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A PHASE I STUDY OF CONVECTION-ENHANCED DELIVERY OF LIPOSOMAL-IRINOTECAN USING REAL-TIME IMAGING WITH GADOLINIUM IN PATIENTS WITH RECURRENT HIGH GRADE GLIOMA

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BACKGROUND: Chemotherapy for high grade glioma (HGG) is limited by poor activity of available agents and compromised delivery across the blood brain barrier (BBB). Convection enhanced delivery (CED) improves chemotherapy delivery by utilizing fluid convection established as a result of a pressure gradient, obviating the challenges of crossing the BBB while minimizing systemic toxicity. CED of nanoliposomal irinotecan (MM-398) has been optimized in rat, dog, and primate models. A recent study in mice with intracranial glioblastoma xenografts compared routes of delivery for liposomal irinotecan by CED or IV and showed superior anti-tumor activity of CED. A major clinical advance in the use of CED over recent trials is the development of real time CED (RCD), which utilizes MRI to visualize the CED process with the aid of co-convected contrast agents and thus monitor delivery into the brain and to take corrective action for technical complexities. METHODS: With support from an R21 we will conduct the first in human phase I study of CED of liposomal-irinotecan using real-time imaging with gadolinium in patients with recurrent HGG. This is a single center, prospective, 3 + 3 dose escalating, single-arm, phase I trial with a four-level dose escalation, expecting to enroll at least 3 patients in each level and expanding the highest level to 12 patients total. Dose levels are 20 mg, 40 mg, 60 mg, and 80 mg liposomal-irinotecan, given via up to 3 catheters surgically placed in an intra-tumoral (IT) location. Concentration of gadoteridol will be 2 mM for all dose groups; both agents will be combined and co-infused via the same catheters. Subjects in the two lowest dose groups will have tumor volumes of 1-4 cm3, the third dose group will be 2-5 cm3 and the highest dose group will have tumor volume 2-6 cm3. Maximum total volume infused will be 1.0 ml for two lowest dose groups, 1.5 ml for the third dose group, and 2.0 ml for the highest dose group. RESULTS: Interim safety, efficacy, and imaging response results will be presented. Utilizing imaging software, we'll present the correlation of pre-infusion modeling of the drug distribution with post-infusion imaging and determination of the total volume of distribution (Vd) and the Vd to volume infused (Vi) ratio for each infusion. CONCLUSIONS: Image-guided distribution allows for real-time placement and adjustment of cannula for real time CED of MM-398 into the brains of patients with recurrent HGG. SECONDARY CATEGORY: Imaging.