- 25% of the total activity. The injected dose was adapted to the size of the resection cavity. Dosimetry was performed with planar whole-body scintigraphy and SPECT/CT 12h, 24h, 48h, 76h and 5-7 days after injection. RESULTS: Patient 1 (IDH1-Mutation) received three doses of RIT (total of 592 MBq) with stable disease 12 months after therapy and 26 months after initial diagnosis. Patient 2(IDH-Wildtype) had histologically proven tumor progression after the second cycle (total of 526 MBq). Patient 3 (IDH-Wildtype) has so far received one cycle of RIT (327 MBq of a planned total of 1300 MBq). No toxicity according to CTCAE version 6.0 or other adverse events related to RIT were observed. Dosimetry did not reveal absorbed doses above the upper dose limits for organs at risk. CONCLUSIONS: Intracavitary radioimmunotherapy with Lu-177 labeled 6A10-Fab fragments appears to be a safe maintenance therapy for glioblastoma patients, albeit only assessed in three compassionate use situations far. A multicenter confirmatory phase-I-trial will be was initiated in May 2022 (EudraCT-No: 2015-004417-25) to determine the maximum tolerated dose and safety of adjuvant RIT with Lu-177 labeled 6A10-Fab fragments.

DDEL-10. ULTRASOUND-ENHANCED DRUG DELIVERY IN HUMANS ALTERS ENDOTHELIAL PHENOTYPE AND PERTURBS THE ULTRASTRUCTURE OF THE BLOOD BRAIN BARRIER

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The use of low-intensity pulsed ultrasound with concomitant injection of microbubbles (LIPU/MB) achieves local and reversible opening the blood-brain barrier (BBB), enhancing the delivery of systemically administered drugs to the brain parenchyma. Electron microscopic studies conducted in animals proposed that LIPU/MB enhances paracellular diffusion across the cerebral vasculature, by disrupting tight junction proteins between endothelial cells, as well as enhancement of caveolar transcytosis. The effects of LIPU/MB on the ultrastructure of the human BBB and cerebral endothelial phenotype have not been systematically investigated. Here we report a first in-human electron microscopic study, examining endothelial phenotype and BBB ultrastructure in the peri-tumoral brain of humans after undergoing LIPU/MB-enhanced drug delivery. Non-eloquent peritumoral brain was biopsied at different time points (4-63 minutes) following an intraoperative LIPU/MB procedure in three patients who underwent a surgical resection of recurrent glioblastoma through a phase I clinical trial [NCT04528680]. Transmission electron microscopy was used to examine cross sections of the microvasculature and associated components of the BBB. We observed a significant ($P = 0.0397$) time-dependent decrease in the frequency of endothelial caveolae immediately after sonication compared to non-sonicated control vessels, which resolved within 1 hour of treatment. We also observed a time-dependent increase in membrane-bound vacuoles in the endothelial cytoplasm following sonication ($P = 0.0002$, one-way ANOVA). Sonicated blood vessels occasionally showed swollen astrocytes, convoluted luminal protections, and lightening of otherwise dense tight junction proteins, not frequently observed in non-sonicated biopsies from the same patients. Our study shows that LIPU/MB changes the endothelial phenotype within the cerebral vasculature, and suggests the accumulation of vacuoles in endothelial cells after BBB opening.

DDEL-11. DETERMINING THE DOSE OF REGADENOSON MOST LIKELY TO TRANSIENTLY ALTER THE INTEGRITY OF THE BLOOD-BRAIN BARRIER IN PATIENTS WITH GLIOMAS

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BACKGROUND: The blood brain barrier (BBB) is a major obstacle to the delivery of chemotherapy to the CNS. Regadenoson is an FDA approved adenosine A2 agonist used for cardiac stress tests. In murine models, it transiently increases BBB permeability to a 70KD dextran. This multi-institutional, NIH funded, Adult Brain Tumor Consortium trial was designed to discover a dose of regadenoson that substantially increases vascular permeability in normal appearing white matter (NAWM) where drug delivery is particularly challenging. METHODS: Adults ages 18-45 with supratentorial gliomas at low-risk for regadenoson complications were recruited ($n = 7$). One patient was treated at each of seven dose levels (from 0.05 to 1.4 mg) that are known to be safe in humans. The primary outcome measure is change in vascular permeability via dynamic contrast enhanced (DCE) perfusion MRI estimates of K^{trans}. The primary outcome measure was a 10-fold higher K^{trans} in NAWM than reported in literature ($K^{trans} > 0.04$ min^{-1}). Contrast-enhanced T1 subtraction map estimates of change in contrast enhancement and other measurements in normal brain and non-enhancing tumor were quantified. RESULTS: K^{trans} measures in NAWM averaged $1.13\text{x}10^{-3} \pm 0.44\text{x}10^{-3}$ (SEM) min^{-1}, lower than the target of 0.04 min^{-1}. Normalized, contrast enhanced T1-weighted MR signal intensity in NAWM increased an average of 74.0 ± 22.4% min^{-1} (SEM) min^{-1}, which was significantly higher than zero ($P = 0.0163$). Data available from this limited sample failed to meet the target goal in K^{trans} increase or change in contrast enhancing signal intensity. CONCLUSION: Administration of regadenoson at seven different doses did not significantly elevate K^{trans} for gadolinium in NAWM. This data suggests that single doses of regadenoson are unlikely to substantially increase the delivery of therapeutic agents in non-enhancing brain tissue. This trial design is appropriate for further human testing of other regadenoson schedules and other novel approaches aimed at transiently modifying BBB permeability.

DDEL-12. QUADRUPLE CARBON DOT NANO MODEL FOR ENHANCED TUMOR TARGETING AND DUAL DRUG DELIVERY FOR THE TREATMENT OF PEDIATRIC HIGH-GRADE GLIOMAS.

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High-grade gliomas remain among the most lethal neoplasms. Nanotechnology aims to Improve drug targeting and efficacy. Here we developed a quadruple nano-model (QNM) that specifically targets pediatric high-grade glioma cells and delivers chemotherapies to the cell nucleus. This carbon dot based QNM were fabricated by covalently attaching two drugs (epirubicin and temozolomide) and two targeting peptides. ShPep-1 peptide binds to the IL-13Rα2 receptors allowing for cellular import while lnPep-1h peptide delivers the DNA damaging drugs to the nucleus. Despite demonstrating the lowest measurable drug content (23.3%), the dual peptide linked QNM induced significantly greater cell death than single peptide linked conjugates suggesting enhanced cell uptake. Greatest effect was observed in glioblastoma (SJ-GBM2) and diffuse intrinsic pontine glioma (NP53) cells with IC50s of approximately 60 nM, 3-6-fold lower than single peptide conjugates. Imaging studies using FITC-conjugated carbon dots confirmed the dual peptide conjugate demonstrated greatest cellular uptake and nuclear localization.

DDEL-13. ULTRASOUND-ENHANCED DELIVERY OF LIPOSOMAL DOXORUBICIN ACROSS THE BLOOD BRAIN BARRIER INDUCES AN IFN-GPHENOTYPE IN MICROGLIA, MACROPHAGES, AND T CELLS AND IMPROVES RESPONSE TO PD-1 BLOCKADE IN GLIOMAS

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INTRODUCTION: Given the limited drug penetration across the blood-brain barrier (BBB), the therapeutic potential of new and existing therapies has not been fully exploited for the benefit of glioblastoma (GBM) patients. METHODS: Here we employed a novel drug delivery technology based on low-intensity pulsed ultrasound combined with intravenous microbubbles (LIPU/MB) that temporarily opens the BBB to deliver liposomal doxorubicin (DOX) and anti-PD-1 therapy (aPD-1) in mouse glioma models and 3 recurrent GBM patients. Immunological variables were evaluated in tumor and immune cells as well as efficacy in glioma-bearing mice treated with DOX delivered by LIPU. These included measurement of HLA ABC and HLA DR protein expression by tumor cells, microglia, and macrophages and IFN-g production by glioma-associated microglia and macrophages in mouse and human tumors. We also assessed efficacy of LIPU/MB enhanced combination therapy in glioma-bearing mice. RESULTS: Upregulation of HLA ABC and HLA DR was observed in GBM cell lines at low concentrations of DOX. Tumor cells from GBM patients treated with DOX, aPD-1 and LIPU/MB showed increased expression of HLA ABC and HLA DR compared to paired pretreatment samples. In both mice and humans, LIPU/MB liposomal DOX increased absolute brain drug concentrations and elicited a specific IFN-g phenotype and MHC I expression in glioma-associated microglia and macrophages in mice and humans. Furthermore, LIPU/MB-mediated BBB opening increased brain concentrations of aPD-1 in mice and in peritumoral regions of GBM patients. Combined treatment with liposomal DOX and aPD-1 delivered with LIPU/MB resulted in long-term survival of glioma-bearing mice that relied on the activity of $CD8^+$ T cells for its efficacy. CONCLUSIONS: Overall, this translational study demonstrates the utility of LIPU/MB to stimulate intracranial immune responses in the context of treatment with DOX and aPD-1 for gliomas.