INTRODUCTION: Malignant cells of the central nervous system (CNS) have had largely unchanged survival outcomes despite decades of research. Recently, viral-based therapies have shown some benefit for patients with CNS malignancies in early clinical trials. Adenovirus has been demonstrated as safe and is currently being examined in several phase I and II clinical trials. We recently demonstrated that adenovirus expressing CD40L, and CRead67-CD40L, would maintain this survival benefit in multiple murine models for high grade glioma while decreasing on-treatment toxicity. METHODS: We examined the utility of conditionally replicative adenovirus expressing CD40L in both in vitro and in vivo studies. Human cell lines from diffuse intrinsic pontine glioma (DIPG) and glioblastoma were used to confirm infectivity and CD40L expression, and synergistic murine models of glioma were evaluated for toxicity and survival following intratumoral injection of a conditionally replicative adenoviral vector. RESULTS: CRead67-CD40L generated strong expression of CD40L in human in vitro DIPG XLI and U251 cell lines and induced MHCCII expression on CD11c+ DC's in U251/DCCo-culture. Further, in syngeneic murine models of glioma, conditionally replicative adenoviral treatment significantly reduced toxicity while retaining survival efficacy. CONCLUSIONS: Given these promising results as well as the critical need for novel therapeutics in CNS malignancies, we are now progressing human trials targeting pediatric HGG, an unmet need in pediatric neuro-oncology. This would be the first-in-human study using CRead67-57-CD40L in pediatric HGG. In this Phase 1 clinical trial, we hypothesize that intratumoral injection of CRead67-CD40L will cause selective expression of CD40L, increased infiltration of immune cells into the tumor, and safely enhance tumor clearance.

SAFETY AND FEASIBILITY OF RHEINIUM-186 NANOLOPOSOME (186RN) IN LEPTOMENINGEAL METASTASES [LM] PHASE 1/2A DOSE ESCALATION TRIAL

Abstracts

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PROMISING TREATMENT FOR RECURRENT PEDIATRIC HIGH GRADE GLIOMA

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INTRODUCTION: Low-grade gliomas (LGGs) are the most common primary brain tumors in children. Although LGGs have a relatively indolent natural history, their overall survival is modest. Superior outcomes in the setting of recurrent disease, however, are rare. Therefore, identification of effective treatment options for recurrent pediatric HGG continues to be a high-priority unmet need in pediatric neuro-oncology. 186Rhenium (186Rhenium) emits beta particles (with gamma-rays) with low dose rate and high radiation energy, and has shown promising results both in vitro and in vivo. This study was designed to evaluate the safety and tolerability of a single intrathecal (IT) 186Rhenium administration, following intratumoral injection of a conditionally replicative adenoviral vector that expresses CD40 ligand (CD40L) and tumor necrosis factor α (TNF-α) fused to the Penetratin leader peptide to enhance delivery into the tumor, and safely enhance tumor clearance.

METHODS: This single-center phase 1/2 dose escalation trial evaluated the safety and tolerability of single IT doses of 186Rhenium administered to adult patients (≥18 years) with recurrent high grade glioma. Participants were enrolled from two centers (Southwestern, Dallas, TX, USA and Case Western Reserve University, Cleveland, OH, USA). The primary safety outcome was the number of patients experiencing adverse events (AEs) and serious AEs (SAEs) up to 28 days following treatment.

RESULTS: Thirteen patients were enrolled on 186Rhenium. Median age was 44 years (range: 27–74). All patients had chemotherapy and radiation prior to enrollment. Eleven (85%) patients had undergone at least one surgical resection, and 10 (77%) had undergone repeated surgical interventions with gadolinium-enhanced magnetic resonance imaging (MRI) showing progression of malignant disease. Median number of prior chemotherapies and radiation therapies were 3 (range: 2–5) and 2 (range: 1–4), respectively. Eleven (85%) patients had undergone at least one prior intratumoral injection of an adenoviral vector expressing CD40L (Adeno-CD40L) with 10 (77%) patients receiving at least two prior Adeno-CD40L injections. Based on this single center phase 1/2A dose escalation trial, we hypothesize that intratumoral injection of CRad67-CD40L will cause selective expression of CD40L, increased infiltration of immune cells into the tumor, and safely enhance tumor clearance.

SUPERVISED MACHINE LEARNING IDENTIFIES RISK FACTORS ASSOCIATED WITH LEPTOMENINGEAL DISEASE AFTER SURGICAL RESSECTION OF BRAIN METASTASES

Purpose: To provide a comprehensive retrospective analysis of clinical and pathological predictors of leptomeningeal disease (LMD) after resection of brain metastases (BM).

Methods: A retrospective case-control analysis of 318 patients who underwent resection of BM at Mayo Clinic, Rochester, MN, USA was conducted. The control group consisted of 159 patients who did not develop LMD after BM resection, whereas the case group included 159 patients who developed LMD. Multivariate analyses with a stepwise approach were conducted to identify risk factors. Survival analysis was performed with Kaplan-Meier and logrank tests.

Results: The univariate analysis and multivariate logistic regression analysis identified several predictors of LMD including the presence of leptomeningeal disease at time of surgery, tumor grade, histology, number of BM, and primary site. The presence of extracranial disease was associated with decreased risk of LMD.

Conclusion: The identification of clinically relevant risk factors for LMD after BM resection can help provide a risk score that may be used to guide the decision on further treatment and surveillance after BM resection.
LOCL-07
LOCO-REGIONAL INFUSION OF GB-13 (IL13.E13K-PE4E) AS A POTENTIALLY PROMISING TREATMENT FOR RECURRENT HIGH-GRADE GLIOMA
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INTRODUCTION: High grade gliomas (HGG) are devastating diseases with largely unchanged survival outcomes despite decades of research. Recent studies suggest the interleukin 13 receptor subunit alpha 2 (IL13Rα2) is selectively upregulated in up to 80% of HGGs, including glioblastoma (GBM) and diffuse midline gliomas (DMG) harboring H3K27 alterations. Immunotoxins targeting IL13Rα2 have been demonstrated as safe and have shown some benefit for patients with HGG in previous phase I/II and III clinical trials. We hypothesized that by using GB-13 (IL13.E13K-PE4E), a novel peptide-toxin that binds IL13Rα2 with high specificity and possesses a Pseudomonas exotoxin moiety, we would enhance the anti-tumor effects of this immunotoxin for HGG in vitro and in vivo while decreasing off-target toxicity. METHODS: We examined the pharmacological effects of GB-13 in multiple patient-derived cell lines and rodent models of HGG. GBM and DMG lines were used to confirm IL13Rα2 expression and sensitivity towards GB-13. Tumor naive rats were evaluated for toxicity, and orthotopic PDX mice were used to monitor tumor size and survival following loco-regional infusion of GB-13. RESULTS: GB-13 induced a potent cytotoxic response strongly predicated on IL13Rα2 expression in vitro. No treatment-related adverse effects were noted after 7-day continuous intracranial infusion of GB-13 in tumor naive rats. Further, in IL13Rα2-upregulated orthotopic PDX mice, direct intratumoral administration of GB-13 via convection-enhanced delivery abrogated tumor growth and prolonged survival. CONCLUSIONS: Given these promising results as well as the critical need for novel therapies in CNS malignancies, we are progressing to human trials using GB-13 targeting recurrent HGG. Ongoing safety studies in tumor-bearing animals will be able to define dose levels for the initial adult study-arm and the following pediatric study-arm. In this Phase 1 clinical trial, we hypothesize that loco-regional infusion of GB-13 will safely enhance tumor clearance by causing selective killing of IL13Rα2-upregulated HGG cells.

LOCL-08
SAFETY AND FEASIBILITY OF RHENIUM-186 NANOLIPOSOME (186RNL) IN RECURRENT GliOMA: THE RESPECTTM PHASE 1 TRIAL
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BACKGROUND: Liposomal rhenium-186 (186RNL) is a potent source of electrons with short path length, low dose rate, high radiation density and gamma emission. Preclinically, 186RNL via convection enhanced delivery (CED) achieves very high doses of targeted radiation and a wide therapeutic index. We report the updated results of ReSPECT, the first in man, dose escalation phase 1 trial of 186RNL in recurrent glioma. METHODS: Following computer assisted treatment planning and placement of intracranial catheter(s), we performed a single administration of 186RNL via CED. Whole body planar and SPECT/CT imaging was obtained on days 1-8 following treatment for dosimetry and distribution. Patients were followed for toxicity, progression, and survival. RESULTS: Twenty-one patients across 7 cohorts received 1.0-22.3mCi in a tumor volume of 0.6-8.8mL. Mean tumor volume was 8.3mL (0.9-22.8mL). Patients had a mean of 1.7 recurrences, 3 with prior bevacizumab. 19 (91%) were grade 4 gliomas, and 100% were after that had. Thus far, overall survival (OS) in 16 bevacizumab-naive patients was 49 weeks with 7 patients still alive and a positive correlation of OS to Tu/Tv. CONCLUSIONS: 186RNL achieves high absorbed doses without significant toxicity with favorable overall survival. Updated delivery feasibility, safety and overall survival will be presented.

LOCL-09
SHORT-TERM SEIZURE OUTCOMES IN PATIENTS WITH TREATED WITH LASER INTERSTITIAL THERMAL THERAPY
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Laser interstitial thermal therapy (LITT) is a minimally invasive treatment modality for intracranial tumor and radiation necrosis (RN). A transient increase in edema following LITT typically resolves within three months post-procedure. We sought to characterize the short-term seizure outcomes during this period for patients undergoing LITT for tumor or RN. A retrospective analysis was conducted with LITT from a single institution was conducted. Data on baseline demographics, treatment details, and clinical course were collected. Thirty-one (36%) had a seizure within one year following LITT, 19 (22%) of which occurred within the first 90 days post-LITT (71% of all seizures). Fourty-three (50%) patients had documented pre-LITT seizures, with 27 (65% of all seizures) of those occurring within 90 days post-LITT. Between patients with and without post-LITT seizures within the first 90 days, there were no significant differences in gender, age, pre-LITT KPS, pre-LITT volume, pre-LITT resection, pre-LITT stereotactic radiotherapy, pre-LITT chemo- or immuno-therapy, use of AEDs or steroids before or after LITT, location, or pathology at the time of treatment. Patients with seizures in the first 90 days post-treatment were significantly more likely to have received pre-LITT stereotactic radiosurgical (SBRT) (32% vs. 9%, p<0.02). Of the 18 patients with pre-LITT seizures within 90 days, 9 (50%) were entirely seizure free in the 90-day post-LITT period. In summary, seizure is a known complication of LITT for intracranial lesions, with the majority occurring in the first 90 days post-LITT. Seizures occurring within 90 days of post-LITT, which may represent a diminished neurologic reserve in these patients. These findings may help guide clinicians in determining patients appropriate for LITT and those who may require closer monitoring and longer AED tapering in the short-term period following ablation.

LOCL-10
EVOLUTION OF FUNCTIONAL OUTCOMES AFTER LASER INTERSTITIAL THERMAL THERAPY (LITT) VERSUS RESECTION IN THE TREATMENT OF LESIONS IN OR NEAR THE PRIMARY MOTOR CORTEX
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Laser interstitial thermal therapy (LITT) has become increasingly common, particularly in the treatment of progressive lesions after stereotactic radiosurgery for brain metastases. Previous work has illustrated the sensitivity to its use near critical structures, including the corticospinal white matter tracts. A single-surgeon retrospective study was performed of patients with underwent LITT or open resection for lesions located in or near the primary motor cortex, with functional outcomes graded relative to pre-treatment symptoms at 30, 90, and 180 days. Forty patients met inclusion criteria, with median age 64 years (57-72), and estimated baseline KPS 80 (70-100). Eighteen (45%) LITT and 21 (55%) resections with intra-operative motor mapping. LITT patients trended towards smaller maximum diameters (2.1 cm vs 2.8 cm, p<0.01), with shorter ICU (0 vs 1 day, p<0.01) and hospital stays (1 vs. 2 days, p<0.01). At 30 days after treatment, 88.9% of resected patients had stable or improved symptoms compared to 35.3% of the LITT cohort (p<0.01). At 90 days, the difference was 87.5% to 50% (p=0.04), and at 180 days 100% to 85.7% (p=0.3684). When separated by new vs. progressive lesions, steroid responsiveness, and lesion histology, similar though not statistically significant trends were identified. In summary, LITT and resection provided similar functional outcomes in the treatment of lesions in or near the primary motor cortex for patients who survived at least 180 days post-treatment. Patients who received resection tended to have better functional outcomes in the nearer term. These differences are likely due to transient, expected post-LITT edema that subsides with time.

LOCL-11
EGFR-MUTATED NON-SMALL CELL LUNG CANCER (NSCLC) LEPTOMENINGEAL DISEASE (LMD) IN A LARGE STEREOTACTIC RADIOSURGERY PATIENT COHORT: INCIDENCE AND OUTCOME
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AIM: Patients with EGFR-mutated NSCLC brain metastases (BM) treated with targeted agents +/- radiosurgery (SRS) have increasing life expectancies. Systemic treatment may become less effective in preventing CNS progression.