Clinical Trial Lancet Oncol. 2023 May;24(5):509-522. doi: 10.1016/S1470-2045(23)00112-2.

Repeated blood-brain barrier opening with an implantable ultrasound device for delivery of albumin-bound paclitaxel in patients with recurrent glioblastoma: a phase 1 trial

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PMID: 37142373 DOI: 10.1016/S1470-2045(23)00112-2

Abstract

Background: Low-intensity pulsed ultrasound with concomitant administration of intravenous microbubbles (LIPU-MB) can be used to open the blood-brain barrier. We aimed to assess the safety and pharmacokinetics of LIPU-MB to enhance the delivery of albumin-bound paclitaxel to the peritumoural brain of patients with recurrent glioblastoma.

Methods: We conducted a dose-escalation phase 1 clinical trial in adults (aged ≥18 years) with recurrent glioblastoma, a tumour diameter of 70 mm or smaller, and a Karnofsky performance status of at least 70. A nine-emitter ultrasound device was implanted into a skull window after tumour resection. LIPU-MB with intravenous albumin-bound paclitaxel infusion was done every 3 weeks for up to six cycles. Six dose levels of albumin-bound paclitaxel (40 mg/m^2, 80 mg/m^2, 135 mg/m^2, 175 mg/m^2, 215 mg/m^2, and 260 mg/m^2) were evaluated. The primary endpoint was dose-limiting toxicity occurring during the first cycle of sonication and albumin-bound paclitaxel chemotherapy. Safety was assessed in all treated patients. Analyses were done in the per-protocol population. Blood-brain barrier opening was investigated by MRI before and after sonication. We also did pharmacokinetic analyses of LIPU-MB in a subgroup of patients from the current study and a subgroup of patients who received carboplatin as part of a similar trial (NCT03744026). This study is registered with ClinicalTrials.gov, NCT04528680, and a phase 2 trial is currently open for accrual.

Findings: 17 patients (nine men and eight women) were enrolled between Oct 29, 2020, and Feb 21, 2022. As of data cutoff on Sept 6, 2022, median follow-up was 11·89 months (IQR 11·12-12·78). One patient was treated per dose level of albumin-bound paclitaxel for levels 1 to 5 (40-215 mg/m^2), and 12 patients were treated at dose level 6 (260 mg/m^2). A total of 68 cycles of LIPU-MB-based blood-brain barrier opening were done (median 3 cycles per patient [range 2-6]). At a dose of 260 mg/m^2, encephalopathy (grade 3) occurred in one (8%) of 12 patients during the first cycle (considered a dose-limiting toxicity), and in one other patient during the second cycle (grade 2). In both cases, the toxicity resolved and treatment continued at a lower dose of albumin-bound paclitaxel, with a dose of 175 mg/m^2 in the case of the grade 3 encephalopathy, and to 215 mg/m^2 in the case of the grade 2

encephalopathy. Grade 2 peripheral neuropathy was observed in one patient during the third cycle of 260 mg/m^2 albumin-bound paclitaxel. No progressive neurological deficits attributed to LIPU-MB were observed. LIPU-MB-based blood-brain barrier opening was most commonly associated with immediate yet transient grade 1-2 headache (12 [71%] of 17 patients). The most common grade 3-4 treatment-emergent adverse events were neutropenia (eight [47%]), leukopenia (five [29%]), and hypertension (five [29%]). No treatment-related deaths occurred during the study. Imaging analysis showed blood-brain barrier opening in the brain regions targeted by LIPU-MB, which diminished over the first 1 h after sonication. Pharmacokinetic analyses showed that LIPU-MB led to increases in the mean brain parenchymal concentrations of albumin-bound paclitaxel (from 0·037 μM [95% CI 0·022-0·063] in non-sonicated brain to 0·139 μM [0·083-0·232] in sonicated brain [3·7-times increase], p<0·0001) and carboplatin (from 0·991 μM [0·562-1·747] in non-sonicated brain to 5·878 μM [3·462-9·980] μM in sonicated brain [5·9-times increase], p=0·0001).

Interpretation: LIPU-MB using a skull-implantable ultrasound device transiently opens the blood-brain barrier allowing for safe, repeated penetration of cytotoxic drugs into the brain. This study has prompted a subsequent phase 2 study combining LIPU-MB with albumin-bound paclitaxel plus carboplatin (NCT04528680), which is ongoing.

Funding: National Institutes of Health and National Cancer Institute, Moceri Family Foundation, and the Panattoni family.