p53, suggesting inactivation of this tumor suppressor pathway. Reactivation of p53 could be a potential therapeutic strategy for inhibiting ATRT growth. Our laboratory specializes in researching mechanisms contributing to ATRT pathogenesis and potential therapies. In line with this, we investigated an anti-malarial drug called quinacrine that has been safely used in children for decades and can induce p53 in renal cell carcinoma. We used 5 patient-derived ATRT cell lines (BT-37, BT-12, CHLA-06, CHLA-266, CHLA-05) for our studies. We show that ATRT cell lines treated with quinacrine for 6 hours show increased expression of p53, suggesting its activation. Treatment of ATRT cell lines with increasing doses of quinacrine for 24 hours showed dose-dependent decrease in cell growth and proliferation (assessed by MTS assay and BrdU incorporation, P<0.05) and increase in apoptotic cell death (CC-3 and cleaved PARP expression). Nude mice harboring flank tumors of ATRT cell lines and treated with quinacrine for 3 weeks showed significant reduction in tumor growth compared to control animals (P<0.05). Since quinacrine is a substrate for the drug-efflux proteins P-gp/BCRP, we used quinacrine in combination with elacridar (Pgp/BCRP inhibitor) in our intracranial xenograft experiments to increase quinacrine's retention in the brain. Mice harboring intracranial xenografts of ATRT cells showed increased survival when treated with quinacrine and elacridar (median survival 46 days) compared to control animals (median survival 25 days). These results suggest that quinacrine inhibits ATRT growth, partly by activating p53. Our studies are the first to show quinacrine's effect on ATRTs and our current experiments include further investigation of quinacrine's mechanism.

**ATRT-06. RESULTS OF MULTICENTER TRIAL CONCERNING THE TREATMENT OF CHILDREN WITH ATYPICAL TERATOID RHABDOID TUMORS OF THE CENTRAL NERVOUS SYSTEM UNDER 3 YEARS OLD**

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Objective: To evaluate the prognostic factors in children with AT/RT aged under 3 years. Patients and methods: The prognostic factors were analyzed in 106patients under 3 years who got treatment and follow-up from 2008 to 2020.There were 41children younger than 12 months and 65patients older than 12 months. The location of the tumor was infratentorial in 58 patients, supratentorial in 46, and spinal cord in 2. There were 54 boys and 52 girls. Among the patients,57 had stage M0,36 had stage M+ or a multifocal tumor, and 13 had stage Mx. All the patients had undergone surgical treatment: total tumor removal in 27, subtotal-33, partial-42, biopsy - 4;67patients had got chemoradiotherapy according to the ATRT-2006(IRS III) protocol; 15, MUV-ATRT protocol; 3, CWS protocol; 9, EU-RHAB protocol; 6, HIT-SKK protocol; and 6 according to individual treatment schemes.12 patients received HDC with AuHCR. Results: 47 are alive,1 was lost to follow-up, and 58 died:52 of progressive disease,6 of chemotherapy complications. The five-year PFS was 0.27; the five-year OS was 0.40. The PFS was significantly better in patients older than 12months old compared to patients under 12months: 0.33 and 0.17, respectively; $p$=0.0047. The PFS after total resection was higher than after subtotal resection, partial resection, and tumor biopsy: 0.51, 0.29, 0.09, and 0%, respectively ($p$=0.025).The PFS after radiotherapy was markedly higher compared to patients without radiotherapy: 0.63 and 0.0, respectively (p<0.001). The tumor location, stage, and gender did not affect the PFS. The survival rate was statistically significantly higher among the patients who had got treatment according to the ATRT-2006 protocol compared to MUV-ATRT,EU-RHAB, individual therapeutic regimens, CWS, and HIT-SKK: 0.33, 0.26, 0.11, 0.30, and 0.0, respectively; $p$=0.0020. The PFS was higher among the patients who had got intraventricular/intrathecal chemotherapy; $p$=0.0002. HDC with AuHCR did not statistically affect the PFS; $p$=0.0546.In multivariate analysis, the PFS was influenced by the age, tumor location, extent of surgery, radiotherapy, regional chemotherapy, HDC with AuHCR. Conclusions: The survival of patients with CNS AT/RT aged under 3years significantly depended on the patients' age, extent of surgery, chemotherapy protocol, radiotherapy, and regional administration of chemotherapeutic drugs.

**ATRT-07. DEFINING LOST AND GAINED TRANSCRIPTIONAL REGULATORY NETWORKS IN ATYPICAL TERATOID RHABDOID TUMOR**

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Atypical teratoid rhabdoid tumor (ATRT) is a central nervous system cancer of infancy and early childhood that may occur anywhere along the neuraxis and is associated with a high rate of mortality. While contemporary multimodal therapeutic approaches have significantly improved overall survival, targeted therapy remains elusive, and treatment is often associated with significant morbidity. ATRT is unique in its genomic stability, with the only recurrent genetic abnormality being bi-allelic loss of the *SMARCB1* gene, which encodes a core subunit of the BAF chromatin remodeling complex. The epigenetic mechanisms by which SMARCB1 loss leads to tumorigenesis are not yet well-defined and addressing this gap in understanding is necessary for creating efficacious, targeted therapeutics. To better understand the epigenetic features gained and lost in ATRT, we re-expressed SMARCB1 in a library of patient-derived and established ATRT cell lines of multiple molecular subtypes. SMARCB1 restoration significantly reduced or eliminated the proliferative and clonogenic capacity of each cell line. We performed assay for transposase-accessible chromatin with high-throughput sequencing (ATAC-Seq) and RNA sequencing (RNA-Seq) to define putative transcriptional regulatory networks that are gained and lost in ATRT. SMARCB1 restoration was associated with global changes in chromatin openness consistent with the creation of new regulatory elements throughout the genome, and these were associated with induction of a diverse developmental transcriptional signature. Motif enrichment analysis of regions with increased accessibility defined a small but consistent number of centrally enriched transcription factor motifs across cell lines indicative of putative pioneer factors whose functions may be lost in ATRT. Pertinent chromatin immunoprecipitation with sequencing (ChIP-Seq) data will be discussed in the context of lost and gained transcriptional regulatory networks in ATRT and normal cellular development.

**ATRT-08. TARGETING THE TP53-MDM2 ENHANCES RADIATION SENSITIVITY IN ATRT**

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Atypical Teratoid Rhabdoid Tumor is a highly aggressive pediatric brain tumor. Despite radiation, aggressive chemotherapy and autologous stem cell rescue, the children usually have poor survival. A functional genomic screen identified the TP53-MDM2 axis as a therapeutic vulnerability in ATRT. Gene expression demonstrates that all ATRT subgroups have high level of MDM2 a negative regulator of p53. We demonstrate that MDM2 inhibition by shRNA or with small-molecule drugs, Nutlin3 and Idasanutlin resulted in decreased ATRT cell growth, inhibition of clonogenic potential and induction of apoptosis in vitro and in vivo. MRI imaging of intracranial tumors shows that Apparent Diffusion Coefficient (ADC), a good marker for successful treatment, significantly increased with Idasanutlin treatment showing tumor necrosis. Moreover, Idasanutlin significantly decreased growth of intracranial orthotopic ATRT brain tumors as evaluated by T2 MRI imaging and prolonged survival compared to control animals. Further idasanutlin potentiated radiation induced DNA damage and increased sensitivity to radiaton of ATRT cells. These findings highlight the TP53-MDM2 axis as a rational therapeutic target in ATRT.