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INTRODUCTION: Malignant rhabdoid tumors (MRT) predominantly affect infants. Patients below six months represent a particularly challenging group: intensity of therapy is limited by toxicity to developing organs. Information on prognostic factors, toxicity and long term outcome is sparse. METHODS: Clinical, genetic, and treatment data of 100 patients (less than 6 months at diagnosis) from 13 European countries were analyzed (2005-2020). Tumors and matching blood samples were examined for SMARCB1 mutations using FISH, MLPA and Sanger sequencing. DNA-methylation subgroups (ATRT-TYR, ATRT-SHH, and ATRT-MYC) were determined using DNA methylation arrays. RESULTS: A total of 45 patients presented with ATRT, 29 with extracranial, extrarenal (eMRT) and 9 with renal rhabdoid tumors (RTK). Seventeen patients demonstrated synchronous tumors (SYN). Distant metastases at diagnosis (M+) were present in 27% (26/97). A germline mutation (GLM) was detected in 55% (47/86). Methylation subgroup status was available in 50% (31/62) of ATRT or SYN (SHH=13, TYR=13, MYC=4, SHH+TYR=1). The 5-year overall- (OS) and event free survival (EFS) rates were 23.5±4.6% and 19±4.1%, respectively. Male sex (11±5% vs. 35.8±7.4%), M+ (6.1±5.4% vs. 36.2±7.4%), presence of SYN (7.1±6.9% vs. 26.6±5.3%) and -GLM (7.7±4.2% vs. 45.7±8.6%) were significant prognosticators of 5-year OS, in univariate analysis. Molecular subgroup and survival analyses confirmed the previously described survival advantage of ATRT-TYR. In an adjusted multivariate model clinical factors that influence prognosis were: male sex [HR: 2.1 (1.2 – 3.6)], M+ [3.3 (1.8 – 6)], GLM [HR: 2 (1.1 – 3.6)] and maintenance therapy [HR: 0.3 (0.1 – 0.8)]. CONCLUSION: In this large cohort of homogenously treated infants with MRT, significant predictors of outcome were sex, M+, GLM and maintenance therapy. We confirm the need to stratify which patient group benefits from multimodal treatment, and which patients need novel therapeutic strategies. Biomarker-driven tailored trials may be a key option.

ATRT-06. ATYPICAL TERATOID RHABDOID TUMORS (ATRT): RESULTS FROM A SINGLE INSTITUTION IN BRAZIL - SÃO PAULO UNIVERSITY

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OBJECTIVES: Atypical teratoid/rhabdoid tumor (AT/RT) is a rare, highly malignant tumor of the central nervous system with poor prognosis. Nowadays, multimodal management, including surgery, chemotherapy (CMT), radiation therapy (RT) and Bone Marrow Transplantation (BMT). The aim of this study was to assess the experience and survival in a center of reference of treatment in childhood cancer in Brazil. PATIENTS AND METHODS: Medical records of AT/RT patients who underwent surgery from 2008 to 2020 at a center of childhood cancer treatment (ITACI) in São Paulo University were retrospectively reviewed and statistically analyzed. RESULTS: Eight patients (2 males and 6 females) were presented with AT/RTs. Median age during presentation was 22 months (range, 0 - 6 years). Seven patients (88%) were < 18 months and one patient were >18 months. Tumor location was supratentorial in four patients, infratentorial in 2 patients. Kidney disease as the primary diagnosis in 2 patients (25%). Surgical treatment was performed in 4 patients. Seven children underwent total CMT and 3 children were treated with RT. Only 3 patients underwent Autologous Bone Marrow Transplantation (ABMT). The chemotherapy management protocol of the patients was variable: 2 patients received the EU-RHAB protocol, 2 patients received the HEAD START III protocol, 3 patients received chemotherapy in the ICE regimen (Ifosfamide + Carboplatin + Etoposide) and 1 patient received chemotherapy in the CDDP+CTX+VCR (Cyclophosphamide + Cisplatin + Vincristine) regimen. All patients had episodes of neutropenic fever when they received chemotherapy, requiring hospitalization and use of an antibiotic treatment. Among the 8 patients analyzed, all died. CONCLUSIONS: Despite progress in treatment, AT/RT of the CNS disease or primary kidney disease associated with a lack of standardization in a regimen contributes to the dismal prognosis. There is a high mortality in patients with AT/RT, similar to that found in the literature.

ATRT-07. LOW-GRADE DIFFUSELY INFILTRATIVE TUMOR, SMARCB1-MUTANT: A CLINICAL AND HISTOPATHOLOGICAL DISTINCT ENTITY SHOWING EPIGENETIC SIMILARITY WITH ATRT-MYC

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Most atypical teratoid/rhabdoid tumors (ATRTs) occur in infants, but children and adolescents may also be affected. ATRTs occurring in older patients often comprise the molecular subgroup ATRT-MYC. Recently, central nervous system low-grade diffusely infiltrative tumor with INI1 deficiency (CNS LGDIT-INI1) has been described as a rare low-grade lesion (Nobusawa et al. Am J Surg Pathol 2020;44:1459-1468). Little is known on the molecular relationship of CNS LGDIT-INI1 and ATRT. We therefore further explored a series of six CNS LGDIT-INI1. The median age of the four males and two females was 16 years (range: 10-28 years). All tumors were of supratentorial location and showed low to moderate cellularity, diffuse growth of inconspicuous small SMARCB1-deficient tumor cells and reactive pleomorphic neuronal and glial cells with retained SMARCB1-staining in the background. In addition, two cases also displayed a high-grade rhabdoid component. After DNA isolation, purification and bisulfite conversion, samples were subjected to DNA methylation profiling (MethylationEPIC BeadChip array). Using DNA methylation-based classification and the Heidelberg Brain Tumor Classifier (version v11b4), all tumors were classified as ATRT-MYC (median calibrated score: 0.97). On t-SNE analysis, DNA methylation profiles grouped closely together in proximity to ATRT-MYC. Follow-up information was available for four cases (including the two cases with a high-grade component). Patients received heterogeneous treatments (including chemotherapy according to AT/RT protocols) and experienced stable disease or complete remission after an observation time of three to 56 months. In conclusion, CNS LGDIT-INI1 is a clinically and histologically

distinct entity with relatively favorable outcome. Nevertheless, epigenetic similarity with ATRT-MYC and the potential of malignant progression warrants close follow-up examinations. In line with recent developments of WHO nomenclature, we propose to refer to these tumors as "low-grade diffusely infiltrative tumor, SMARCB1-mutant".

ATRT-08. SMARCB1- AND SMARCA4-DEFICIENT MALIGNANT BRAIN TUMORS WITH COMPLEX COPY NUMBER ALTERATIONS AND *TP53* MUTATIONS MAY REPRESENT THE FIRST CLINICAL MANIFESTATION OF LI-FRAUMENI SYNDROME

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Atypical teratoid/rhabdoid tumor (AT/RT) is a malignant central nervous system tumor predominantly affecting infants. Mutations of *SMARCB1* or (rarely) *SMARCA4* causing loss of nuclear SMARCB1 or SMARCA4 protein expression are characteristic features, but further recurrent genetic alterations are lacking. Most AT/RTs occur de novo, but secondary AT/RTs arising in other central nervous system tumors have been reported. Malignant gliomas, IDH-wildtype, arising in patients with Li-Fraumeni syndrome typically show somatic mutations of *TP53* as well as complex copy number alterations, but little is known about loss of SMARCB1 or SMARCA4 protein expression in this context. Here we report two children, in whom malignant supratentorial brain tumors with SMARCB1-deficiency, complex copy number alterations and somatic *TP53* mutations lead to the discovery of pathogenic/likely pathogenic *TP53* variants in the germ line. Screening of the molecularneuropathology.org data set for cases with similar genetic and epigenetic alterations yielded another case with SMARCA4-deficiency in a young adult with Li-Fraumeni syndrome. In conclusion, SMARCB1- or SMARCA4-deficient malignant brain tumors with complex copy number alterations and somatic *TP53* mutations in children and young adults may represent the first clinical manifestation of Li-Fraumeni syndrome and should prompt genetic counseling and investigation for *TP53* germline status.

ATRT-09. OUTCOME AND THERAPEUTIC INTERVENTIONS IN RELAPSED AND REFRACTORY ATRT – THE EU-RHAB PERSPECTIVE

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Currently an internationally accepted consensus treatment for relapsed/refractory ATRT is missing. Little is known about relapse patterns, prognostic factors and outcome. In a recently published cohort of 143 ATRTs from the EU-RHAB registry, progression on therapy or relapse occurred in 64% (n=91). Previously published strategies for treatment failure have been restricted to individual, mostly clinically guided, attempts or early phase trials with limited sample sizes. We present a cohort of 55 patients with relapsed/refractory ATRT identified between 2015 and 2021 (total ATRT recruited n=147). Median age was 19 months; in 27.3% (n=15) a germline mutation was identified. A total of 43/55 tumors were subgrouped [60.5% SHH (n=26), 14.0% MYC (n=6), 23.3% TYR (n=10), one patient with SHH+TYR]. Salvage therapy was applied to 83.6% (46/55). Sixty therapy attempts with 17 different regimens subclassified into conventional chemotherapy, epigenetic, targeted or metronomic therapy were applied to 40/55 patients. Median overall survival (OS) was 20±1.8 weeks following the first event, median time to progression was 11±1.8 weeks. 12 months OS was 23.1%. No significant differences in survival were noted between different molecular subgroups; neither was germline mutation in SMARCB1 prognostic. Patients <12 months (n=9;16.4%) had a significantly reduced OS compared to older patients. (9±6.0wks vs. 22±3.2wks, $p<0.05$) Those who received therapy according to metronomic approaches such as MEMMAT (8/55;14.5%) survived longer than patients treated with other regimens, including epigenetic and targeted therapy. (72±36.8wks vs. 25±6.2wks, $p<0.05$) Our data provide valuable insights into a vulnerable group of patients deserving evidence based clinical management and access to clinical trials of all phases. Prospectively we aim to merge the results with data from other, international cohorts to generate more robust and valuable results.

ATRT-10. SINGLE-CELL TRANSCRIPTIONAL PROFILING OF ATRTS REVEALS HETEROGENEOUS SIGNATURES OF TUMOR AND NON-MALIGNANT CELL POPULATIONS

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Atypical Teratoid/Rhabdoid Tumors (ATRTs) are known for exhibiting high inter-tumor heterogeneity, even though they are almost all characterized by a common loss of SMARCB1 (or rarely SMARCA4). Three subgroups have been identified at bulk methylome and transcriptome level: ATRT-TYR, ATRT-SHH, and ATRT-MYC. To better understand the biology underlying each subgroup and potentially unveil their (different) cell(s) of origin, we performed single-cell transcriptomic analyses in 22 ATRTs using fresh frozen samples and both 10X and Smartseq technology. All data, grouped by technology, underwent quality control and normalization, regressing out the biases introduced by each sample. Tumor microenvironment (TME) and tumor bulk (TB) clusters were characterized by a combination of copy number variant analyses, enrichment in literature lists of marker genes for specific cell populations, and in-depth analysis of differentially enriched (DE) genes. Non-negative Matrix Factorization (NMF) was applied to TB to reveal major transcriptional profiles, which were grouped into