IMMU-19. HDAC INHIBITORS SENSITIZE MYC-AMPLIFIED MEDULLOBLASTOMA TO IMMUNOTHERAPY BY ACTIVATING THE NF-KB PATHWAYS

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Medulloblastoma is the most common malignant brain tumor in childhood and comprises four distinct molecular subgroups with further layers of intertumoral heterogeneity. Amplification of the oncogene MYC drives tumorigenesis and constitutes a hallmark feature underlying Group 3 biology. Employing our in-house drug screening pipeline, we evaluated a library of existing HDAC inhibitors (n=78) in various brain tumor models (n=6) to identify potential second-line HDAC inhibitor candidates. As a result of this study, we identified a highly potent and selective HDAC inhibitor, PCI-34043, which inhibited the viability of various tumor cell lines, including medulloblastoma, with an IC50 in the low nanomolar range. In a xenograft model, PCI-34043 significantly suppressed tumor growth and increased T-cell infiltration, indicating a promising therapeutic potential for medulloblastoma.

CONCLUSION: PCI-34043 represents a promising second-line HDAC inhibitor for medulloblastoma treatment.

IMMU-20. EVALUATION OF CAR T CELLS IN EPENDYMOMA

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BACKGROUND: Ependymoma is the third most common pediatric brain tumor and current treatment still results in a 10-year relapse rate of over 70% in the highest risk groups. The treatment refractory nature of ependymoma to standard therapies strongly supports the development of novel interventions. Ependymoma tumor cells express HER2 and there are active clinical trials treating children with ependymoma using local delivery of second-generation HER2 CAR T cells. METHODS: Two high-risk patient-derived ependymoma cell lines, MAF811 and MAF928, that display CD47 expression were used for testing. The HER2 protein expression was confirmed using western blot analysis. RESULTS: HER2 CAR T cells were effective in killing tumor cells in vitro and in vivo. RESULTS: HER2 CAR T cells effectively kill ependymoma tumor cells in culture, but this strategy cannot eradicate the same tumor cells in mice when implanted in the fourth ventricle of the brain. HER2 CAR T cells proliferate and traffic into the tumor, but this causes a dramatic influx of immune cells, tumor swelling and lethal toxicity in a subset of mice. Mice that survive this initial tumor swelling, display significant tumor shrinkage but all tumors eventually start growing again. Ependymoma tumor cells release large amounts of inflammatory chemokines that strongly attract neutrophils and monocytes to the tumor, compared to other brain tumors, and can downregulate HER2 expression to escape recognition by CAR T cells. CONCLUSION: The immunosuppressive microenvironment as well as tumor heterogeneity may make HER2 CAR T cells ineffective in ependymoma. Studying these two hurdles in CAR T cell therapy is critical to effectively treat brain tumors with CAR T cells.

IMMU-21. INVESTIGATION OF WHITE BLOOD CELL CHARACTERISTICS IN CSF SAMPLES AT PEDIATRIC BRAIN TUMOR DIAGNOSIS

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BACKGROUND: There has been a recent surge in investigation of immune cell characteristics in pediatric brain tumors. However, this work is incompletely defined. We hypothesized that investigating an understudied dataset, WBC and differential results in CSF drawn at the time of pediatric brain tumor diagnosis to look for microscopic metastases, would provide insight into the role of immunology and potential for immunotherapy in these diseases and correlate with prognosis and/or metastasis. METHODS: We conducted a retrospective comparison analysis of CSF values in 349 patients at our institution from samples drawn within 60 days of initial CNS tumor diagnosis from 1998–2018. We examined total nucleated cell count, absolute counts and percentages for WBC subtypes. We compared CSF values from tumor cell presenting patients to non-presenting patients, and their disease group: atypical teratoid rhabdoid tumor, ependymoma, germinoma, high-grade glioma (HGG), low-grade glioma (LGG), medulloblastoma, non-germinomatous germ cell tumor, and other embryonal tumors (OET). We used Wilcoxon and Kruskal-Wallis tests for comparisons. RESULTS: Overall, higher lymphocyte percentage (p=0.002) and lower monocyte percentage (p=0.007) were associated with survival. WBC characteristics did not differ significantly based on tumor cell presence. Compared to medulloblastoma, ependymoma showed a more active CSF immune response while HGG, HGG, and OET showed a less active response, based on total WBC and absolute neutrophil count (p=0.001–0.007). CONCLUSIONS: Higher lymphocyte and lower monocyte percentages in CSF correlated with better prognosis overall; causality requires further investigation. Tumor subtypes varied in their immune status in all patients offering potential insight into which will be amenable to immunotherapy.

IMMU-22. PHASE IB IMMUNOTHERAPY CLINICAL TRIAL WITH THE USE OF AUTOLOGOUS DENDRITIC CELLS PULSED WITH AN ALLOGENIC TUMORAL CELL LYSATE IN PATIENTS WITH NEWLY DIAGNOSED DIFFUSE INTRINSIC PONTINE GLIOME (DIPG)

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BACKGROUND: Diffuse intrinsic pontine glioma (DIPG) is a lethal condition, and therefore novel approaches are needed. Myeloid-derived dendritic cells (mDCs) pulsed with tumor antigens, as professional antigen-presenting cells, are a promising strategy for immunotherapy of invasive brain tumors. METHODS: Our Ib pilot study explored the use of immunotherapy with mDCs for the treatment of newly diagnosed DIPG. Patient’s mDCs were extracted after irradiation and were primed with an autologous tumor lysate from five patients with K27M-mutated DIPG. The principal goal of this study was to establish the feasibility and safety of the intradural administration of these mDC vaccines in patients with DIPG. In the absence of progression, patients received maintenance boosts of tumor lysate. Additionally, we evaluated the non-specific and antitumoral immune response generated in peripheral blood mononuclear cells (PBMC) and in cerebrospinal fluid (CSF) cells. RESULTS: Nine patients were included in the study (2016–2018). Vaccines fabrication was feasible and administered in all cases without severe side effects. Furthermore, DBLs (89% of patients) specific responses were identified in PBMC. Immunological responses were also confirmed in T-lymphocytes from the CSF of two patients. Twenty-four months overall survival and progression free survival was 33.3% (95% CI 14.1% to 52.5%) and alive overall and progression free survival was 50% (95% CI 20.1% to 79.9%) respectively. DISCUSSION: Our results demonstrate that mDC vaccination is feasible, safe, and generates a DIPG-specific immune response detected in PBMC and CSF. There was a trend in improved OS when compared to historic controls. This strategy shows a promising immunotherapy backbone for future combination schemas.

IMMU-23. A NOVEL MASS CYTOMETRY-BASED MULTIPLE-PARAMETER CHARACTERIZATION OF NEONATAL-REACTIVE CD8+ T-CELLS IN PATIENTS PARTICIPATING IN PNOC007 H3.3K27M PEPTIDE VACCINE CLINICAL TRIAL

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BACKGROUND: We have identified an HLA-A*02:01-restricted neoantigen epitope encompassing the H3.3 K27M mutation and implemented a multi-center clinical trial of the peptide vaccine through the Pacific Pediatric Neuro-Oncology Consortium (PNOC007) for patients with diffuse midline glioma (DGM), including diffuse intrinsic pontine glioma (DIPG). We sought to characterize vaccine-reactive CD8+ T-cells subpopulations post vaccination preclinical development and in pediatric brain tumor associations with clinical outcomes. METHODS: Mass cytometry (CyTOF) analysis was performed on patient-derived peripheral blood mononuclear cells collected at baseline as well as pre-specified time points throughout the study. Each cell subtype was characterized via tSNE-Clustering based on their expression profiles and quantified as a fraction of total CD8+cells. H3.3K27M-reactive CD8+ T-cells were evaluated using an H3.3K27M-
Immune checkpoint inhibitors that target programmed death receptor-1 (PD-1) have recently been shown to be a promising option for the management of recurrent mismatch repair (MMR) deficient GBM following radiotherapy. A 9-year-old boy who presented with a 6 cm fronto-temporo-parietal lobe mass, history of frontal headaches and was found to have a left frontal lobe mass. Pathology obtained from a gross total resection (GTR) was consistent with classic GBM, WHO Grade IV. Neoantigenic peptides following initial radiation therapy were evaluable for local recurrence. The patient underwent another GTR of the tumor at our center. While pathology again confirmed GBM, GlioSequencing of tumor tissue from second resection showed MSI-H, NF2 mutation p.R338H, NF1 mutation p.R2450* and p.I193Yfs*11, TP53 mutations p.R133* and p.R273C, EGFR mutation, and multiple variants of uncertain significance. Germline testing was negative for MMR deficiency or other deleterious mutations. Parents opted to defer radiotherapy and consented to monotherapy treatment with Nivolumab (Opdivo, BMS pharmaceuticals). A few months later, a PD-1 inhibitor was added at a dose of 3 mg/kg administered every two weeks. Our patient is now 22 months post-second resection and continues to receive Nivolumab without evidence of recurrent disease or adverse autoimmune effects from PD-1 blockade. He has remained in school with good academic performance and has exhibited no regression of functional status during the entirety of his treatment course. This case provides evidence of possible efficacy of PD-1 blockade without focal radiotherapy in this child with GBM and somatic MSI instability.