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Pineoblastoma (PB) is an aggressive embryonal brain tumor comprising 1% of pediatric CNS tumors. The clinico-molecular heterogeneity and developmental origins underlying PB are poorly understood; therefore, we have assembled a molecular cohort of histologically defined PBs (n=43) with corresponding outcome data. Methylation profiling revealed four molecularly and clinically distinct PB subgroups, including two novel entities. Mutational and transcriptional analysis identified characteristic molecular features of each subgroup, such as mutations in the miRNA processing pathway or *FOXR2* proto-oncogene overexpression. Furthermore, subgroups exhibited differences in propensity for metastasis, cytogenetics, and clinical outcomes. To dissect PB developmental origins and resolve PB subgroup biology, we have employed a combination of single-cell genomics and genetically engineered mouse modeling. We created a single-cell transcriptional atlas of the developing murine pineal gland across 11 timepoints and are currently integrating these data with single nuclei RNA-seq data of human PB (n=25). Single-cell analysis of the developing pineal gland revealed three distinct populations of pinealocytes, referred to as early, mid and late pinealocytes, which segregate by developmental stage yet lie along a single developmental trajectory. Preliminary results implicate significant associations between PBs and the early pinealocyte population as well as subgroup-specific differences in intratumoral heterogeneity. Furthermore, this knowledge has informed the downstream generation of biologically faithful disease models, including a transgenic mouse model of the PB-RB subgroup. Remarkably, this model shows up-regulation of key markers of PB such as *Crx*, *Asmt* and *Otx2* and substantiates early pinealocytes as the probable cell-of-origin for this PB subgroup.

ETMR-07. ETANTR: A RARE TUMOR IN A RESOURCE-LIMITED SETTING

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INTRODUCTION: Embryonal tumor with abundant neuropil and true rosettes (ETANTR) is a rare aggressive brain tumor with low survival rates. There are about 80 cases reported in literature since 2000 when it was first described. There is no standard treatment scheme for ETANTR yet. CASE REPORT: A 2 years old boy presented with a month-long of headache and inability to hold his head. CT scan and MRI revealed a large mass in the right frontal lobe with midline shift. Subtotal tumor resection was done. Histological and immunohistochemical analyses was consistent with ETANTR in one laboratory and PNET in another. The second opinion suggested by the Center of Pediatric Oncology, Hematology and Immunology in Moscow the diagnosis ETANTR was confirmed. Taking into account certain similarities with medulloblastoma was decided to provide treatment according to HIT-2014 protocol. Control MRI done after 2 cycles of Block SKK Carboplatin/Etoposide found tumor progression and for that reason patient underwent second surgical resection. Considering the age of the child radiation therapy was not expedient and the decision was to continue treatment with HIT 2014 intensified regimen, which includes Cisplatin, Vincristine, Etoposide, Cyclophosphamide and intravenous High dose Methotrexate with intrathecal Methotrexate. Aiming to evaluate the effectiveness of treatment we are planning to perform MRI after this 2nd cycle of intensified regimen. DISCUSSION: There are difficulties in diagnosis of rare types of cancers in Armenia. Since there is no approved treatment for ETANTR, there is a need for ongoing research to improve its prognosis.

ETMR-08. INTERNATIONAL CONSENSUS PROTOCOL FOR EMBRYONAL TUMOR WITH MULTILAYER ROSETTES

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Embryonal tumors with multilayer rosettes (ETMR) are rare and highly-aggressive central nervous system (CNS) neoplasms which occur primarily in young children and carry a dismal prognosis. To date, no large clinical investigations have been conducted to determine the optimal therapy for ETMR. Data from retrospective case series suggest that our most aggressive standard therapies are not sufficient for cure in the majority of cases. New treatment approaches incorporating pre-clinical data and the known biology of ETMR are therefore urgently needed. A German drug screen using the patient-derived ETMR BT183 cell line and its xenograft revealed anti-tumor activity of topotecan, doxorubicin, and actinomycin D; three agents used infrequently for treating infant CNS tumors. Additional results from a small series of ETMR patients suggest that optimization of induction chemotherapy using these active agents may improve response and survival outcomes. In 2019, an international panel of pediatric neuro-oncology experts convened to advance therapy for ETMR. A consensus protocol was developed incorporating maximal safe surgical resection, induction chemotherapy with active pre-clinical agents, intrathecal chemotherapy, radiotherapy, and high-dose chemotherapy. This international consensus protocol represents the first prospective clinical investigation specific to ETMR and will be available through a treatment registry globally and as a clinical trial at select centers. The study aims to improve survival by providing aggressive, optimized therapy for ETMR and will serve as a platform to explore new biologically-promising agents. The investigation will also provide valuable prospective outcome data and correlative biological studies to serve as baseline comparators for future clinical trials.

ETMR-09. THE ROLE OF RADIATION FOR EMBRYONAL TUMOR WITH MULTILAYERED ROSETTES

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BACKGROUND: Embryonal tumor with multilayered rosettes (ETMR) is a challenging tumor. The prognosis of the patients suffering from this tumor is extremely poor. We have survival cases of more than 12 months. However, the status of illness is different. In order to clarify the cause of this difference, we reviewed our treatments in this study. TREATMENT COURSE: We have two cases. Both have relapsed after the same chemotherapy after the same radiation therapy. After the recurrence we used protocols that were included extended resection, second radiation therapy with bevacizumab. METHODS: We compared molecular biological evaluations for the initial and recurrent tumors. The resection rate at the time of second removal and the intensity of radiation therapy intensity were compared. RESULTS: We succeeded to remove the tumors with the confirmation of intraoperative MRI. No apparent differences could be seen in molecular biological characters of tumors before and after treatment. There was a difference between the period until radiation therapy and the irradiation methods. CONCLUSIONS: This tumor is untreatable only by resection. We need the second radiation therapy with bevacizumab. It was presumed that tumor should be irradiated quickly with appropriate irradiation field and dose.

ETMR-10. EARLY FOCAL RADIOTHERAPY AND TEMOZOLOMIDE FOLLOWING COMPLETE RESECTION APPEAR SUPERIOR TO INTENSIVE CHEMOTHERAPY AND DELAYED RADIOTHERAPY IN CHILDREN WITH EMBRYONAL TUMORS WITH MULTILAYERED ROSETTES (ETMR)

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BACKGROUND: Embryonal tumor with multilayered rosettes (ETMR) is a rare, aggressive embryonal central nervous system tumor characterized