EPCT-23 PRE-CLINICAL STUDY OF FOCUSED ULTRASOUND-MEDIATED BLOOD-BRAIN BARRIER OPENING AND PANOBINOSTAT FOR DIFFUSE INTRINSIC PONTINE GLIOMA TREATMENT

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Diffuse intrinsic pontine glioma (DIPG) is the lethal high-grade brain tumor in children with no effective treatment options to date. Despite excessive clinical trials, the prognosis remains poor, with a median overall survival (mOS) of less than 1 year. Genomic studies of DIPG tissue have identified highly recurrent mutations in genes encoding histone H3 resulting in the substitution of lysine to methionine at position 27 (K27M), which is found in approximately 80% of DIPG. Recent drug screening studies identified the histone deacetylase (HDAC) inhibitors panobinostat as a highly effective drug against DIPG in vitro. However, due to the poor Blood-Brain Barrier (BBB) penetration of systemic administration, to enhance the delivery of panobinostat to improve treatment efficacy is needed. Focused ultrasound (FUS) has been shown to be able to safely and non-invasively open BBB to enhance drug delivery. Hence, in this study, we hypothesize that FUS-mediated BBBO (BBBO) can enhance the delivery of panobinostat for a therapeutic benefit in DIPG. Herein we established the syngeneic DIPG model by intracranially injecting mouse DIPG cells (PDGFB+, H3.3K27M, p53−/−) and used FUS and microbubbles to open BBB and enhance the panobinostat delivery. Magnetic resonance (MR) imaging was utilized to evaluate BBBO and tumor progression. We first demonstrated that FUS-mediated BBB-opening is safe and feasible to mice with DIPG tumors by MR imaging and passive cavitation detection. Moreover, this DIPG cell line is very sensitive to panobinostat in in vitro cytotoxicity assay. The combined treatment of FUS-mediated BBBO and panobinostat showed benefits in both local control and overall survival. The current results demonstrated FUS could increase the treatment efficacy of panobinostat to DIPG animals may be due to the increase of targeted delivery of systemic panobinostat to DIPG tumors in brainstem.

EPCT-24 THE REMIND TRIAL: MULTI-ANTIGEN TARGETED T CELLS FOR PEDIATRIC CNS TUMORS

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Background: Patients with relapsed CNS malignancies or DIPG face terrible prognoses. We hypothesized that T cells specific for 3 tumor-associated antigens (TAA), WT1, PRAME and survivin, would be safe and elicit anti-tumor immunity. Methods: Patients (n=18) received autologous tumor antigen-associated T cells (TAAT) (up to $8x10^7/m^2$) for newly diagnosed DIPG (Group A) or recurrent CNS malignancies (Group B) on a Phase I dose-escalation study (NCT03652545) and were monitored for safety and response. Results/Discussion: 16/18 patients who received TAAT completed the 45-day safety monitoring phase with no dose-limiting toxicities. Adverse events were minimal despite multiple pretreatments in Group B. Infused cells were predominantly CD3+ T cells (median 96%; range: 87–99%), with CD4+ and CD8+ comprising 16% (range: 5–87%) and 40% (range: 4–67%) respectively. Specificity for 1–3 TAAs was demonstrated in 11/18 TAAT by a-IFN-γ ELISPOT. Dose escalation is complete, and clinical and immunologic response assessments are ongoing. Plasma cytokine and proteomic analyses demonstrated dynamic post-infusion immune cytokine and protein responses. Consistent with an infusion-mediated immune response all patients in Grp A showed increased T cell effector, inflammatory and immune-stimulatory cytokines IFN-γ, TNF-α, IL-2, IL-5, IL-7, IL-1β, IL-6, IL-8, IL-12p70, IL-17A and GM-CSF at Weeks 1 and 2 post-infusion (n = 6). Of 9 patients who have been tested, 29/92 plasma proteins showed significant differences between dose levels 1 and 2, including increased IL-7 (p <0.0004) and CD40L (p <0.046) and reduced IL-4 (p <0.0004). T cell receptor sequencing showed expansion and persistence of clones detected in infusion products. In summary, TAAT have thus far been safe and elicit immune responses in vivo. Clinical and immunologic response assessments are ongoing.

EPCT-25. SMO PROTEIN DEPLETION IN SHH MEDULLOBLASTOMAS USING MICROBUBBLE-ENHANCED ULTRASOUND AND SIRNA LOADED CATIONIC NANOPARTICLES

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RNA-based therapies offer unique advantages for treating pediatric brain tumors. However, the systemic delivery remains a major problem due to degradation of unmodified RNA in biological fluids, poor brain accumulation, and poor cancer cell uptake or escape from the endosomal lipid bilayer barrier. While nanoparticle encapsulation can prolong circulation time and facilitate cellular uptake, their accumulation in brain tumor remains particularly poor due to their low permeability across the blood-brain barrier and limited intratumoral penetration. Focused ultrasound, when combined with circulating microbubbles (MB-FUS) provides a physical method to transiently modulate the brain tumor microenvironment (TME) and improve nanoparticle delivery. Here, we have examined the delivery of siRNA targeting the Smoothened (SMO) pathway, packaged in 50 nm cationic lipid-polymer hybrid nanoparticles (cLPH:siRNA-SMO), combined with MB-FUS in murine SmoA2 sonic hedgehog (SHH) medulloblastoma. At 30 hours after treatment, we observed the depletion of the SMO protein target, responsible for driving SHH medulloblastoma formation and growth, in mice that had received treatment with MB-FUS and cLPH:siRNA-SMO, but not with cLPH:siRNA-SMO alone. We also confirmed that SMO protein depletion was spatially achieved in the tumor regions with detected cLPH:siRNA-SMO using FISH assay, and that there was 15 fold induction of tumor cell apoptosis compared to tumors in mice that had received cLPH:siRNA-SMO alone. The limited induction of apoptosis was observed with either cLPH:siRNA (non-targeting) or MB-FUS and cLPH:siRNA (non-targeting), suggest that the observed apoptosis induction in the SmoA2 model was the direct result of SMO depletion rather than nonspecific effects of MB-FUS or cLPH:siRNA. Our findings provide a paradigm shift in drug delivery in brain tumors, where physical methods and nanotechnology are tuned together to develop rational strategies for the effective delivery of nucleic acids in brain tumors.