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ABSTRACTS

ABSTRACTS FROM THE 2021 SOCIETY FOR NEURO-ONCOLOGY PEDIATRIC NEURO-ONCOLOGY RESEARCH CONFERENCE

Submission Categories and Abbreviations

ATRT – ATYPICAL TERATOID RHABDOID TUMORS
BIOL – BASIC BIOLOGY
EMBR – EMBRYONAL TUMORS
EPEN – EPENDYMOMA
GERM – GERM CELL TUMORS
HGG – HIGH GRADE GLIOMA
IMMU – IMMUNOLOGY/IMMUNOTHERAPY
LGG – LOW GRADE GLIOMAS
TMOD – MODELS
OMIC – OMICS
RARE – RARE TUMORS/OTHER
EPCT – TRANSLATIONAL/EARLY PHASE CLINICAL TRIALS

ATRT

ATRT-01. IDENTIFICATION OF MICRORNA-BASED PROGNOSTIC BIOMARKERS AND CANDIDATE THERAPEUTIC AGENTS FOR ATYPICAL TERATOID/RHABDOID TUMOR

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Background: MicroRNA (miRNA) has been found to be involved in development of many malignant pediatric brain tumors, including atypical teratoid/rhabdoid tumor (AT/RT) that is highly aggressive and carries a dismal prognosis. The current study investigated the potential value of miRNAs and pivotal genes associated with AT/RT using bioinformatics analysis, aiming to identify new prognostic biomarkers and candidate drugs for AT/RT patients. Methods: Differentially expressed miRNAs (DEMs) and genes (DEGs) between AT/RT and normal control samples were obtained from GEO database. The target genes of DEMs were predicted via TargetScanHuman7.2 and miRDB, and then intersected with DEGs. Gene Ontology and Kyoto Encyclopedia of Genes and Genomes analyses of overlapping genes were conducted, followed by construction of protein-protein interaction network. Hub genes were determined by Cytoscape 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-02. THE DUAL MTORC1/2 INHIBITOR, TAK-228 COMBINES SYNERGISTICALLY WITH THE BH3 MIMETIC, OBATOCLAX TO IMPROVE SURVIVAL IN MICE BEARING ORTHOTOPIC XENOGRAFTS OF AT/RT

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mTOR activation drives tumorigenicity by regulating transcription factor expression and downstream growth and survival pathways. We have previously shown that mTORC1 and mTORC2 are highly activated in AT/RT and the dual mTORC1/2 inhibitor, TAK-228 (Sapanisertib) improves survival in mice bearing orthotopic xenografts of AT/RT. To design a rational combination therapy that enhances TAK-228's efficacy and durability, we performed RNASeq 4 hours after TAK-228 treatment of AT/RT cell models. Pathway analysis revealed disruption of the NRF2-mediated stress response. NRF2 is a cap'n'collar leucine zipper transcription factor that regulates expression of genes involved in redox homeostasis, energy metabolism, cell proliferation, and survival. Analysis of publicly available RNASeq data on 32 human tumors identified elevated expression of NRF2 in AT/RT (median expression 40.78, normal brain 18.81). Short-hairpin knockdown of NRF2 decreased the expression of NRF2 as well as the anti-apoptotic proteins MCL-1, BCL-xL, and BCL-2 (western blot), and intracellular concentrations of reduced glutathione ($p<0.005$, *t*-test). TAK-228 similarly decreased expression of NRF2, MCL-1, and glutathione ($p<0.005$, *t*-test) demonstrating that TAK-228 compromises AT/RT defenses against oxidative stress and cell death. The brain-penetrant BH3 mimetic, Obatoclax increases oxidative stress and induces apoptosis in AT/RT (MUSE oxidative stress, cPARP western blot, *t*-test $p<0.05$). These complementary mechanisms of action synergize to slow AT/RT cell growth (MUSE Cell viability assay, ANOVA $p<0.05$) and induce high rates of cell death (MUSE ANNEXIN V assay, ANOVA $p<0.05$, Western blot for cPARP, Compusyn Synergy analysis CI<1.0). Once-weekly treatments of TAK-228 combined with Obatoclax in orthotopic mouse models of AT/RT is well tolerated, slows tumor growth (bioluminescence imaging, ANOVA $p<0.05$) and significantly extends median survival from 35 to 55 days (Log-rank $p<0.05$). These findings support a new clinical trial aimed at improving AT/RT survival.

ATRT-04. CORRELATION OF CLINICOPATHOLOGIC FEATURES AND CUMULATIVE INCIDENCE OF RELAPSE FOR PATIENTS WITH ATYPICAL TERATOID RHABDOID TUMOR ON ACNS0333: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP

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Purpose: Intensive multi-modal regimens have improved survival for patients with atypical teratoid rhabdoid tumor, however relapse rates remain high. A better understanding of clinical and pathologic features associated with tumor relapse is critical to risk-stratifying patients. Patients and Methods: ACNS0333 treatment consisted of multi-agent chemotherapy, high-dose chemotherapy, and radiation therapy, lasting approximately 6 months. Variables including patient age, sex, tumor location, M-stage, degree of resection, order of therapy, germline status, and molecular subgroup were analyzed. Cumulative incidence (CI) of event free survival due to relapse was evaluated for each variable. Results: Thirty-three of 65 evaluable patients had tumor relapse. For the entire cohort, the CI of relapse was 21.8% at 6 months, 40.6% at one year and 50.3% at 4 years. For patients with infratentorial tumors, CI of relapse was 26.3%, 34.2% and 37.2%, at 6 months, 1 and 4 years respectfully compared to 15.3%, 49.9%, and 69.7% for those with supratentorial tumors (p 0.051). Patients with SHH subtype had no relapses in the first 6 months and CI of relapse of 37.5% at 4 years, while those with TYR and MYC subgroups had CI of relapse of 33.3% and 26.7% at 6 months and 46.3% and 73.3% at 4 years respectfully (p 0.088). Patients with germline mutations had a cumulative incidence of relapse of 20% at 6 months and 60% at 12 months compared to 22.6% and 37.7% respectfully for those without. No obvious trends were noted based on other analyzed variables. Conclusions: ACNS0333 was not powered to determine prognostic indicators of relapse, however, this data suggest interesting trends based on tumor location, subtype and germline status. Infratentorial location and SHH subtype maybe associated with lower risk of relapse. Larger data sets must be compiled to further investigate these variables, perform multivariate analyses and inform risk-stratification on future trials.

ATRT-05. REPURPOSED ANTI-MALARIAL QUINACRINE ACTIVATES P53 AND INHIBITS ATRT TUMORIGENICITY

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Atypical teratoid rhabdoid tumors (ATRTs) are fatal pediatric brain tumors that warrant improved therapies urgently. ATRTs are characterized by loss of INI1, a subunit of the SWI/SNF chromatin-remodeling complex. ATRTs grow aggressively despite majority of primary tumors expressing