software, and their prognostic values were evaluated using Kaplan-Meier analysis. Connectivity Map database was used to identify latent therapeutic agents. RESULTS: A total of 11 DEMs (hsa-miR-1224-5p, hsa-miR-128-3p, hsa-miR-17-5p, hsa-miR-18b-5p, hsa-miR-29c-5p, hsa-miR-329-3p, hsa-miR-379-5p, hsa-miR-433-3p, hsa-miR-488-5p, hsa-miR-656-3p and hsa-miR-885-5p) were screened. By intersecting 3275 predicted target genes and 925 DEGs, we finally identified 226 overlapping genes that were enriched in pathways in cancer and MAPK signaling pathway. Four hub genes (GRIA2, NRXN1, SLC6A1 and SYT1) were significantly associated with the overall survival of AT/RT patients. Candidate drugs included histone deacetylase inhibitor (givinostat), DNA synthesis inhibitor (floxuridine), cyclin-dependent kinase inhibitor (purvalanol) and janus kinase inhibitor (lestaurtinib). CONCLUSION: In summary, this study systematically analyzed AT/RT-related miRNAs and pivotal genes to provide novel prognostic biomarkers and potential therapeutic agents.

ATRT-04. INHERITED RHABDOID PREDISPOSITION SYNDROME: A CASE OF CHOROID PLEXUS CARCINOMA AND ATYPICAL TERATOID RHABDOID TUMOR IN SIBLINGS

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Choroid plexus carcinoma (CPC) and Atypical teratoid/rhabdoid tumor (ATRT) are aggressive, malignant brain cancers most commonly arising in children less than 3 years of age. These tumors often have genetic alterations in the tumor suppressor gene SMARCB1/INI1. Rhabdoid predisposition syndrome (RTPS) categorizes patients with germline mutations in SMARCB1 or SMARCA4, leading to a markedly increased risk of developing rhabdoid tumors. Both CPC and ATRT have been demonstrated in patients with these rhabdoid predisposition syndromes. In general, these tumors tend to have a poor prognosis. However, with the presence of a SMARCB1 mutation they may have improved overall survival. We present two interesting cases of siblings with maternally inherited SMARCB1 mutations: one a 21-month-old male who presented with an ATRT and another a 10 month old female who presented with a CPC. The ATRT was treated as per the Children's Oncology Group study ACNS0333 with high dose chemotherapy and stem cell rescue as well as cranial radiation. The CPC was treated as per CPT-SIOP 2009 with etoposide, cyclophosphamide and vincristine. Unlike other patients with these aggressive tumors, both of these patients are alive without evidence of disease recurrence 8 and 7 years post therapy, respectively. Additional genomic testing on both tumors is currently pending in order to potentially identify other mutations that may impact survival. These cases further illustrate the similar profile of two very different tumors with improved overall survival that may be secondary to mutations in SMARCB1 in RTPS.

ATRT-05. RESULTS OF MULTICENTER TRIAL CONCERNING THE TREATMENT OF CHILDREN WITH ATYPICAL TERATOID/RHABDOID TUMORS (ATRT) OF THE CENTRAL NERVOUS SYSTEM

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We analyzed 105 patients under 18 years. The median age was 21 months. There were 54 boys and 51 girls. The supratentorial tumors were in 53 patients, infratentorial in 48, and in spinal cord in 4. 60 had stage M0,29-M+and 16-Mx. All the patients got surgical treatment:total tumor removal in 34,subtotal in 37,partial in 30,and biopsy in 4;75 patients got chemoradiotherapy to ATRT-2006;6-CWS;13-EU-RHAB;5-HIT-SKK;individual schemes in 6. RESULTS: 47 are alive,1 was LFU, and 57 died. PFS was 32%±0.05; the five-year OS 40%±0.05. The median survival-30 months, the median progression-free survival-12 months, and the median of follow-up-23 months. PFS was significantly better in patients more than 12 months compared to patients younger than 12 months:40 and 12%;p=0.00161.After total resection PFS was higher compared to subtotal resection, partial resection, and tumor biopsy:48,38,0,and 0%(p=0.025). After chemoradiotherapy, PFS was higher compared to patients without radiotherapy: 49and 0%(p=0.0000000).PFS for stage M0 was higher compared to stage M+and stage Mx:41,15,and 27%,respectively(p=0.00032). PFS was better for the tumors in the spinal cord and infratentorial location compared to the supratentorial location:67,37,and 25%(p=0.0876). The survival rate was higher among the patients who got treatment according to the ATRT-2006 protocol compared to EU-RHAB, individual regimens, CWS, and HIT-SKK:39,19,17,17,and 0% respectively;p=0.00159. The survival was higher among the patients who got intraventricular/intrathecal Methotrexate,Cytarabine, Prednisolone than among the patients who got only Methotrexate or none at all:40,0,and 5%, respectively; p=0.00015. CONCLUSIONS: Survival was significantly better in patients more than 12month, without metastases, with total removal tumor, chemotheradiotherapy by ATRT-2006 protocol with i/t, i/v Methotrexate/Cytarabine/Prednisolone.

ATRT-06. SMARCB1 LOSS DRIVEN NON-CANONICAL PRC1 ACTIVITY REGULATES DIFFERENTIATION IN ATYPICAL TERATOID RHABDOID TUMORS (ATRT)

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Loss of SMARCB1 is the hallmark genetic event that characterizes ATRT. SMARCB1 is a member of the SWI/SNF chromatin remodeling complex that is responsible for determining cellular pluripotency and lineage commitment. To identify co-operating epigenetic factors, we performed an unbiased shRNA screen targeting 408 epigenetic/chromatin molecules in patient-derived ATRT cell lines and identified BMI1, a component of the Polycomb Repressive Complex 1 (PRC1), as essential for ATRT cell viability. Genetic and Chemical inhibition of BMI1 inhibited clonogenic potential and induced apoptosis *in vitro*. *In vivo* PTC 596 significantly decreased growth of intracranial orthotopic ATRT tumors as evaluated by T2 MRI imaging and significantly prolonged survival compared to control animals. Using RNA-seq and ChIP-Seq our studies show that BMI1 co-operates with SMARCB1 loss to suppress transcription of pro-differentiation pathways and promote self-renewal of tumor stem cells. We then used a doxycycline-inducible SMARCB1 expression system and performed Immunoprecipitation for BMI1, followed by and mass spectrometry analysis. In SMARCB1 deficient cells BMI1 forms a partial PRC1 complex devoid of DNA binding components. Re-expression of SMARCB1 activates two PRC1 chromatin localizing components CBX4 and CBX8. CBX4 is implicated DNA damage response, tumor angiogenesis and self-renewal. CBX8 activates lineage-specific genes during differentiation of ESC. Our data suggest that SMARCB1 deletion results in reprograming of BMI1 chromatin occupancy away from lineage

specification by altering the components of the PRC1 complex. These studies identify the mechanistic basis of BMI1 co-operation with SMARCB1 loss in ATRT and establish BMI1 inhibition as a novel therapeutic approach in ATRT.

ATRT-07. HIGH-DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION FOR AN ADULT PRESENTATION OF THE ATYPICAL TERATOID-RHABDOID TUMOR (ATRT)

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BACKGROUND: ATRT is a rare primary CNS tumor occurring predominantly in children with the peak age of onset at less than 3 years old. Adult presentations are exceedingly rare, associated with poor prognosis and no standard therapies exist. METHODS: Case presentation. RESULTS: 61 y old woman presented with headaches, sinus pressure, and cognitive decline. She was found to have a pineal tumor causing obstructive hydrocephalus. The patient underwent gross total resection of the tumor with pathology reported as ATRT. Her CNS staging, including CSF, was negative. She subsequently received radiotherapy to the resection bed. There was no consensus on what should be the next step in her therapy given lack of data in adults. Ultimately, we adopted a pediatric regimen and treated the patient with a combination of high-dose chemotherapy with cisplatin, cyclophosphamide, and vincristine followed by autologous stem cell transplantation (ASCT). This regimen called for up to 4 cycles of chemotherapy with ASCT and we had collected enough cells to complete 3 cycles. The patient completed 2 cycles of therapy with moderate toxicity. Her CNS imaging remained stable with no evidence of recurrence 14-months from the original diagnosis. CONCLUSIONS: ATRT continues to be an exceedingly rare diagnosis in adults. No standard therapies exist and treatment decisions are challenging given lack of data and lack of prospective clinical trials. Pediatric regimens can frequently be adopted for adults although high-dose chemotherapy with ASCT can be challenging. Our case exemplifies the feasibility of treating ATRT in an adult in the most aggressive fashion.

ATRT-08. A PHASE II STUDY OF CONTINUOUS LOW DOSE PANOBINOSTAT IN PAEDIATRIC PATIENTS WITH MALIGNANT RHABDOID TUMORS/ATYPICAL TERATOID RHABDOID TUMORS

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BACKGROUND: Panobinostat treatment has been shown to terminally differentiate malignant rhabdoid tumor (MRT)/atypical teratoid rhabdoid tumors (ATRT) in pre-clinical models. This is an open label, phase II study of panobinostat in patients with newly diagnosed or relapsed MRT/ATRT. AIMS: To assess the anti-tumor activity of low dose, continuous panobinostat, its associated toxicities, the biological activity of low dose panobinostat by measuring histone acetylation status in peripheral mononuclear cells (PMNC), and markers of differentiation in fresh tumor tissue specimens. METHODS: Following cycles of induction and consolidation chemotherapy and/or radiation treatment, patients were enrolled and commenced on panobinostat as a continuous daily oral dose starting at 10mg/m^2 following a three-week wash out period between therapies. Real-time acetylation status, measuring acetylated H4 on PMNC, was performed to determine the pharmacodynamics of panobinostat. Patients were monitored for drug toxicities with the possibility of dose reductions in decrements of 2mg/m^2. RESULTS: Six patients with newly diagnosed ATRT/MRT and one patient with relapsed MRT have been enrolled to date. The average age at enrollment was 2.5 years. Currently, six patients (85.7%) remain on study with a mean treatment duration of 170 days (range 44–327 days). One patient was removed from study at day 44 due to disease progression. The main dose-limiting toxicity observed to date has been myelosuppression. Panobinostat, at a dose of 10mg/m^2, caused significant acetylation of H4 in PMNC. CONCLUSIONS: Treatment with panobinostat appears to be well tolerated in infants with MRT/ATRT, with successful real-time pharmacodynamic assessment of H4 acetylation.

ATRT-09. IDENTIFICATION OF HUB GENES IN ATYPICAL TERATOID/RHABDOID TUMORS BY MULTIPLE-MICROARRAY ANALYSIS

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BACKGROUND: Atypical teratoid/rhabdoid tumors (ATRT) are rare, highly malignant neoplasms arising in infants and young children. However, the biological basis of ATRTs remains poorly understood. In the present study, we employed integrated bioinformatics to investigate the hub genes and potential molecular mechanism in ATRT. METHODS: Three microarray datasets, GSE35943, GSE6635 and GSE86574, were downloaded from Gene Expression Omnibus (GEO) which contained a total of 79 samples including 32 normal brain tissue samples and 47 ATRT samples. The RobustRankAggreg method was employed to integrate the results of these gene expression datasets to obtain differentially expressed genes (DEGs). The GO function and KEGG pathway enrichment analysis were conducted at the Enrichr database. The hub genes were screened according to the degree using Cytoscape software. Finally, transcription factor (TF) of hub genes were obtained by the NetworkAnalyst algorithm. RESULTS: A total of 297 DEGs, consisting of 94 downregulated DEGs and 103 upregulated DEGs were identified. Functional enrichment analysis revealed that these genes were associated with cell cycle, p53 signaling pathway and DNA replication. Protein-protein interaction (PPI) network analysis revealed that CDK1, CCNA2, BUB1B, CDC20, KIF11, KIF20A, KIF2C, NCAPG, NDC80, NUSAP1, PBK, RRM2, TPX2, TOP2A and TTK were hub genes and these genes could be regulated by MYC, SOX2 and KDM5B according to the results of TF analysis. CONCLUSIONS: Our study will improve the understanding of the molecular mechanisms and provide novel therapeutic targets for ATRT.

ATRT-10. ATYPICAL TERATOID/RHABDOID TUMOR OF THE PINEAL REGION IN A PEDIATRIC PATIENT

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BACKGROUND: Atypical teratoid/rhabdoid tumor (ATRT) is a malignant neoplasm of the central nervous system and corresponds to 1.5% of all intracranial tumors. Mainly affects children under three years of age and shows aggressive behavior (most pediatric patients succumb to their disease within a year after the initial diagnosis, despite the treatment performed). Its place of occurrence in children is preferably in the posterior fossa, and it is rare to appear in other regions. There are only seven patients with ATRT reported on literature; all of them are adults. We present the case of a pediatric patient with a tumor in the pineal region diagnosed as ATRT. CASE REPORT: Three-year-old female patient admitted with occipital headache, vomiting, and seizure. Magnetic resonance imaging (MRI) showed obstructive hydrocephalus secondary to a solid-cystic lesion located at the pineal region that was 3.0 x 3.0 x 3.5 cm in size. Spine MRI did not reveal leptomeningeal spreading. We performed an occipital transtentorial approach to achieve the best safe resection possible, and a ventriculoperitoneal shunt. Histological examination revealed ATRT. The patient received adjuvant treatment with radiotherapy and chemotherapy according to the "Head Start" protocol. One year after the surgery, MRI did not identify any remaining lesion. CONCLUSION: ATRT is an aggressive and rare neoplasm whose clinical picture depends on the location of the tumor; however, it must be considered in the differential diagnosis of tumors of the pineal region in the pediatric population.

ATRT-11. PREVALENCE OF GERMLINE VARIANTS IN SMARCB1 INCLUDING SOMATIC MOSAICISM IN AT/RT AND OTHER RHABDOID TUMORS

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