Abstracts

RARE-07. EFFICACY AND SAFETY OF LABOROTECINIB IN PEDIATRIC PATIENTS WITH TROPOMYOSIN RECEPTOR KINASE (TRK) FUSION-POSITIVE PRIMARY CENTRAL NERVOUS SYSTEM (CNS) TUMORS

Sebastien Perichon1, Philippe François Duf1, Birgit Goerger2, Karsten Nyssom3, Ingrid Öra4, Valentina Bond5, Julia Chisholm6, Steven G. DuBois7, Nicolas U. Altewerki8, Hansford9, Michael Caplin10, Francesco H. Schulte11, Makoto Tahara12, David S. Ziegler13, Richarda Norenb erg14, Laura Dima15, Esther De La Cuesta16, Theodore W. Laetsch17, and Cornelis M. van Tilburg18

Background: NTRK gene fusions are oncogenic drivers in various CNS and non-CNS tumors. Laborotecinib is a highly selective TRK inhibitor approved to treat patients with TRK fusion cancer, with an objective response rate (ORR) of 78% across multiple non-CNS cancers (McDermott et al, ESMO 2020). We report updated data on pediatric patients with TRK fusion-positive primary CNS tumors. Methods: Patients aged <18 years with primary CNS tumors harboring an NTRK gene fusion enrolled in two clinical trials (NCT02637687, NCT02576431) were identified. Laborotecinib was administered until disease progression, withdrawal, or unacceptable toxicity. Response was investigator assessed. Results: By July 2020, 26 pediatric patients with TRK fusion-positive CNS tumors were treated. Tumor histologic subtypes included high-grade glioma (n=13), low-grade glioma (n=7), glioneuronal tumor (n=2), neuroepithelial tumor (n=2), CNS neuroblastoma (n=1), and small round blue cell tumor (n=1). Median age was 7.0 years (range 1.3–16.7). The ORR was 38% (95% CI 20–59%): 3 complete responses, 7 partial responses (including 2 pending confirmation), 14 stable disease, and 2 progressive disease. The ORR in patients with high-grade glioma was 38% (95% CI 14–68%). Nineteen of 21 patients (90%) with measurable disease had tumor shrinkage. The 24-week disease control rate was 77% (95% CI 56–91%). Median duration of response (DoR), PFS and overall survival (OS) were not reached. The 12-month rates for DoR, PFS and OS were ≥75%, 63%, and 86%, respectively. Duration of treatment ranged from 1.2 to 33.1 months. Treatment-related adverse events were reported for 15 patients (58%) and were Grade 3–4 in 12 patients (12%), with no discontinuations related to laborotecinib. Conclusions: In pediatric patients with CNS NTRK fusion-positive tumors, laborotecinib demonstrated durable responses, high disease control rate, and good tolerability. These results support testing for NTRK gene fusions in pediatric patients with CNS tumors.

RARE-08. POTENTIAL NEW THERAPIES FOR DIFFUSE INTRINSIC PONTINE GLIOMA IDENTIFIED THROUGH HIGH THROUGHPUT DRUG SCREENING

Damian Dünge1, S. Santosh Valvi2, Jie Liu3, Nicole Yeung3, Sandra George1, Caitlin Ung1, Aaminah Khan1, Laura Franshawe1, Anahid Ehteda1, Han Shen1, Isabella Oriente1, Giovanna Farruggia2, Patrick Reynolds1, Maria Tsoli2, and David Ziegler1,4

Background: Diffuse Intrinsic Pontine Gliomas (DIPGs) are the most devastating of all brain tumors. There are no effective treatments, hence almost all children will die within 12 months. There is an urgent need for effective therapies for this aggressive tumor. We performed a high-throughput drug screen with over 3,570 biologically active, clinically approved compounds against a panel of neurosphere-forming DIPG cells. We identified 7 compounds - auranofin, fenretinide, parthenolide, SAHA and melphalan - that were confirmed to have potent anti-tumor activity against a panel of DIPG-neurospheres, with minimal effect on normal cells. Using cytotoxicity and clonogenic assays, we found that these drugs were able to inhibit DIPG-neurosphere proliferation and colony formation in vitro. To determine whether in vitro efficacy could be replicated in vivo, we tested the activity of each of these compounds in an orthotopic DIPG model. Of the agents tested, fenretinide, auranofin and SAHA were the most active against DIPG cells and significantly enhancing the survival of tumor bearing animals. Mechanistic studies showed fenretinide enhancing apoptotic cell death of DIPG cells via inhibition of PDGFRα transcription and downregulation of the PI3K/AKT/MTOR pathway. We therefore examined the therapeutic efficacy of fenretinide using a second orthotopic model with PDGFRα amplification. We used two different fenretinide formulations which were found to enhance survival. Fenretinide is clinically available with safety data in children. Validation of the activity of Fenretinide in PDGFRα-amplified or overexpressed DIPGs will lead to the development of a clinical trial, allowing the advancement of fenretinide as potentially the first active therapy for DIPG.

RARE-09. POORLY DIFFERENTIATED CLIVAL CHORDOMA IN EXTREME YOUNG AGE; CASE ILLUSTRATION AND REVIEW OF LITERATURE

Malak Alterweiri1, Abdullah AI-Ramadan2, Hindi AI-Hindi2, and Essam AI-Shal1

Background: Clival chordomas are rare tumors believed to be originated from notochordal remnants. Of all intracranial neoplasms, the incidence of chordoma is less than 1%. The youngest patient with an intracranial chordoma reported in the literature was a newborn in the first few days after birth. Intracranial chordomas are more prevalent in males compared to females. The clinical features of intracranial chordoma in the pediatric age group commonly include increased Intracranial pressure, lower cranial nerves palsy, and torticollis. There is no optimum treatment, however, surgical resection of the tumor followed by radiation therapy reported successful outcome. This is a case of a poorly differentiated clival chordoma of a 23-month old boy. The clinical features, pathological, radiological findings, and surgical technique are discussed with an elaboration of the current review of the literature of clival chordoma in the extreme young age group.

RARE-10. PRIMARY INTRACRANIAL EWING SARCOMA IN A 12 MONTH OLD MALE

Clay Hoering1, Aaron Goldberg2, Jody Pathare3, Tian Dao4, Ali Nael Amzajerd1, William Loudon1, Ashley Plant-Fox1, Joffre Olaya1, and Chenue Abongwa1

Abstracts • JUNE 2021

1. This is a case of a poorly differentiated clival chordoma of a 23-month old boy. The clinical features, pathological, radiological findings, and surgical technique are discussed with an elaboration of the current review of the literature of clival chordoma in the extreme young age group. To the best of our knowledge, this is the youngest age of clivus chordoma reported in Saudi Arabia.

Background: Ewing sarcoma (EWS) is a rare type of pediatric bone and soft tissue tumor that accounts for approximately 1% of all pediatric ma-
Abstracts

Ligancies. It most commonly occurs in the long bones or axial skeleton, and rarely includes extraskeletal sites or intracranial involvement. Reports of primary intracranial EWS are minimal. Pediatric intracranial EWS is extremely rare and difficult to diagnose. A 17-year-old female first presented with severe headaches and was diagnosed with primary intracranial EWS. A young woman presented with a retroperitoneal primary Ewing sarcoma. A rare case of primary intracranial Ewing sarcoma with focal proton beam radiation was reported. A pediatric case of primary intracranial Ewing Sarcoma was presented, with long-term follow-up and large numbers of prospective studies recommended to determine such infection is not increased by the endonasal approach. Long-term infection to patient or any of the surgical team. We believe that the risk of infection should be employed to limit the possibility of transmission of any possible infection to patient or any of the surgical team. We believe that the risk of infection should be employed to limit the possibility of transmission of any possible infection to patient or any of the surgical team.

RARE-11. PRIMARY INTRACRANIAL LEIOMYSARCOMA IN A PATIENT WITH NEUROHORMATOSIS TYPE 1

Primary intracranial leiomyosarcoma (LMS) is very rare, with only a few reported cases. Only one prior case report of intracranial LMS in a patient with neurofibromatosis type 1 (NF1) was identified. We report a case of primary intracranial LMS with known history of NF1. Our patient is a 17-years-old female without history of immunocompromise presenting with severe headaches representative of right frontal hemorrhagic tumor found to be primary intracranial LMS. In prior reported cases, most primary intracranial LMS were treated with surgical chemotherapy and radiation therapy. Our patient underwent multiple resections, as well as focal radiation. Her chemotherapy initially included ifosfamide, carboplatin, and etoposide, but when she failed etoposide twice due to severe allergic reactions, she completed treatment successfully with the combination of ifosfamide and doxorubicin. She continues to be doing well with no evidence of disease at 41 months post-treatment.

RARE-12. PITUTARADY ADENOMA SURGERIES IN COVID-19 ERA: EARLY LOCAL EXPERIENCE FROM EGYPT

Background: The pandemic of COVID-19 has a great impact on all health-care services worldwide. Neurosurgical recommendations are to postpone the endoscopic endonasal pituitary surgeries during the pandemic. We would like to express our experience with urgent pituitary adenomas during the current COVID-19 pandemic. Methods: In our country, COVID-19 has started to become a paramount problem by March 2020. Nine cases of pituitary adenomas have presented with urgent manifestations. The endoscopic endonasal approach was performed in eight patients, while a craniootomy was selected for a recurrent pituitary adenoma. Pre- and postoperative thorough clinical evaluations with chest CT scans were performed. Other strict infection control measures have been applied. Results: In 8 weeks duration starting from the past days of February 2020, we have operated on four females and five males of pituitary adenomas. Visual deterioration was the main presenting symptom. The driving factor for surgery was saving vision in eight patients. All patients data were collected and analyzed. Results: Basically, 24 patients (18 females and 6 males) were radiologically diagnosed as EES. 13 females and only one male were having symptoms of BHI. 17 patients (70.83%) had headache as the first presentation and most common presentation in our study was visual in 14 patients (58.3%). Two patients (8.3%) had pituitary hypersecretion namely growth and prolactin hormones. In those (58.3%) confirmed to have BHI thechere-pterional shunts were inserted. Incidental cases (29.17%) without symptoms were followed up. Conclusion: Although (ESS) is a well-known radiological hallmark for BHI, no clear standard all patients had BHI. Surprisingly, pituitary hyperfunction may be the first presentation in some rare cases. Generally, natural history of that entity was bengin. Frequent follow-up by neurosurgeons and increased awareness of associations are advised. We believe a more prospective large number cohort is important to outline the natural history.

RARE-14. DISRUPTION OF GEMC1-MCIDAS MULTICILIOGENESIS PROGRAM PROMOTES CHOROID PLEXUS CARCINOMA

Tumors of the choroid plexus (CP) are rare primary brain neoplasms mostly found in children. CP tumors exist in three forms: CP papilloma (CPP), atypical CP, and CP carcinoma (CPC). Though CPP is more benign, CPC is a highly lethal and little understood cancer. CPC typically present with severe headache, hydrocephalus, and raised intracranial pressure. Rare cases of CPC have been reported in patients who received low and high dose cranial irradiation and secondary meningiomas are a late effect. Secondary meningiomas are thought to arise from CP epithelial cells that secrete cerebral spinal fluid and generate multiple cilia on their apical surface. Here we show that aberrant NOTCH and Sonic Hedgehog signaling in mice drive tumors that resemble CPC in humans. In contrast to CP epithelial cells with clusters of multiple cilia, NOTCH-driven CP tumors were monociliated, and disruption of the NOTCH complex restored multiciliation and decreased tumor growth. NOTCH suppressed multiciliation in tumor cells by inhibiting the expression of Geminin Coiled-Coil Domain Containing 1 (GEMC1), and multiciliate differentiation and DNA synthesis associated cell cycle protein (MCIDAS), early transcriptional regulators of multiciliated cell (MCC) differentiation. Consistently, Gemc1-Mcidas deficiency led to a lack of MCCs in the CP, and impaired the correction of the multiciliation defect in tumor cells by a NOTCH inhibitor. Disturbances to the GEMC1 program are commonly observed in human MCCs characterized by solitary cilia and frequent somatic TP53 mutations. Accordingly, CPC driven by deletion of tumor suppressor Trp53 and Rb1 exhibit a cilia phenotype consistent to loss of Gemc1-Mcidas expression. Taken together, these findings reveal that the GEMC1-MCIDAS multicilogenisis program in the CP is critical for inhibiting tumorogenesis, whereas a defective multiciliation program promotes CPC and may represent a therapeutic avenue for this cancer.

RARE-15. THE MOLECULAR PROFILE OF SECONDARY MENINGIOMAS IN SURVIVORS OF CHILDHOOD NON-CENTRAL NERVOUS SYSTEM CANCERS

Introduction: Cranial irradiation remains part of childhood cancer therapy and secondary meningiomas are a late effect. Secondary meningiomas are reported in patients who received low and high dose cranial irradiation and arise ~ 20 years post exposure. The molecular and genetic profile of primary meningiomas has been well studied; however, only a few studies have examined the unique profile in radiation-induced meningiomas (RIM). Methods: We identified patients followed at the Childhood Cancer Survivor Clinic, Stollery Children’s Hospital who had a history of non-central nervous system malignancies and received cranial irradiation who developed meningiomas between clinic inception in 1971 and June 2013. Whole exome sequencing (WES) as well as DNA methylation profiling were performed for patients where tumor and germline DNA were available. Results: Of 96 patients who received cranial irradiation, 16 (16.7%) developed symptomatic meningiomas. The median age of all 16 patients received 2000–2400 cGy, suggesting a threshold dose. 9/16 (56%) had WHO Grade 2 meningiomas or greater and 7/16 (44%) were infiltrative. Post-surgical recurrences occurred in 43%. Patients experienced considerable morbidities directly attributable to the meningiomas or their treatment. 14 patients had samples suitable for further analysis. Preliminary analysis showed a large heterogeneous supratentorial cystic and solid mass centered in the right parietal region measuring 9.1cm x 10.3cm x 12.3cm. All 16 patients were diagnosed with primary empty sella syndrome (ESS) for two years who were diagnosed radiologically as ESS. Fundus and other ophthalmological examinations were done. Lumbar puncture and cerebrospinal fluid (CSF) manometer were also done. All 16 patients were diagnosed with primary empty sella syndrome (ESS) for two years who were diagnosed radiologically as ESS. Fundus and other ophthalmological examinations were done. Lumbar puncture and cerebrospinal fluid (CSF) manometer were also done. All 16 patients were diagnosed with primary empty sella syndrome (ESS) for two years who were diagnosed radiologically as ESS. Fundus and other ophthalmological examinations were done. Lumbar puncture and cerebrospinal fluid (CSF) manometer were also done.