinzak[1], Duane Michell[2], David Ashley[1], and John Sampson[1]; [1]Duke University, Durham, NC, USA, [2]University of Florida, Gainesville, FL, USA

Introduction: The cytomegalovirus (CMV) antigen, pp65, is ubiquitously expressed in malignant glioma and medulloblastoma but not in healthy brain. The objective of this Phase I trial (NCT03299309) was to assess the safety and feasibility of a novel pp65 peptide vaccine (PEP-CMV) in children and young adults with recurrent medulloblastoma and malignant glioma. Methods: Vaccines contain a synthetic long peptide (SLP) of 26 amino acids encoding multiple potential class I, class II, and antibody epitopes of CMV pp65 across several haplotypes. This SLP is administered as an emulsion in Montanide ISA 51. Patients receive a single course of temozolomide to induce lymphopenia, tetanus/diphtheria toxoid site preconditioning, then vaccines administered intradermally every two weeks for 3 doses, then monthly. Results: To date, 22 patients have been enrolled. Diagnoses include medulloblastoma (n=2), glioblastoma (n=12), anaplastic oligodendroglioma (n=2), anaplastic astrocytoma (n=3), and malignant glioma NOS (n=3). Mean number of prior treatment regimens is 4.9 (range 1–12). Mean age is 22yo (range 6–35) and 45% of patients are male. The median KPS is 80. The median number of vaccines given at time of analysis is 3.3 (range 1–12). There have been no ≥ 3 Grade toxicities related to the vaccine. One patient developed nausea, vomiting, palpitations, and tachycardia after vaccination and had elevated inflammatory cytokines consistent with cytokine release syndrome. Median PFS is 2.5 months (95% CI: 1.7,4.5) and median OS is 6.5 months (95% CI 3.3, 7.9). Immune response to pp65 as determined by ELISpot was found in 75% of patients. On MRI 6 of the 11 evaluable patients have had at least stable disease with three of those having a partial response. Conclusions: Preliminary results demonstrate that PEP-CMV is well-tolerated and elicits an immune response in heavily pretreated, multiply recurrent patients. A multi-institutional Phase II trial is scheduled to open fall 2021.

EPCT-02. COMPARISON OF TARGETED AGENTS RECOMMENDED BY THE CNS-TAP TOOL TO THOSE SELECTED BY A TUMOR BOARD IN A MOLECULARLY-DRIVEN DIPG CLINICAL TRIAL

Holly Roberts[1], Karthik Ravi[1], Bernard Marini[1,2], Cassie Kline[3,4], Sabine Mueller[5], Carl Koschmann[1], and Andrea Franson[1]; [1]University of Michigan Medical School, Ann Arbor, MI, USA, [2]Department of Clinical Pharmacy and Pharmacy Services, University of Michigan, Ann Arbor, MI, USA, [3]Children's Hospital of Philadelphia, Philadelphia, PA, USA, [4]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA, [5]School of Medicine, University of California, San Francisco, San Francisco, CA, USA

Recently, sequencing of diffuse intrinsic pontine glioma (DIPG) biopsy specimens has revealed genomic heterogeneity of these tumors, fueling an interest in individualized, targeted treatment options. The Pacific Pediatric Neuro-Oncology Consortium recently completed enrollment onto a feasibility study PNOC003: Molecular Profiling for Individualized Treatment Plan for DIPG (NCT02274987), in which a multidisciplinary tumor board recommended molecularly-targeted agents based on genomic and molecular profiling of each patient's tumor. Separately, our group developed the Central Nervous System Targeted Agent Prediction (CNS-TAP) tool, which combines pre-clinical, clinical, and CNS penetration data with patient-specific genomic information to allow for numeric scoring of targeted anticancer agents to objectively evaluate these therapies for use in patients with CNS tumors. We hypothesized that highly-scored agents within CNS-TAP would overlap with the agents recommended by the tumor board in this study. For each PNOC003 participant, we utilized the genomic report to identify actionable alterations and input patient-specific data into CNS-TAP to identify the highest scoring agents. We compared high-scoring agents within CNS-TAP with recommendations from the PNOC003 tumor board for each of the enrolled 28 subjects. Overall, 93% (26/28) of patients had at least one agent recommended by both the tumor board and CNS-TAP. Additionally, 38% (37/95) of all agents recommended by the tumor board were also selected by CNS-TAP. Furthermore, we identified factors that likely contributed to the discordance between these two methods. Without clinician input, CNS-TAP is unable to account for drug-drug interactions, includes only designated anticancer agents, and cannot easily be updated in real time. However, CNS-TAP provides an objective evaluation of targeted therapies, whereas tumor boards are inherently subjective. Given the discordance identified between these methods and the strengths of each, a prospective study incorporating both CNS-TAP and a molecular tumor board for targeted therapy selection in DIPG patients is warranted.

EPCT-03. SERIAL PLASMA AND CSF CELL-FREE TUMOR DNA (CF-TDNA) TRACKING IN DIFFUSE MIDLINE GLIOMA PATIENTS UNDERGOING TREATMENT WITH ONC201

Evan Cantor[1], Kyle Wierzbicki[1], Rohinton S. Tarapore[2], Chase Thomas[1], Rodrigo Cartaxo[1], Viveka Nand Yadav[1], Ramya Ravindran[1],