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Abstracts

ABSTRACT CATEGORY CODES

ATRT - ATYPICAL TERATOID RHABDOID TUMOR

RARE - CRANIOPHARYNGIOMA AND RARE TUMORS

DIPG - DIFFUSE MIDLINE GLIOMA/DIPG

DDEL - DRUG DELIVERY/PHARMACOKINETICS

EPCT - EARLY PHASE CLINICAL TRIALS

EPCT - EPENDYMOMA

EPID - EPIDEMIOLOGY

ETMR - ETMR AND OTHER EMBRYONAL TUMORS

GCT - GERM CELL TUMORS

HGG - HIGH GRADE GLIOMA

IMG - IMAGING

IMMU - IMMUNOTHERAPY

LGG - LOW GRADE GLIOMA

MEDB - MEDULLOBLASTOMA

NFB - NEUROFIBROMATOSIS AND OTHER PREDISPOSITION SYNDROMES

QOL - NEUROPSYCHOLOGY/QUALITY OF LIFE

SURG - NEUROSURGERY

NURS - NURSING

OTHR - OTHERS (NOT FITTING ANY OTHER CATEGORY

PATH - PATHOLOGY/CLASSIFICATION

LINC - PEDIATRIC NEURO-ONCOLOGY IN LOW/MIDDLE INCOME COUNTRIES

MODL - PRECLINICAL MODELS/EXPERIMENTAL THERAPY/DRUG DISCOVERY

RONC - RADIATION ONCOLOGY

SWK - SOCIAL WORK/PATIENT SUPPORT/PALLIATIVE CARE

TBIO - TUMOR BIOLOGY (NOT FITTING A SPECIFIC DISEASE CATEGORY)

THER - VIRAL/GENE THERAPY AND OTHER NOVEL THERAPIES

INSP - INVITED SPEAKERS

ATYPICAL TERATOID RHABDOID TUMOR

ATRT-01. RECONSTITUTION OF CGAS/ STING PATHWAY VIA EPIGENETIC REPROGRAMMING LEADS TO ANTI-VIRAL INFLAMMATORY SIGNALING IN ATYPICAL TERATOID RHABDOID TUMORS (ATRTS)

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BACKGROUND: Atypical teratoid rhabdoid tumors (ATRTs) are highly aggressive brain tumors that affect young children characterized by biallelic inactivation of the SMARCB1 gene. Though patients benefit from multimodal therapy, there is no improvement in overall survival which necessitates the exploration of alternative approaches. Innate-based immune and epigenetic therapies have shown benefits in several cancers. The role of innate immune signaling has not been investigated in ATRTs. Our previous data from several ATRT cell lines showed loss of expression of key innate signaling components, like cGAS and STING that are needed for sensing extracellular dsDNA. Additionally, ATRT cell lines do not respond to STING agonists, like cGAMP or ISD. RESULTS: Co-treatment of ATRT cell lines, BT-12 and BT-16 with two epigenetic modulators, panobinostat and decitabine, leads to re-expression of cGAS and STING in a time-dependent manner. Furthermore, treatment with decitabine alone leads to demethylation of several CpG sites on the STING promoter and increased expression of STING mRNA. Panobinostat and decitabine co-treatment reconstitute STING-mediated innate signaling, as measured by IRF-3 and STAT1 phosphorylation and production of ISG-15 and IFIT-1 after treatment with cGAMP, a STING agonist. Co-treatment with panobinostat and decitabine also induced expression of antiviral pro-inflammatory chemokines/cytokines in ATRT cell lines, including type III IFN, IL-6, IL-8, IL-28, and IL-29. CONCLUSION: Our data suggest that ATRT cell lines are unresponsive to innate agonists possibly due to the loss of expression of key innate immune components. However, the cGAS/STING pathway is reactivated by epigenetic drugs, specifically the combination of panobinostat and decitabine. This is further potentiated by treating with STING agonists like cGAMP. Combination treatment of ATRT cell lines with panobinostat and decitabine also induced antiviral inflammatory signaling. This response could be a potential treatment modality to inhibit tumor growth and/or mediate cancer immunotherapy in these aggressive tumors.

ATRT-02. NEUROPSYCHOLOGICAL FUNCTION IN INFANT ATYPICAL TERATOID/RHABDOID TUMOR VERSUS LOW-GRADE GLIOMA SURVIVORS REFLECTS TUMOR MALIGNANCY AND MULTIMODAL TREATMENT

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BACKGROUND: Therapy of infants with brain tumors predisposes these patients to increased risks for cognitive sequelae, especially following radiotherapy. Neuropsychological outcome gains importance for those 40-60% of patients with an atypical teratoid/rhabdoid tumor (ATRT) who survive beyond 2 years. Still, reports on cognitive late-effects in children with ATRT are scarce compared to other pediatric brain tumor groups. We analyzed neuropsychological outcome for long-term ATRT-survivors registered in EU-RHAB and infant low-grade glioma (LGG) survivors from the SIOP-LGG 2004-study and LGG-registry. PATIENTS+METHODS: Age at diagnosis of both cohorts was 0-36 months. ATRT-patients (n=13) treated with up to 54Gy radiotherapy (median age 22 months (±7.1)) were evaluated with the "ATRT-Neuropsychology" tool based on SIOPE-BTG QoS-Group recommendations at median 6.8 years (±2.8) after diagnosis. LGG-patients (n=15) treated without radiotherapy (4/15 with chemotherapy) were analyzed with the German "Neuropsychological-Basic-Diagnostic" tool 5.2 years (±0.6)

post-diagnosis. RESULTS: The ATRT- vs. LGG-cohorts were comparable for median age at diagnosis, sex-ratio and tumor-localization, though they differed slightly in median age at assessment (9.5/7.2 years (±2.5/1.1)). Results of age-appropriate tests showed increased impairments for ATRT-patients in fluid intelligence (FI) (p=.006, d=1.214) and in visual-spatial processing (VSP) (p<.001, d=2.233) compared to LGG-patients. The median for neuropsychological test results of ATRT-patients spanned from considerably below the normal to the lower normal range (median=65-90), while results of LGG-patients were mostly in the lower normal range (median=83-103). Results for psychomotor speed abilities (PMS) were distinctly below the norm for both patient groups (p=.002-.007). **CONCLUSION:** Infant ATRT- and LGG-patients develop significant impairments in PMS abilities following multimodal treatment. Long-term survivors of ATRT suffer from additional FI and VSP deficits. Our data suggest that high malignancy requiring multimodal treatment determines the inferior cognitive outcome for the ATRT-cohort. Long-term neuropsychological monitoring (and treatment options) should be implemented as standard of care in ATRT- and LGG-trials.

ATRT-03. ADAPTED TREATMENT PROTOCOL: SYNCHRONOUS ATYPICAL TERATOID/RHABDOID CNS TUMOR AND EXTRA CNS DISEASE

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Atypical teratoid/rhabdoid tumors (AT/RTs) of the central nervous system (CNS) are rare, aggressive, early childhood tumors with unfavorable prognosis. There have been 31 cases reported of children with AT/RT of the CNS and extra CNS primary tumors. In addition to its aggressive tendencies, malignant rhabdoid tumors (MRTs) of the kidney have also shown a common genetic abnormality-inactivating mutation of SMARC B1/INI-gene. We report a 22-month-old male who presented at 15 months of age with metastatic AT/RT of the posterior fossa and synchronous malignant rhabdoid tumor of the left kidney. MRI of the brain demonstrated a midline posterior fossa mass and left renal mass was noted incidentally on imaging of spine. Pathology was consistent with MRT of the kidney and pathogenic variant was found in the tumor sample, specifically SMARCB1 homozygous/biallelic deletion. Patient underwent a subtotal resection of the posterior fossa tumor and subsequent radical resection of the mass on kidney rhabdoid tumor. He was treated as per ACNS033 protocol with 2 cycles of induction with high-dose methotrexate followed by vincristine, cyclophosphamide, cisplatin, and etoposide with complete response followed by three tandem stem cell transplants with thiotepa and carboplatin for which he has been tolerating and responding favorably. Focal radiation therapy to the brain and flank area is planned at end of therapy. In a large series of synchronous AT/RTs reported in 2017 only 3 of the 31 patients were considered long-term survivors. All received a combination of high dose intrathecal or intravenous chemotherapy, total resection of at least one of the tumors, focal radiation, and autologous peripheral blood stem cell transplant. We demonstrated a case with a favorable response with our treatment. Treatment continues to be challenging given the tumor's rarity and mortality as there are no standardized protocols or randomized controlled trials.

ATRT-04. CLINICAL AND (EPI)GENETIC CHARACTERISATION OF PATIENTS WITH ATYPICAL TERATOID/RHABDOID TUMOR (ATRT) AND EXTRACRANIAL MALIGNANT RHABDOID TUMOR CONCEIVED FOLLOWING ASSISTED REPRODUCTION TECHNOLOGIES (ART)

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INTRODUCTION: Anecdotal case reports suggest an association between assisted reproduction technologies (ART) and malignant rhabdoid tumors (MRT). We performed a multi-institutional retrospective analysis of the EU-RHAB database, complemented by additional cases outside of EU-RHAB to compile clinical, (epi)genetic characteristics and outcome data of children with MRT following ART. METHODS: Data of 14 patients (from 311 patients with MRT) from 9 countries were analyzed (2010-2018). Tumors and matching blood samples were examined for *SMARCB1* mutations using FISH, MLPA and sequencing. Molecular subgroups were determined using DNA methylation arrays and correlated with a validation cohort (n=22, tumor samples of MRT; n=39 blood samples of patients small for gestational age). RESULTS: The median age at diagnosis of the 13 girls and 1 boy was 9 months (0 – 66). 8 patients with ATRT, 3 with extracranial, extrarenal-, 1 with renal rhabdoid tumor and 2 with synchronous tumors were identified. Distant metastases at diagnosis were present in 6 patients. A germline mutation (GLM) was detected in 5 patients. In 11 tumors complete data on SMARCB1 mutational status were available. DNA methylation subgrouping was available in 10 tumors and 6 blood samples. A female predominance was noted as compared to the EU-RHAB cohort with MRT born without ART (n=213, p=0.009). A total of 8 patients received gross total resection, n=12 patients received conventional chemotherapy (EU-RHAB=9, Head Start II=2, IRS III=1). Radiotherapy was applied to 6 patients. 10 patients achieved CR, and 5 remain in continuing CR. Significant genome-wide DNA methylation differences (including imprinted genes) between patients born after ART and patients born without ART could not be demonstrated. CONCLUSIONS: Long-term survival is achievable in patients who develop MRT after ART, even in cases with GLM, metastatic disease at diagnosis, or relapse. Larger epidemiological studies are needed to confirm a potential association between MRT and ART.

ATRT-05. INFANTS AND NEWBORNS WITH ATYPICAL TERATOID/RHABDOID TUMORS (ATRT) AND EXTRACRANIAL MALIGNANT RHABDOID TUMORS: A UNIQUE AND CHALLENGING POPULATION

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