

inhibitors of EPN cell line growth. We performed in-vitro cell growth assays combining increasing doses of radiation and 5FU and found a significant synergistic effect on cell growth and apoptosis in 1q+ PFA EPN cell lines. Further growth attenuation was seen when ATRA was added 48 hours following radiation and 5FU treatment. This led us to development of preclinical studies in the 1q+ PFA orthotopic xenograft models MAF-811_XF and MAF-928_XF. In the initial cohort, tumors were allowed to establish prior to treatment start confirmed by MRI. In both MAF-811 and MAF-928, chemotherapy improved survival compared to no treatment. As consistent with standard of care, radiation significantly improved survival ($p=0.0016$) but there was no added benefit to combining 5FU or 5FU+ATRA with radiation. A second cohort was treated using the same treatment approach, however radiation and 5FU were started with minimal to no visible tumors by MRI. Interestingly, we found a significant increase in survival between vehicle control and combination 5FU+ATRA (HR 5.121, 95% CI: 0.2506, 2.409, $p=0.048$) in MAF-811 mice. However, again with radiation, there was no significant change in survival with only a single cycle of 5FU+ATRA. This led to continued maintenance of 5FU+ATRA cycles of 6 weeks with 2 weeks off for 4 cycles post radiation in mice with minimal tumor. When 5FU with radiation is followed by 5FU+ATRA and is continued in mice with minimal disease, survival significantly improved when compared to radiation alone (HR 9.020, 95% CI: 1.933 to 42.09, $p=0.007$). These studies highlight the importance of chemotherapy in minimal disease and is the rationale for a Phase I/II study in relapsed PFA EPN and in upfront 1q+ PFA EPN.

EPEN-31. DEVELOPMENTAL AND ONCOGENIC TRANSCRIPTION FACTOR CIRCUITS AS DEPENDENCIES IN EPENDYMOMA

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Brain tumors are the most common cause of cancer death in children. ZFTA-RELA gene fusion is one the most potent drivers of cancer and is sufficient to induce tumors when expressed during brain development. ZFTA-RELA (denoted ZRFUS) fusion is the most frequent events that occurs in an aggressive childhood brain tumor called ependymoma (> 70% of cases). ZFTA recruits RELA to novel DNA binding sites and is necessary to activate ependymoma oncogene transcription. There are currently no targetable treatments for ependymoma, thus studying the mechanisms that regulate ZRFUS oncogenic programs may yield opportunities to develop effective therapies. To study proteins that regulate gene expression programs in brain cancer, the Mack lab and others have comprehensively characterized the active chromatin landscapes of several adult and pediatric brain cancers. This genome-wide analysis has identified highly active TFs, termed core regulatory circuit (CRC) TFs that govern gene expression programs such as MYC, GLI2, SOX2, and OLIG2, previously described in brain tumors such as glioblastoma and medulloblastoma. Critically, a glial cell fate specification TF, SOX9, showed the highest levels of activity in ependymoma. A functional RNA interference screen of CRC TFs prioritized SOX9 as the top cancer dependency gene required for ZRFUS ependymoma cell proliferation. To study ZRFUS ependymoma, we developed one of the first genetic mouse models of the disease, and show in preliminary data, that SOX9 knockout abolishes tumor initiation. Surprisingly, SOX9 KO has no impact on tumor initiation in an aggressive glioma model, suggesting tumor-specific contributions of SOX9. This concept is supported by our data that shows SOX9 co-recruitment to a vast majority of ZRFUS binding sites in the genome. Our data supports that SOX9 regulates ZFTA-RELA target cistrome; presenting a potential pathway that may be explored for therapeutic benefit.

EPEN-32. LEVERAGING CELL SURFACE TARGETS AS THERAPEUTIC VULNERABILITIES FOR PEDIATRIC EPENDYMOMA

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Brain tumors are the leading cause of cancer-associated death in children. Ependymoma, an aggressive type of childhood brain tumor, is currently treated with surgery and radiotherapy. Ependymomas are a molecularly heterogeneous group of tumors driven by distinct genetic and epigenetic alterations. In children, 90% of ependymomas arise intracranially, with two thirds occurring in the posterior fossa (PF) and one third in the supratentorial brain (ST). PF ependymomas are divided into at least two groups termed, PFA and PFB, with PFA tumors associated with poor clinical outcomes. Over 70% of ST ependymoma are characterized by an oncogenic fusion between ZFTA and RELA and shown in some cohorts to have poor clinical outcome, particularly in the context of CDKN2A tumor suppressor gene loss. A major challenge in identifying therapies against ependymoma, has been the paucity of genetic abnormalities available for targeting. PFA ependymomas harbor largely balanced genomes with no recurrent CNVs, fusions, or somatic mutations that are amenable to pharmacologic inhibition. ZFTA-RELA ependymoma while representing a clear disease driver, functions as a transcription factor and lacks clear binding surfaces available for direct inhibition using small molecules. Therefore, alternative approaches are needed to identify new targets and effective therapies in ependymoma to be evaluated in pre-clinical models. In both human ependymoma cell culture lines and

PDX models, we demonstrate that a multi-omic approach is promising for cell surface target discovery, and further, focused cell surface profiling can identify lead targets that can be rapidly translated for CAR T-cell therapy.

EPIDEMIOLOGY

EPID-01. DIFFERENCES IN FIRST-LINE TREATMENT BUT COMPARABLE SURVIVAL OUTCOMES FOR PEDIATRIC BRAINSTEM AND NON-BRAINSTEM HIGH-GRADE GLIOMAS IN THE NETHERLANDS – A POPULATION-BASED STUDY

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INTRODUCTION: Pediatric high-grade gliomas (pHGG) are among the most devastating childhood cancers. Due to their limited treatment options and tumor biology, brainstem (BS) pHGG are considered to have worse survival outcomes compared to non-brainstem (NBS) pHGG. **METHODS:** Detailed clinical data were gathered by trained registrars for all children diagnosed with a pHGG (including radiologically diagnosed brainstem tumors) in the Netherlands for the period 2003-2017. Tumors were grouped into BS and NBS tumors according to the ICD-O-3 topography codes. Differences in treatment characteristics were tested with the Chi-squared, Fisher exact or Mann-Whitney-Wilcoxon test. Median survival time was determined by Kaplan-Meier method. Trends and survival differences were tested with Cox Proportional-Hazards Models. **RESULTS:** In total, 276 pHGG patients (BS n=166, NBS n=110) were diagnosed during 2003-2017. Differences in first line treatment were found for neurosurgery (25% of BS versus 95% of NBS patients, $p<0.001$) and systemic therapy (20% of BS versus 70% of NBS, $p<0.001$). Notable, 10% of BS patients received temozolomide compared to 55% of NBS patients ($p<0.001$). No significant difference was found for first-line radiotherapy. However, total cumulative dose and number of fractions differed significantly (BS: median 44.8 Gy and 16 fractions; NBS: median 57.4 Gy and 30 fractions, both $p<0.001$), reflecting hypofractionation regimens in BS pHGG. Survival remained stable over time for both BS ($p=0.9$) and NBS ($p=0.3$). Median survival time was comparable between BS (9.7 months) and NBS patients (9.8 months, $p=0.6$). **CONCLUSION:** Despite differences in treatment characteristics we found comparable survival outcomes for BS and NBS pHGG. It remains unclear why survival for both BS and NBS pHGG in this retrospective population-based study is substantially inferior to published data. If the underlying reasons can be found in differences in treatment characteristics, data type (hospital-based versus population-based) or incompleteness of non-microscopically verified cases, is subject to further research.

EPID-02. SURVIVAL EXPERIENCE IN PEDIATRIC PATIENTS OF CENTRAL NERVOUS SYSTEM (CNS) TUMOUR IN CANADA

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Established in 2016, the Brain Tumour Registry of Canada Surveillance Research Collaboration aims to address the lack of detailed information on CNS tumours in Canada. Using Canadian Cancer Registry (CCR) data with linked vital status, we present survival estimates for all primary CNS tumours (excluding Quebec) among pediatric patients (age 0-14). Pediatric patients diagnosed with primary CNS tumours during 2010-2017 were included. Vital status was obtained by Statistics Canada through linkage to the Canadian Vital Statistics Database and the income tax returns file, with a cut-off date of December 31, 2017. We used the Pohar-Perme method to estimate the net survival rate (NSR) through the period approach. International Classification of Diseases for Oncology (3rd edition) site/histology codes were grouped into 25 histological categories, irrespective of tumour behaviour, according to the schema developed by the Central Brain Tumor Registry of the United States. Of 1725 pediatric CNS tumours, the 1-, 2- and 5-year NSR are 0.89 (95%CI 0.87-0.90), 0.84 (95%CI 0.81-0.86) and 0.80 (95%CI 0.78-0.82), respectively. All non-malignant CNS tumours have a median survival over 8 years. The 5-year NSR range from 0.90 (95%CI 0.47-0.99) for unique astrocytoma variants, 0.95 for tumour of sellar region (95%CI 0.85-0.98) and germ cell tumours, cysts and heterotopias (95%CI 0.67-0.99), to 1.0 for choroid plexus tumours, tumours of cranial and spinal nerves, and meningioma. For malignant CNS tumours, NSR vary greatly depending on histology grouping. 5-year NSR from lowest to highest are glioblastoma (0.10, 95%CI 0.03-0.23), anaplastic astrocytoma (0.19, 95%CI 0.05-0.40), glioma not otherwise specified (0.54, 95%CI 0.46-0.62), embryonal tumours (0.72, 95%CI 0.65-0.79), diffuse astrocytoma (0.74, 95%CI 0.59-0.85), ependymal tumours (0.78, 95%CI 0.67-0.87), germ

cell tumours, cysts and heterotopias (0.85, 95%CI 0.70-0.93) and pilocytic astrocytoma (1.0). We report the most comprehensive and up-to-date data on the pediatric primary CNS tumour survival experience in Canada.

EPID-03. EPIDEMIOLOGY, TREATMENT AND OUTCOMES OF CHILDREN AND YOUNG ADULTS WITH CNS TUMORS IN ARMENIA

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BACKGROUND: CNS tumors are the most common solid tumors in children and the leading cause of cancer related deaths. The incidence of CNS tumors is 1.7-6.21 cases per 100000 children. The aim of current study is to analyze epidemiological data, treatment and outcomes of children and young adults (<25 years) with CNS tumors in Armenia during last 25 years. **METHODS:** We have collected data of pediatric and young adult patients treated in neurosurgery department, three major chemotherapy clinics and radiation therapy department from 01.01.1995 to 31.12.2020 in Armenia. Incidence by gender, age at diagnosis, the time from first complaints to diagnosis, histopathology results and overall survival rates were calculated. **RESULTS:** The population-based data revealed 176 patients diagnosed with primary CNS tumors during 25 years. Among them 98 (55.7%) were males. Mean age at diagnosis was 7.07 years and the mean time from the first complaints to diagnosis was 6.55 months. Medulloblastomas and other embryonal tumors (26.7%), low grade gliomas (16.5%), retinoblastomas (12.5%) and high grade gliomas (10.8%) were the most common diagnosed malignancies. Craniopharyngiomas, germ cell tumors and other malignancies were observed in 9.1% of patients. For 24.4% histopathological data was missing. Surgery, chemotherapy and radiation therapy were performed in Armenia for 62.5%, 33.5% and 19.3% patients respectively. Follow up information was available for 119 (67.6%) patients. 5-year overall survival was 76%. **CONCLUSION:** Embryonal tumors and gliomas were the most common diagnosed CNS malignancies in Armenia which is consistent with international data. Multimodal treatment was often not available in Armenia during study period, especially for early cases. We hope recent advances in surgery, chemotherapy, and radiotherapy will help to improve treatment outcomes.

EPID-04. PREDCAP, THE FRENCH REGISTRY OF PREDISPOSITION TO PEDIATRIC CANCERS

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A pathogenic or likely pathogenic variant (PV) in a major cancer predisposition gene is identified in almost 10% of children or young adults who developed a cancer, regardless of their family history. This incidence may increase by the development of wide tumor sequencing programs leading to identify germline PVs in cancer patients and new cancer predisposition syndromes (CPS) associated with childhood cancers. Due to the rarity of each CPS, we still lack information about phenotype associated with most CPS especially cancer risks according to age as well as tumor characteristics and response to treatment. Within the French genetic multidisciplinary network involving pediatric oncologists, oncogeneticists and researchers, we have created a clinico-molecular registry for pediatric-CPS according to data protection regulation. The PREDCAP database collects clinical, genetic and molecular data from patients who developed pediatric tumors associated with a CPS, both retrospectively and prospectively. It includes a mandatory set of data on clinical phenotype, tumor characteristics (including treatment and outcome), family data and results of genetic analyses, with annual data updates. Interoperability with existing databases is planned, allowing for pooling of data collection and management. Aims of PREDCAP registry are to obtain reliable clinical and molecular data on pediatric CPS with a simplified and effective access. By collecting all available data on a large number of patients thanks to international collaborations, we hope to improve the knowledge on rare CPS, in particular, to better define the tumor

spectrum and the penetrance of PVs, to analyze the specificity of tumors associated with these germline PVs. With this tool, we wish to facilitate future projects using structured and centralized data, associated with a virtual bank of available tumor and constitutional DNA, to evaluate and improve the relevance of management recommendations established for each syndrome.

EPID-05. A NOVEL, CLINICALLY-RELEVANT CLASSIFICATION OF PEDIATRIC CNS TUMORS FOR CANCER REGISTRIES USING A CLUSTERING ANALYSIS

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To accurately evaluate the burden of pediatric central nervous system (CNS) tumors, estimate resources for cancer control, and monitor outcomes, a classification system that segregates tumors into clinically relevant groups is essential. The current classification of CNS tumors included in the third revision of the International Childhood Cancer Classification does not identify key clinical groups, such as low- and high-grade gliomas. To address this need, a novel classification was embarked upon using ICD-O-3 codes, CBTRUS grouping, incidence, survival, and treatment modalities as inputs. For each ICD-O-3 code with >50 new cases/year in CBTRUS from 2000 to 2016, 2 clinicians reached consensus defining the efficacy of three treatment modalities: surgical resection, radiotherapy, and chemotherapy. Then, patient level 5-year overall survival (OS) times were simulated based on total incidence and 5-year OS for each code. Subsequently, 5 factors were included as potential classifiers: tumor behavior, CBTRUS sub-group, and efficacy of the three treatment modalities. A "survival tree" was developed by using partitioning. Starting with the patient cohort (root), univariate cox proportional hazards model was used to identify statistically significant ($P < 0.05$) factors. The factors with the largest hazard ratio were selected manually to create child nodes. Within each child node, the partitioning process was repeated on remaining factors until no statistically significant factor remained. This clustering yielded 4 main groups (low-, intermediate-, high-, and very high-risk tumors) and 11 subgroups, including "embryonal tumors" and "low-risk glial and glioneuronal tumors". Further validation of the classification will be sought through a structured consensus process using multidisciplinary experts. This systematic method to develop a classification for pediatric CNS tumors will allow for more relevant estimations of outcomes and better estimation of resource utilization. Furthermore, this strategy could be replicated for other disease groups.

EPID-06. TRANSFUSION RELATED IRON OVERLOAD IN PEDIATRIC PATIENTS WITH CNS TUMORS

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BACKGROUND: Patients receiving chemotherapy or autologous hematopoietic stem cell transplant (autoHSCT) routinely receive red cell transfusions as supportive care. Each unit of transfused red cells contains approximately 150mg of iron which the body has no natural mechanism for excreting. Transfusion-related iron overload (TRIO) is an under-recognized complication of therapy which left untreated may result in long-term damage to the liver, heart, or endocrine organs. We sought to identify the prevalence of TRIO in patients with pediatric CNS tumors and evaluate specific risk factors. **METHODS:** A retrospective record review of pediatric CNS tumor patients treated at Children's Hospital Colorado was conducted including patients who completing therapy between 1/1/2014 – 12/1/2021. Patients at high risk for TRIO were defined as having a cumulative transfused blood volume of more than 150mL/kg or 4000mL total. The diagnosis of TRIO was confirmed if patients had a serum ferritin greater than 1000ng/mL or elevated liver iron content of 7mg/g dry weight or greater by MRI. **RESULTS:** There were 173 evaluable patients (40% embryonal tumors, 15% germ cell tumors, 10% ependymomas, 26% low grade gliomas, 5% high grade gliomas, and 3% other tumors). The mean age at completion of therapy was 8 years (range: 0.67 – 25 years). Patients receiving autoHSCT (24% of cohort) were at higher risk for TRIO based on transfused volumes ($p < 0.0001$) than patients not treated with autoHSCT (72% vs 6%, RR 12.0). The prevalence of TRIO in autoHSCT patients was 7.5% (3/40) vs 0.8% (1/121) in patients not undergoing autoHSCT (RR 9.37). For autoHSCT patients at high risk by transfused volume the prevalence of TRIO was 10.3% (3/29). **CONCLUSIONS:** Pediatric CNS tumor patients who have received an autoHSCT are at higher risk for TRIO than those who have not. Routine screening for TRIO should be offered to patients receiving autoHSCT.