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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Summary

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/m², 80 mg/m², 135 mg/m², 175 mg/m², 215 mg/m², and 260 mg/m²) 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/m²), and 12 patients were treated at dose level 6 (260 mg/m²). 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/m², 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/m² in the case of the grade 3 encephalopathy, and to 215 mg/m² in the case of the grade 2 encephalopathy. Grade 2 peripheral neuropathy was observed in one patient during the third cycle of 260 mg/m² 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.

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See **Comment** page 420

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Research in context

Evidence before this study

The blood–brain barrier remains a major challenge for treatment of malignant gliomas. This disease is characterised by the presence of unresectable clusters of tumour cells that infiltrate into the peritumoural brain in humans, where the blood–brain barrier limits the penetration of most chemotherapeutic drugs. Low-intensity pulsed ultrasound with concomitant administration of intravenous microbubbles (LIPU-MB) is an emerging approach to transiently open the blood–brain barrier for drug delivery. We searched PubMed using the terms "ultrasound", "blood-brain barrier", and "clinical trial" within the title or abstract, with no date or language restrictions, yielding 28 articles published between 2003 and 2023. We also searched ClinicalTrials.gov using the terms "glioma" for condition, "ultrasound" for intervention, and "drug" as other term, to identify trials evaluating this approach registered as of Feb 9, 2023. We found 21 clinical trials, some of which reported outcomes supporting the safety of LIPU-MB for blood–brain barrier opening in humans. These studies showed blood–brain barrier opening on MRI or single-photon emission CT in a small volume of brain following sonication. The direct effect of LIPU-MB on drug concentrations in the human brain shortly after LIPU-MB procedure has not yet been described. Moreover, the restoration rate of blood–brain barrier integrity within the first few hours after LIPU-MB, information that is crucial for delivering systemic drugs to the brain with this approach, was not reported in humans.

Added value of this study

Our study provides data on the safety of applying LIPU-MB to large areas of the brain, in the context of delivery of albumin-bound paclitaxel—a drug that has poor distribution in the human brain and is associated with peripheral neurotoxicity. In this phase 1 study, we report that the delivery of albumin-bound paclitaxel across the blood–brain barrier is safe and, overall, well tolerated. The results of our pharmacokinetic studies are direct evidence of drug penetration into the human brain following this procedure and provide an insight into the magnitude drug brain permeability achieved for two different cytotoxic agents (paclitaxel and carboplatin), allowing initial observations on how drug size might affect its permeation into the brain following LIPU-MB. We also characterised the timing of restoration of blood–brain barrier integrity following LIPU-MB, elucidating a critical time window for delivery of systemic drugs to the brain with this approach.

Implications of all the available evidence

This study provides the first direct evidence that LIPU-MB substantially increases the brain concentration of systemically administered drugs in humans. We report that large-volume blood–brain barrier opening is safe, reproducible, and can be repeated over multiple cycles of chemotherapy. Thus, large size drugs that previously were not used for gliomas could now be considered for the treatment of diseases in the brain, including glioblastoma. Whereas the approach of opening the blood–brain barrier with ultrasound-activated microbubbles is under investigation with use of various technologies, our study indicates that the blood–brain barrier closes rapidly after LIPU-MB, a factor that must be considered to optimise timing of drug infusion relative to LIPU-MB to accomplish robust drug penetration into the human brain.

Introduction

The inability of most drugs to cross the blood–brain barrier limits the availability of agents to treat brain diseases.[1] In the case of infiltrative high-grade gliomas, the blood–brain barrier remains intact in the peritumoural brain, where tumour cells migrate and infiltrate into the parenchyma while protected from exposure to drugs.[2] Consequently, 80–90% of glioblastomas recur within the 2 cm margin of peritumoural brain around the resection cavity.[3,4]

Paclitaxel is a chemotherapeutic agent that is approximately 1400-times more potent than temozolomide, the standard chemotherapeutic agent used for gliomas. Paclitaxel has similar activity in glioma cell lines as in other cancers for which this agent is part of the standard regimen.[5,6] In contrast to temozolomide, paclitaxel does not cross the blood–brain barrier[7] and has not shown efficacy in phase 1/2 trials when systemically administered for malignant gliomas.[8,9]

Low-intensity pulsed ultrasound with concomitant administration of intravenous microbubbles (LIPU-MB) can be used to open the blood–brain barrier. In brain capillaries, microbubbles oscillate upon stimulation by ultrasound, generating mechanical stress on the endothelial wall that opens the blood–brain barrier. The effect of LIPU-MB on the permeability of the blood–brain barrier has been shown in animal models and in human clinical trials.[10–13]

Early phase 1/2 clinical trials of LIPU-MB in patients with glioblastoma, brain metastases, Alzheimer's disease, and amyotrophic lateral sclerosis have shown the safety of this approach.[12,14–17] The opening of the blood–brain barrier has been shown indirectly on MRI or by single-photon emission CT with radiolabelled antibodies.[10,12] However, the magnitude of the effect of LIPU-MB-based opening of the blood–brain barrier on drug concentrations in the brain tissue shortly after LIPU-MB has not been quantified, and the timing of blood–brain barrier closure after the procedure remains poorly understood.

We previously showed that LIPU-MB enhances the penetration of paclitaxel through the blood–brain barrier in mice, and that a US Food and Drug Administration-approved, Cremophor-free, albumin-bound paclitaxel

formulation (Abraxane; Bristol-Myers Squibb, New York, NY, USA) is well tolerated in this setting.[6] In this Article, we report the results of a phase 1 clinical trial in which albumin-bound paclitaxel was administered in conjunction with LIPU-MB-based blood–brain barrier opening with a skull-implantable ultrasound device every 3 weeks, in patients with recurrent glioblastoma. To investigate the pharmacokinetics of LIPU-MB, our trial included intraoperative sonication of peritumoural brain with concomitant administration of chemotherapy before tumour resection in subsets of patients in whom resection of peritumoural brain was clinically justified. The primary objectives were to evaluate the safety and maximal tolerated dose of albumin-bound paclitaxel after LIPU-MB-based opening of the blood–brain barrier in patients with recurrent glioblastoma, and to assess the effect of LIPU-MB-based blood–brain barrier opening on paclitaxel concentrations in the peritumoural brain.

Methods

Study design and participants

In this dose-escalation phase 1 clinical trial, we recruited patients with recurrent glioblastoma, being treated at Northwestern University Feinberg School of Medicine (Chicago, IL, USA).

Patients were eligible if they were aged 18 years or older, had a histologically confirmed diagnosis of glioblastoma (*IDH* wild-type), with radiologically confirmed recurrence after failure of one or two previous lines of therapy, with an interval of at least 12 weeks since the end of radiotherapy, and a WHO performance status of 2 or lower (which is equivalent to a Karnofsky performance status of ≥70). Patients were required to be amenable to tumour resection, with measurable disease (ie, contrast-enhancement on MRI) at inclusion of 70 mm or smaller in maximal diameter or expected residual peritumoural brain (after resection) of 70 mm or smaller (see appendix p 2 for anatomical considerations). Full eligibility criteria are in the protocol (appendix p 19).

Additionally, as part of our pharmacokinetic analysis, we report data from patients being treated with LIPU-MB in conjunction with carboplatin, in the context of a site-specific amendment of a separate clinical trial (NCT03744026). Briefly, the carboplatin clinical trial had similar inclusion criteria to our study, with the main difference being that it also allowed inclusion of high-grade gliomas with *IDH1* mutation, and carboplatin was the chemotherapy agent delivered. Details on the inclusion criteria for this study can be found on ClinicalTrials.gov.

The study was approved by the institutional review board of Northwestern University Feinberg School of Medicine (STU00212298), and all patients provided written informed consent, which included consent for the translational pharmacokinetic study and for non-identifiable data collected to be included in scientific publications. Quality assurance monitors from the Clinical Trials Office at the Robert H Lurie Comprehensive Cancer Center of Northwestern University verified the underlying study data and confirmed the accuracy of the results presented in this Article. The protocol and a summary of its amendments are provided in the appendix (p 18).

Procedures

LIPU-MB was done with use of a novel device composed of nine ultrasound emitters (SonoCloud-9 [SC9]; Carthera, Lyon, France). To allow ultrasound waves to bypass the skull, we created a 6×6 cm cranial window during surgery for resection of recurrent glioblastoma, under neuronavigation guidance. Following standard microsurgical resection of the tumour and closing of the dura, we implanted the device (figure 1A). The implant was fixed to the bone using standard surgical screws (figure 1D; appendix p 2).

For each therapeutic cycle, to open the blood–brain barrier, the SC9 was activated by connecting the implanted device to a pulse generator through percutaneous access using a single-use sterile transdermal needle and cable (figure 1B). The pulse generator was controlled with a touchscreen interface (figure 1C; appendix p 2). Simultaneously with intravenous injection of microbubbles (perflutren lipid microsphere Definity 10 µL/kg; Lantheus, North Billerica, MA, USA) over 30 s, the pulse generator activated the SC9 device for 4 min 30 s, immediately followed by intravenous administration of the chemotherapy.

For the therapeutic aspect of the trial, which involved all patients, the first cycle of sonication and chemotherapy was scheduled within 1–3 weeks after surgery and was preceded by a new baseline MRI obtained 1–2 days before sonication. Immediately after the sonication procedure, albumin-bound paclitaxel was administered intravenously over the course of 30 min. For the first cycle, a bolus of gadolinium (gadobutrol 0·1 mL/kg) was injected either within minutes of initiating LIPU-MB, before administration of chemotherapy (figure 1E), or at the time of post-sonication MRI after completion of albumin-bound paclitaxel infusion (approximately 60 min after LIPU-MB; appendix p 14), similar to procedures done before.[18] The same procedure (without gadolinium injection and post-sonication MRI) was repeated every 3 weeks as clinically indicated until disease progression or for up to six cycles. All treatments were delivered in the outpatient setting, and patients were monitored for acute toxicities for 4–6 h after the procedure. Guidance for dose reductions and delays is found in the protocol (appendix p 45).

See Online for appendix

We evaluated albumin-bound paclitaxel dose levels of 40 mg/m², 80 mg/m², 135 mg/m², 175 mg/m², 215 mg/m², and 260 mg/m², all administered with concomitant LIPU-MB every 3 weeks. We used a Bayesian optimal interval (BOIN) design to optimise identification of the maximal tolerated dose while

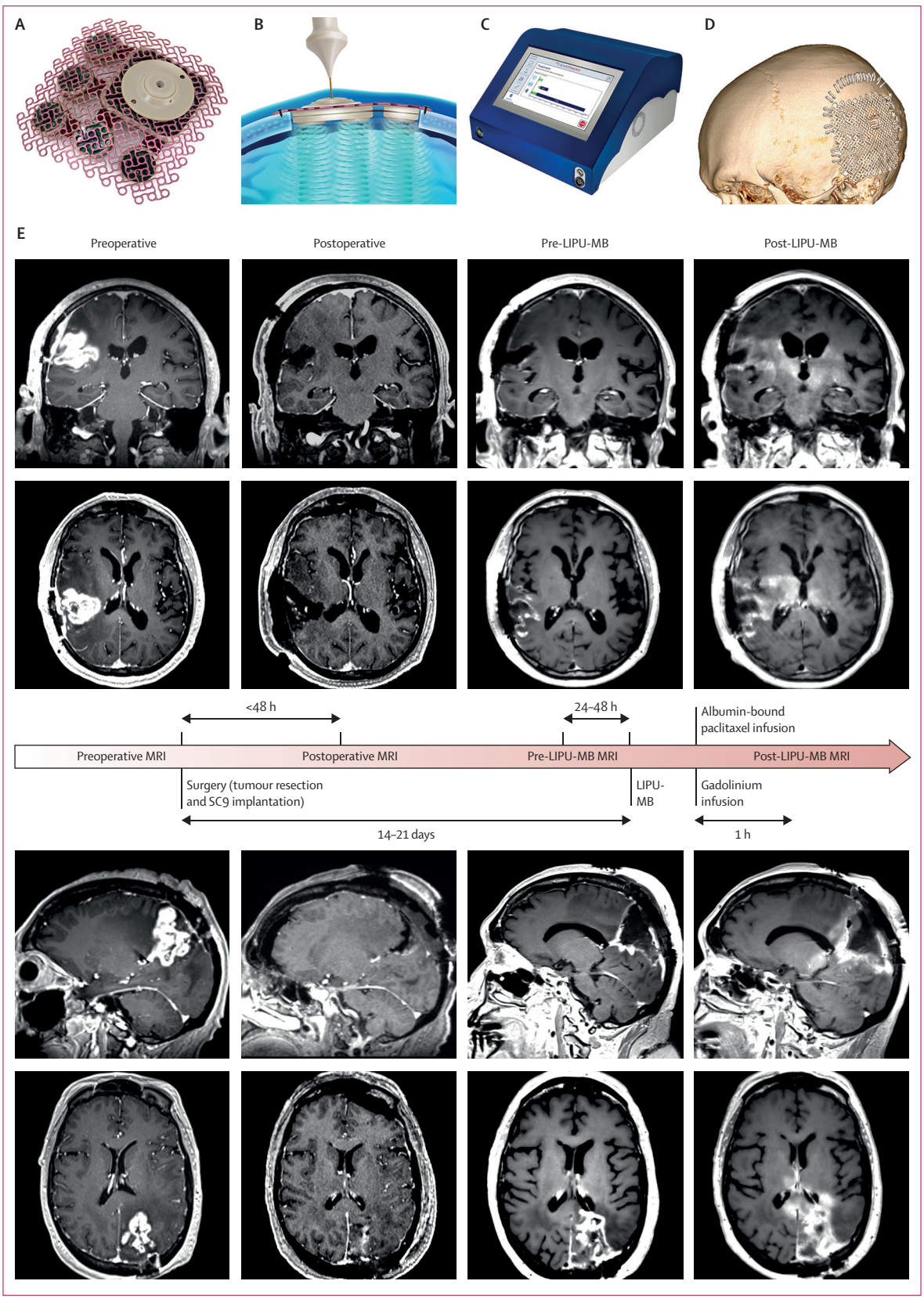

Figure 1: **Opening of the blood–brain barrier in peritumoural brain tissue with use of a skull-implantable ultrasound device**

The SC9 system consists of an implantable device with nine 1 MHz ultrasound emitters (A) that is implanted into a window in the skull during resection surgery, and a single-use transdermal needle (B) that is used to connect the implantable ultrasound to a pulse generator (C) with a touchscreen interface. (D) 3D reconstruction of postoperative CT showing the implanted SC9 device in a window in the skull. (E) Representative examples of blood–brain barrier opening in two patients. T1-weighted MRI scans with contrast sequences show gadolinium leaking into the peritumoural brain after sonication (post-LIPU-MB images), with pre-sonication images (preoperative, postoperative, and pre-LIPU-MB) shown for comparison. Brain enhancement (seen as hyperintensity) on post-LIPU-MB images that is not seen on pre-LIPU-MB images represents blood–brain barrier opening elicited by SC9, with permeation of gadolinium. Post-LIPU-MB scans show patients who had gadolinium injection before paclitaxel infusion, within approximately 2 min of LIPU-MB. LIPU-MB=low-intensity pulsed ultrasound with concomitant administration of intravenous microbubbles. SC9=SonoCloud-9.

minimising the risk of assigning patients to sub-therapeutic or overly toxic doses; the decision for dose-level allocation was assessed at the completion of the dose-limiting toxicity assessment period (first cycle, 21 days) of the previous patient, based on occurrence or absence of a dose-limiting toxicity (appendix p 3). Upon occurrence of dose-limiting toxicity or upon reaching the highest dose level, the cohort was expanded to a total of 12 treated and evaluable patients. Dose-limiting toxicities were assessed throughout all interventions and treatments, and treatment-emergent symptoms scored according to Common Toxicity Criteria Adverse Events (CTCAE; version 5.0). Patients were closely monitored for both acute and late or cumulative toxicities and were clinically examined at least once per cycle before the next administration (weekly during cycle 1). During the first cycle and for subsequent cycles, complete blood counts were drawn at least once per week. MRI for disease evaluation was done every three cycles or as clinically indicated.

Pharmacokinetic studies were done in a subset of patients for whom tumour location justified the resection of peritumoural brain per standard neurosurgical technique. At the time of resection, these patients underwent intraoperative LIPU-MB of peritumoural brain with concomitant administration of sodium fluorescein (500 mg intravenously as a bolus) and albumin-bound paclitaxel (intravenously over 30 min) or carboplatin (intravenously over 30 min) in the context of a site-specific amendment of a separate clinical trial (NCT03744026). Biopsy samples of sonicated and non-sonicated peritumoural brain tissue were collected 45 min after LIPU-MB (with non-sonicated samples obtained from a separate region of peritumoural brain than the sonicated samples) for quantification of drug and haemoglobin concentrations to assess the effect of blood–brain barrier opening on drug concentrations in the brain and collection of blood samples were done to assess brain-to-plasma drug concentration ratios. For pharmacokinetic studies, the intraoperative albumin-bound paclitaxel dose was 80 mg/m² for all patients (except for those in the lowest dose level, who received 40 mg/m²), and the intraoperative carboplatin dose was an area under the curve (AUC) of 3·5. Further details are in the appendix (pp 4–5). All patients included in the pharmacokinetic analysis had visually confirmed blood–brain barrier opening with use of fluorescein, and availability of paired sonicated and non-sonicated peritumoural brain samples that were at least 1 cm from the enhancing tumour (determined by stereotaxic coordinates) as well as sufficient tissue for paired measurement of drug and haemoglobin concentration.

After completion of study treatment, follow-up visits occurred as clinically indicated. Follow-up until disease progression usually included a clinical visit at least every 2 months and an MRI every 2–3 months. All patients were followed up for survival, either clinically or by regular telephone follow-up at least every 2 months. No restrictions on subsequent treatments were specified.

Outcomes

The primary endpoint was dose-limiting toxicity occurring during the first cycle of sonication and albumin-bound paclitaxel chemotherapy. Treatment-emergent adverse events were independently reviewed by the Lurie Cancer Center's Data Safety Monitoring Board, who had to approve each patient's dose level assignment or dose escalation.

Dose-limiting toxicity was defined as toxicity that is treatment-emergent and possibly, probably, or definitely related or attributable to LIPU-MB or to the LIPU-MB plus albumin-bound paclitaxel infusion procedure (excluding intraoperative procedures) occurring during the dose-limiting toxicity period (defined as 21 days from the first SC9 sonication procedure associated with albumin-bound paclitaxel treatment, excluding the intraoperative sonication). Dose-limiting toxicity included any related adverse events of at least grade 3 (as defined by CTCAE version 5.0) that does not respond to optimal medical management (including steroids) within 10 days, with exceptions as follows: CNS adverse event of grade 2 or higher that does not revert to grade 1 or lower within 21 days (ie, in time for the next treatment cycle); grade 4 CNS adverse event; and any treatment-emergent and treatment-related adverse event (except haematotoxicity, nausea or vomiting, fatigue, and hypersensitivity to albumin-bound paclitaxel or microbubble injections) higher than grade 2 that has not reverted to a grade 2 or lower by day 22 after the first round of sonication. Additionally, treatment-emergent adverse events that are unequivocally not related to the sonication or albumin-bound paclitaxel (eg, events attributed to disease progression) were not to be considered as dose-limiting toxicities. The definition and examples of dose-limiting toxicity are provided in further detail in the protocol (appendix p 60).

Prespecified exploratory endpoints were quantification of blood–brain barrier opening by comparison of pre-sonication to post-sonication contrast MRI (reported in this Article). Additional exploratory endpoints (to be reported separately) were drug concentrations in the enhancing tumour tissue; pattern of treatment failure relative to the regions of the brain that were sonicated; objective response rate; the effect of LIPU-MB on circulating cell-free DNA, RNA, or exosomes; and characterisation of the effect LIPU-MB-based blood–brain barrier opening on the brain (including single-cell RNA-seq and various microscopic analysis techniques).

Statistical analyses

The trial was done with an adaptive BOIN design with a target dose-limiting toxicity rate for the maximal tolerated dose of less than 20%. A sample size of up to 17 patients was deemed necessary to test this hypothesis.

If a patient dropped out of the study before the end of the first cycle (the dose-limiting toxicity evaluation period) for any reason other than treatment-related toxicity, replacement of this participant was allowed. Per the BOIN design, interim analysis of dose-limiting toxicity rate was done after every patient completed the dose-limiting toxicity period. The predetermined threshold for significance was $p<0·05$. Assessment of safety and dose-limiting toxicities and MRI assessment of blood–brain barrier opening were done in all treated patients. Pharmacokinetic analysis was done in patients for whom resection of the peritumoural brain was clinically justified. The association between paclitaxel or carboplatin concentrations and fluorescein were investigated with Spearman correlations using Prism (version 9.3.1). For the pharmacokinetic studies, to examine the effect of sonication on carboplatin concentrations, we did the significance calculation for the single-patient analysis using the Wilcoxon rank sum exact test. For the aggregate analysis of patients, we fit a mixed-effects model with random intercepts to account for correlation of within-patient repeated measures for determination of paclitaxel and carboplatin brain parenchymal concentrations, brain-to-plasma ratios, and, in the case of carboplatin, haemoglobin percentage. However, in the case of haemoglobin levels within the paclitaxel sample set, 45% of these values equaled 0%; thus, we applied the mixed-effects model, excluding the samples with 0% haemoglobin. For this case, we also fit a generalised estimating equation model, and obtained an odds ratio associated with haemoglobin levels >0%. These analyses were done with R (version 4.0.5).

In post-hoc analyses, for estimation rate of blood–brain barrier closure, enhancement between two different cycles was compared with Student's two-tailed unpaired *t* test. A linear mixed-effects model was used to describe the association between enhancement on post-sonication MRI and the time between sonication and gadolinium injection or the time between gadolinium injection and MRI acquisition (appendix p 7). We investigated the differences in paclitaxel concentration between deep and superficial peritumoural brain biopsies using the mixed effects model. Progression-free survival was calculated from the date of study registration to the date of unequivocal progression (defined as the date when clinical or imaging-based assessment led to determination of progression, leading to changes in the management of the patient [eg, discontinuation of treatment or introduction of a new treatment]). Overall survival was calculated from the date of study registration to date of death (with no restriction on cause of death specified in the protocol). Progression-free and overall survival estimates were also obtained with the Kaplan-Meier method and calculated with R (version 4.0.5). This trial (NCT04528680) is registered with ClinicalTrials.gov.

Role of the funding source

The funders of the study had no role in study design, data collection, and data interpretation. The manufacturer of the SC9 device (Carthera, Lyon, France) provided technical input and assistance and contributed to the imaging analysis presented.

Results

Between Oct 29, 2020, and Feb 21, 2022, we screened 18 patients for trial participation and 17 patients were enrolled and treated (one consented patient was excluded because of the presence of leptomeningeal disease on their preoperative MRI). Baseline patient and tumour characteristics are summarised in table 1. One patient was treated per dose level of albumin-bound paclitaxel for levels 1–5 (40–215 mg/m²), and 12 patients were treated at dose level 6 (260 mg/m²). As of data cutoff (Sept 6, 2022), median follow-up for the trial cohort was 11·89 months (IQR 11·12–12·78).

We did not observe surgical complications or infections attributed to the SC9 implant. One (6%) of 17 patients had a grade 2 small wound dehiscence, at a remote location from the implant, that was repaired, and the patient was able to continue study treatments. Perioperatively, steroids were administered per standard surgical practice; for patients included in the intraoperative pharmacokinetic study, steroids were given after the intraoperative tissues had been collected.

68 cycles of LIPU-MB-based blood–brain barrier opening were done across all patients. Patients were weaned off of steroids postoperatively and no patients were on dexamethasone during the sonication procedures. The median time between surgery and beginning of the first cycle was 17 days (IQR 14–18). The median number of cycles per patient was 3 (range 2–6). No progressive neurological deficits attributed to LIPU-MB were observed (appendix pp 9–10). LIPU-MB-based blood–brain barrier opening was most commonly associated with immediate yet transient grade 1–2 headache (12 [71%] of 17 patients), and other grade 1–2 neurological deficits—ie, paraesthesia (two [12%]), facial or limb weakness (four [24%]), dysphasia (two [12%]), dysarthria (two [12%]), dysaesthesia (three [18%]), and blurred vision (five [29%]). These acute treatment-emergent adverse events were anatomically associated with the brain region being sonicated (eg, sonication of the left temporal LIPU-MB led to transient grade 1 dysphasia). LIPU-MB-related neurological adverse events per patient and per cycle are described in the appendix (pp 11–12).

No dose-limiting toxicity was observed for escalating dose levels up to 215 mg/m². At 260 mg/m², one patient had a grade 3 encephalopathy 2 h after administration of the first cycle, which was considered to be a dose-limiting toxicity. Another patient had a grade 2 encephalopathy, also 2 h after sonication and albumin-bound paclitaxel administration on the second cycle. In both patients, encephalopathy completely resolved within 1–2 days.

	Patients (n=17)
Demographics	
Age, years	
Median	57 (52–63)
Range	33–72
Sex	
Male	9 (53%)
Female	8 (47%)
Race	
White	16 (94%)
Black	1 (6%)
Ethnicity	
Hispanic	1 (6%)
Non-Hispanic	14 (82%)
Not reported	2 (12%)
Clinical characteristics	
WHO performance status	
Median	1 (0–1)
Range	0–1
Time since initial diagnosis, months	
Median	12 (9–20)
Range	6–51
Previous treatment	
Temozolomide	16 (94%)*
Radiotherapy, 60 Gy	17 (100%)
Number of previous lines of treatment	
1	16 (94%)
2	1 (6%)
Corticosteroid therapy (<6 mg/day)	2 (12%)
Antiepileptic therapy	12 (71%)
Tumour characteristics (before implant surgery)	
Largest enhancing tumour diameter, mm	
Mean	28·7 (7·4)
Range	20–41
Tumour location	
Left frontal lobe	1 (6%)
Left parietal lobe	4 (24%)
Left temporal lobe	1 (6%)
Right frontal lobe	4 (24%)
Right parietal lobe	3 (18%)
Right temporal lobe	2 (12%)
Right occipital lobe	2 (12%)
Pathology of resected sample: glioblastoma (*IDH* wild-type, sequenced)	17 (100%)
MGMT gene promoter	
Methylated	5 (29%)
Unmethylated	12 (71%)
(Table 1 continues in next column)	

	Patients (n=17)
(Continued from previous column)	
Treatment characteristics	
Number of sonication and chemotherapy cycles received	
Total	68
Median, per patient	3 (3–5)
Range, per patient	2–6
Treated dose levels 1–5 (40–215 mg/m²)	5 (29%)
Received ≥5 cycles	1 (20%)
Treated at dose level 6 (260 mg/m²)	12 (71%)
Received ≥5 cycles	6 (50%)

Data are n (%), number of events, median (IQR), mean (SD), or range.
*One patient with an MGMT gene promoter unmethylated tumour was treated on a protocol that omitted temozolomide in favour of an investigational agent.

Table 1: **Baseline demographic and clinical characteristics of patients and treatments received**

Both patients were treated with supportive care including steroids. With a dose reduction to 175 mg/m² in the case of the grade 3 encephalopathy, and to 215 mg/m² in the case of the grade 2 encephalopathy, these patients subsequently completed a total of five and three cycles, respectively, without further occurrence of encephalopathy. Grade 2 or worse treatment-emergent adverse events associated with the first cycle (the dose-limiting toxicity period) and all cycles are shown in the appendix (p 13). Grade 2 peripheral neuropathy was observed in one patient treated at 260 mg/m² on the third cycle, and subsequent cycles were reduced to 215 mg/m², yet the neuropathy (a known side-effect of paclitaxel) persisted at grade 2. Treatment-emergent adverse events are reported in table 2. The most common grade 3–4 adverse events were neutropenia (eight [47%]), leukopenia (five [29%]), and hypertension (five [29%]). No treatment-related deaths occurred.

Blood–brain barrier opening was demonstrated by comparing enhancement on contrast MRI before sonication (1–2 days before cycle 1) with an MRI performed immediately after sonication, which allowed identification of regions of the peritumoural brain where LIPU-MB led to blood–brain barrier opening as evidenced by gadolinium-based enhancement observable in the brain parenchyma (figure 1E; appendix p 14). The SC9 can target an approximate brain volume of 53 mL, corresponding to nine cylinders, each 10 mm in diameter and 75 mm in depth. The volume of targeted peritumoural brain that showed enhancement attributed to sonication (on post-sonication MRI) ranged from 3·5 mL to 20·9 mL (median 12·6 mL [IQR 9·4–15·6]). This volume varies because the region targeted by the ultrasound can contain resection cavity or tissue that shows enhancement before sonication (eg, tumour tissue or scar), which we subtracted from in the calculation of volume of brain with blood–brain barrier opening.

We investigated the timing of restoration of blood–brain barrier integrity. Initially, post-sonication contrast MRI was done after finishing albumin-bound paclitaxel infusion, approximately 1 h after LIPU-MB, and gadolinium was injected at the time of MRI acquisition (n=4), leading to faint contrast enhancement of the area

with blood–brain barrier opening (appendix p 14). For subsequent patients (n=13), gadolinium was injected within approximately 2 min after LIPU-MB (with some variation between patients; figure 2), before MRI acquisition (appendix p 14). For a patient who received gadolinium infusion within 2 min of sonication and whose MRI showed robust enhancement of the sonicated brain in the first cycle, a post-sonication MRI after the second cycle was repeated with a delay in gadolinium infusion (69 min) and MRI acquisition (174 min) from the time of LIPU-MB, which resulted in a decrease in the enhancement related to blood–brain barrier opening (figure 2A).

	Grade 1–2	Grade 3	Grade 4
Anaemia	15 (88%)	0	0
Headache	15 (88%)	0	0
Leukopenia	10 (59%)	5 (29%)	0
Hypertension	9 (53%)	5 (29%)	0
Lymphopenia	11 (65%)	3 (18%)	0
Hyperglycaemia	12 (71%)	0	0
Neutropenia	4 (24%)	7 (41%)	1 (6%)
Fatigue	10 (59%)	1 (6%)	0
Seizure	5 (29%)	3 (18%)	0
Bradycardia	8 (47%)	0	0
Alopecia	7 (41%)	0	0
Dysphasia	6 (35%)	1 (6%)	0
Nausea	7 (41%)	0	0
Increased alanine aminotransferase	6 (35%)	0	0
Increased aspartate aminotransferase	6 (35%)	0	0
CNS abnormality, other	6 (35%)	0	0
Thrombocytopenia	6 (35%)	0	0
Scalp pain	6 (35%)	0	0
Blurred vision	5 (29%)	0	0
Dysaesthesia	5 (29%)	0	0
Insomnia	4 (24%)	0	0
Upper limb muscle weakness	4 (24%)	0	0
Sinus tachycardia	4 (24%)	0	0
Weight loss	4 (24%)	0	0
Increased alkaline phosphatase	3 (18%)	0	0
Anorexia	3 (18%)	0	0
Dizziness	3 (18%)	0	0
Facial muscle weakness	3 (18%)	0	0
Arthralgia	2 (12%)	0	0
Ataxia	2 (12%)	0	0
Cognitive disturbance	2 (12%)	0	0
Depression	2 (12%)	0	0
Dysarthria	2 (12%)	0	0
Encephalopathy	1 (6%)	1 (6%)	0
Fever	2 (12%)	0	0
Hypercalcaemia	2 (12%)	0	0
Hypokalaemia	2 (12%)	0	0
Hyponatraemia	2 (12%)	0	0
Hypophosphataemia	2 (12%)	0	0
Memory impairment	2 (12%)	0	0
Optic nerve disorder	2 (12%)	0	0
Paraesthesia	2 (12%)	0	0
Somnolence	2 (12%)	0	0

Table includes all events of grade 3 or higher, and any events that occurred in more than 10% of patients. Events are ordered by overall frequency.

Table 2: **Treatment-emergent adverse events in all included patients**

To characterise the rate of closure of the blood–brain barrier after LIPU-MB (ie, the loss of brain permeability to gadolinium over time), we evaluated the time interval between sonication and gadolinium administration compared with the amount of enhancement of peritumoural brain that was targeted by the SC9 ultrasound emitters. Post-hoc analyses showed an inverse correlation suggesting rapid restauration of the blood–brain barrier within 1 h of LIPU-MB (figure 2B). We investigated whether these results were influenced by the clearance of gadolinium from the brain or by the time between gadolinium infusion and MRI versus enhancement of peritumoural brain that was targeted by the SC9 ultrasound probes; however, these variables did not correlate (post-hoc; figure 2C).

We did pharmacokinetic studies that included sonication of non-enhancing peritumoural brain in seven patients who received intraoperative albumin-bound paclitaxel and in three patients who received carboplatin in a separate study. Concomitant administration of fluorescein allowed for dynamic visualisation of LIPU-MB-based blood–brain barrier opening (video; figure 3A; appendix p 15). Biopsies of sonicated and non-sonicated peritumoural brain tissue for drug quantification were obtained approximately 45 min after sonication, after the peak plasma concentration of paclitaxel or carboplatin (appendix p 16). The brain parenchymal concentration of fluorescein correlated with that of albumin-bound paclitaxel (figure 3B), and with carboplatin (figure 3C), similar to our findings in preclinical models.[6]

See **Online** for video

LIPU-MB led to a several times increase in chemotherapy concentration in the brain parenchyma. For one example patient (figure 4A), mean carboplatin concentration in the peritumoural brain tissue after LIPU-MB was 9·3-times higher than in non-sonicated brain tissue. After LIPU-MB, the mean absolute brain concentration of paclitaxel was 3·7-times higher than in non-sonicated brain tissue, and the mean brain-to-plasma ratio was 3·6-times higher than in non-sonicated brain tissue (figure 4B). After LIPU-MB, the mean absolute brain carboplatin concentration was 5·9-times than in non-sonicated brain tissue and the mean carboplatin brain-to-plasma ratio was 5·8-times that in non-sonicated brain tissue (figure 4C).

As a post-hoc analysis, we compared the paclitaxel concentration in sonicated samples obtained from the subcortical white matter (mean paclitaxel concentration 0·1556 μM [95% CI 0·0669–0·3616]) versus sonicated

superficial or cortical biopsy sites (0·1336 μM [0·0770–0·2319]) from three patients for whom paired superficial and deep samples were available, but found no significant difference between these sites (data not shown; p=0·98 from mixed-effects model).

To rule out that the differences in concentration between sonicated and non-sonicated brain samples could relate to blood contamination, we compared the percentage of haemoglobin content between sonicated and non-sonicated peritumoural brain in a subset of the

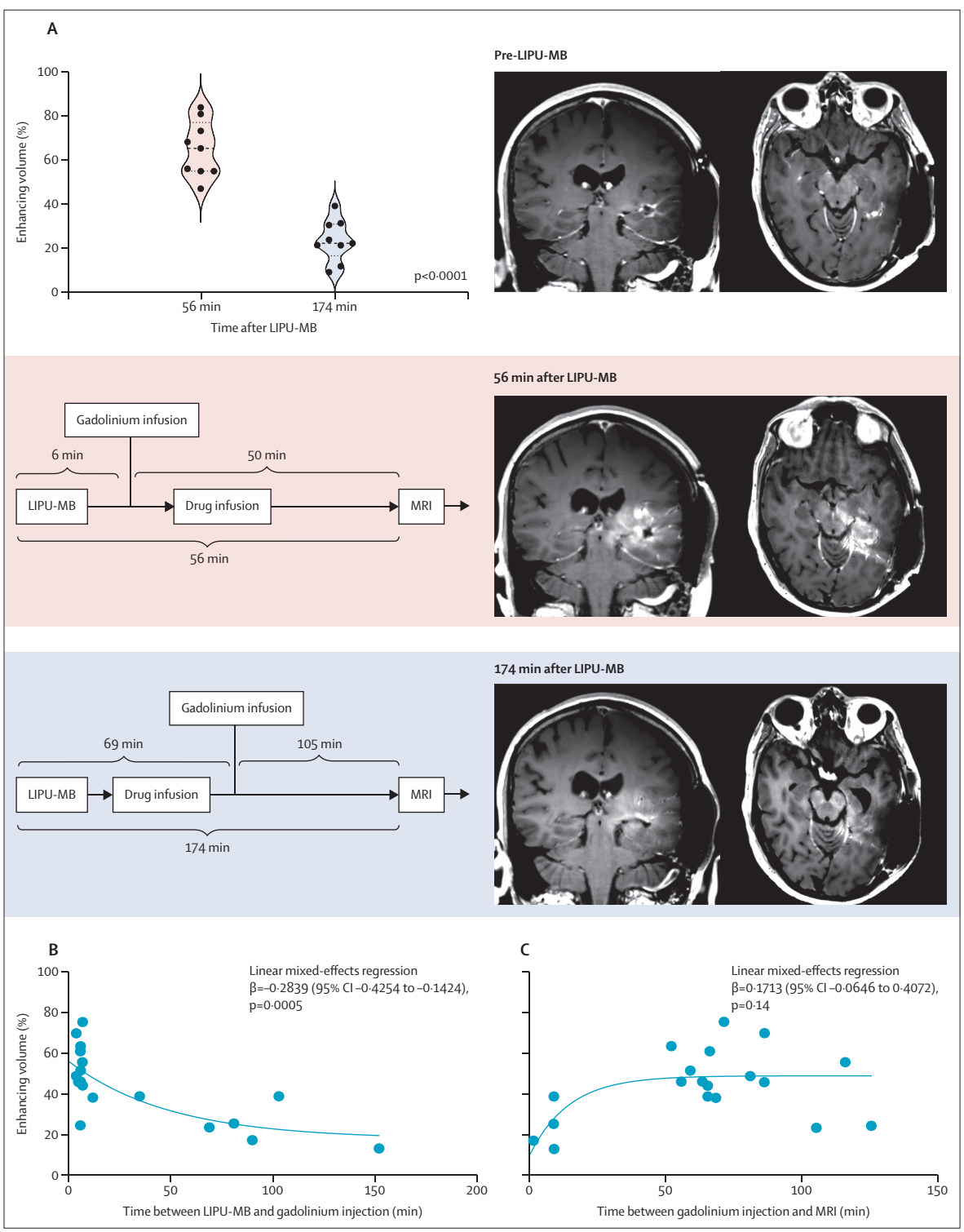

Figure 2: **Effect of timing of brain sonication, gadolinium infusion and MRI on post-LIPU-MB brain enhancement**
(A) MRI scans obtained before LIPU-MB, after drug infusion (56 min after LIPU-MB), and with deliberate delay of gadolinium infusion and MRI (174 min after LIPU-MB) on the same patient, with corresponding schematics showing the timings of gadolinium infusion and MRI relative to LIPU-MB. The violin plot compares the enhancement of peritumoural brain that was targeted by each of the SC9 ultrasound probes (n=9) on the corresponding MRI scans shown. p value was calculated by Student's two-tailed unpaired *t* test (post hoc). Scatter plots showing associations between the volume of ultrasound-targeted peritumoural brain that was enhanced and the time from sonication to gadolinium infusion (B) or the time from gadolinium infusion to beginning of MRI (C). Data are from 19 sonication cycles conducted in 17 patients. A one-phase exponential decay model was fitted to the data and strength of correlation was assessed with a linear mixed-effects regression model. To quantify the percentage of sonicated brain volume with blood–brain barrier opening (ie, enhancement after sonication), a region of interest within the brain that was targeted by each emitter that was not enhancing before sonication was used as the denominator. Images of LIPU-MB based blood–brain barrier opening for all patients are available in the appendix (p 14). LIPU-MB=low-intensity pulsed ultrasound with concomitant administration of intravenous microbubbles.

samples, but found no significant differences between these samples in patients who received paclitaxel (figure 4B) or carboplatin (figure 4C).

As of data cutoff, ten (59%) of 17 patients had died due to disease progression. All patients had disease progression by the date of data cutoff. In a post-hoc

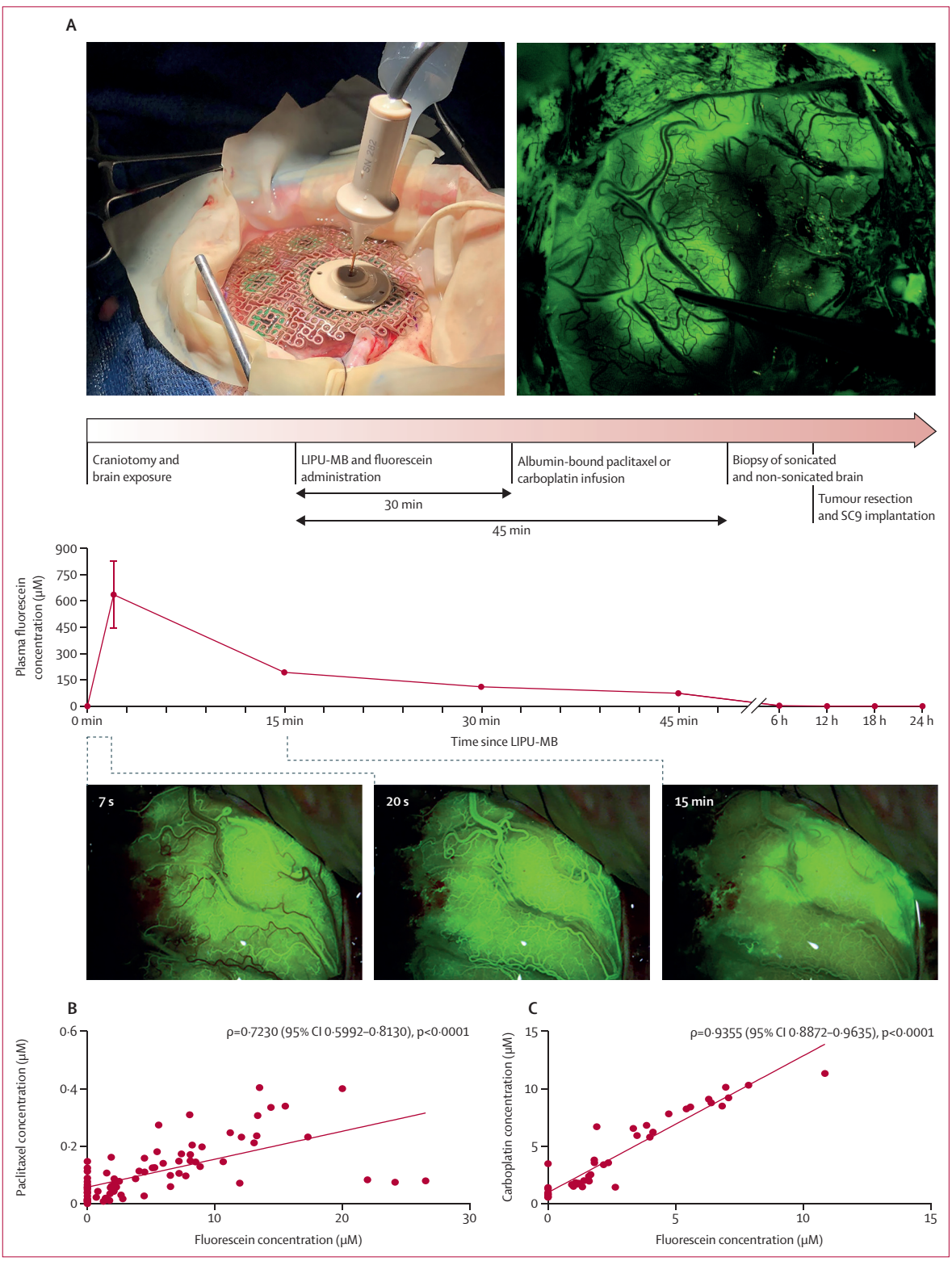

Figure 3: **Visualisation of LIPU-MB-based blood–brain barrier opening for intraoperative pharmacokinetic experiment in the peritumoural human brain**

(A) Schematic, representative intraoperative fluorescence-based microsurgical photographs illustrating how the LIPU-MB procedure was done for visualisation of blood–brain barrier opening using sodium fluorescein, and graph showing plasma clearance of this agent over time (n=10 patients, including n=7 for paclitaxel and n=3 for carboplatin). Error bars show standard error of the mean. Scatter plots show correlation between the concentration of paclitaxel or albumin-bound paclitaxel (n=7 patients, 81 biopsies, 41 sonicated and 40 non-sonicated; B) or carboplatin (n=3 patients, 48 biopsies, 23 sonicated and 25 non-sonicated; C) and the concentration of fluorescein 45 min after LIPU-MB across biopsies of peritumoural brain. Correlations were analysed with Spearman's rank correlation coefficient (ρ), with two-tailed p values reported. LIPU-MB=low-intensity pulsed ultrasound with concomitant administration of intravenous microbubbles.

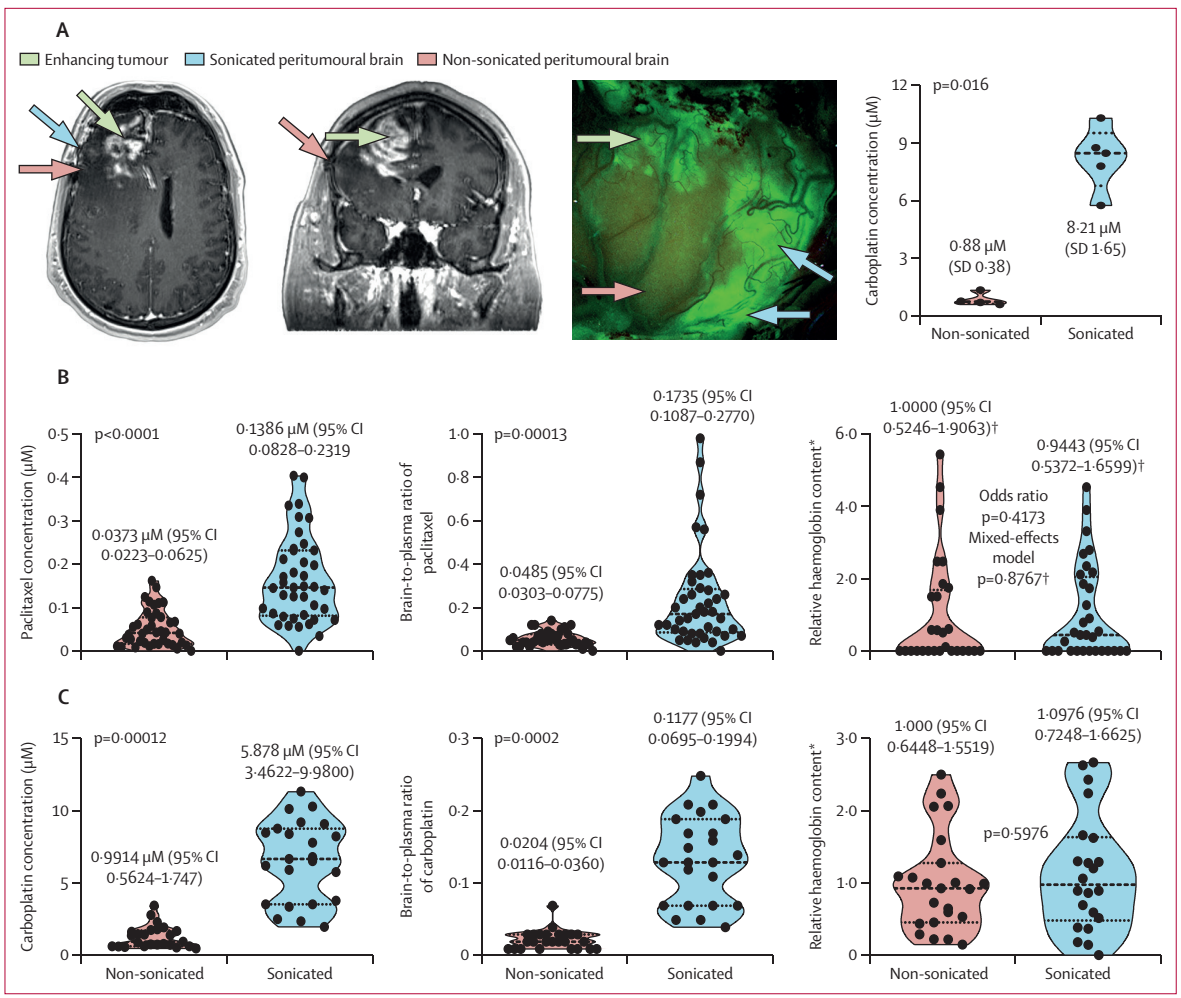

Figure 4: **Analysis of the effect of LIPU-MB on the concentration of paclitaxel and carboplatin in the peritumoural brain**
(A) Example of a case in which intraoperative LIPU-MB was done in the peritumoural brain for pharmacokinetic analysis of carboplatin concentrations. Stereotactic coordinates for each biopsy site recorded on the preoperative MRI are indicated by coloured arrows in axial and coronal planes, and on the photo from surgical microscope. Violin plot shows the absolute carboplatin concentrations for biopsy samples corresponding to the sonicated and non-sonicated peritumoural brain (n=5 biopsy samples for sonicated brain and n=4 for non-sonicated brain). p value was calculated with the Wilcoxon rank sum exact test. (B–C) Violin plots showing absolute drug concentrations (left), brain-to-plasma ratios (using plasma levels at 45 min after LIPU-MB; centre), and corresponding haemoglobin content (right) relative to non-sonicated brain following intravenous administration of albumin-bound paclitaxel (seven patients, 81 biopsy samples [41 sonicated and 40 non-sonicated], of which 28 non-sonicated and 32 sonicated samples were also analysed for haemoglobin; B) and carboplatin (three patients, 48 biopsy samples [23 sonicated and 25 non-sonicated], of which 22 sonicated and 23 non-sonicated biopsies were also analysed for haemoglobin; C) p values and times-increase in means were calculated with a mixed-effects model in the case of differences between non-sonicated and sonicated samples for paclitaxel and carboplatin drug concentrations, brain-to-plasma ratios, and haemoglobin content in carboplatin-related samples. For haemoglobin content in paclitaxel samples, 45% of samples had undetectable haemoglobin; therefore, we fit a generalised estimating equation model, and obtained an odds ratio associated with haemoglobin levels >0% between groups. We also present the mixed model p value, where samples with a value of 0% were excluded from the analysis. *Haemoglobin content was normalised by dividing individual values by the average of haemoglobin values in non-sonicated samples. †Samples with a value of 0 were excluded from these calculations. LIPU-MB=low-intensity pulsed ultrasound with concomitant administration of intravenous microbubbles.

descriptive analysis, the median progression-free survival was 2·9 months (95% CI 2·7–4·6) and overall survival was 11 months (7·95–not reached). Most patients discontinued study treatment because of disease progression, except for two patients, who discontinued treatment in the absence of tumour progression after five cycles to avoid worsening of cumulative chemotherapy-related toxicity. Kaplan-Meier and swimmer's plots summarising per-patient timelines of treatment and outcomes are included in the appendix (p 17). Upon progression, of the 17 participants, three (18%) did not receive additional treatment due to poor clinical condition, seven (41%) underwent additional tumour resection surgery, ten (59%) received immunotherapy (pembrolizumab), five (29%) received chemotherapy (two [12%] were treated with carboplatin and three [18%] with lomustine), and 12 (71%) received bevacizumab. Targeted therapy was used in two (12%) patients, and two (12%) additional patients received vaccine therapy.

Discussion

Our study shows that LIPU-MB can effectively enhance the delivery of albumin-bound paclitaxel and carboplatin across the blood–brain barrier into the human brain, and, in the case of albumin-bound paclitaxel, that this can be done safely. The safety of repeated LIPU-MB with skull-implantable systems has been reported, yet in our study the brain sonication field was 9-times larger than that in initial pilot studies that used a single ultrasound emitter.[10] We achieved blood–brain barrier opening in deep, critical brain structures such as the thalamus and basal ganglia. We sonicated every 3 weeks per the established schedule for albumin-bound paclitaxel at a dose of up to 260 mg/m². Although LIPU-MB has been done every 2 weeks in patients with Alzheimer's disease,[15] too frequent sonication (eg, daily) could lead to skin breakdown at the puncture site. The reproducibility of blood–brain barrier opening over multiple cycles by LIPU-MB has been previously reported.[14] Moreover, the safety of LIPU-MB-based blood–brain barrier opening using transcranial devices has also been shown,[12,13,19] supporting the feasibility of this approach.

We escalated the dose of albumin-bound paclitaxel to 260 mg/m², the approved dose for metastatic breast cancer.[20] Although we observed dose-dependent encephalopathy, a known rare side-effect of paclitaxel, this effect was spontaneously reversible with less than 48 h, and treatments were continued. Overall, we confirmed our preclinical observation that enhancing the brain delivery of albumin-bound paclitaxel with LIPU-MB is well tolerated.[6]

Pharmacokinetic studies done shortly after LIPU-MB showed the effect of blood–brain barrier opening on drug concentrations in the human brain. Our results are in line with preclinical studies reporting that drug penetration into the brain tissue after LIPU-MB is influenced by the molecular weight.[21] LIPU-MB increased carboplatin (molecular weight 371 g/mol) brain-to-plasma ratio by 5·8-times compared with non-sonicated brain samples, while the increase seen with paclitaxel (molecular weight 853 g/mol) was 3·6-times higher than in non-sonicated samples. We observed a tighter correlation between carboplatin and fluorescein concentrations than between paclitaxel and fluorescein concentrations in the brain. Consistently, the molecular weight of fluorescein (412 g/mol) is similar to that of carboplatin.

Preclinical studies cannot inform whether LIPU-MB would lead to meaningful concentrations of circulating drugs in the human brain, because dosing of drugs and microbubbles, infusion rates, biodistribution, sonication parameters, and drug clearance rates vary across species. Measurement of absolute drug concentrations in the human brain after LIPU-MB is especially important in gliomas because the peritumoural brain, where the blood–brain barrier is intact, is infiltrated by glioma cells.

We previously reported an analysis of the susceptibility of human glioma cells to paclitaxel,[5] which showed that half of the cell lines used were resistant to paclitaxel (mean 50% inhibitory concentration [IC_{50}] 1·6 μM) and half were susceptible (mean IC_{50} 0·025 μM), offering an approximation of meaningful paclitaxel concentrations. The pharmacokinetic studies reported in this Article were done with albumin-bound paclitaxel doses of 40–80 mg/m², leading to a mean parenchymal concentration of paclitaxel of 0·1386 μM in sonicated brain tissue. Considering that the 260 mg/m² dose we used in the therapeutic dose-escalation part of the study is 3–6-times higher than the intraoperative doses we used in the pharmacokinetic analyses, and that paclitaxel plasma concentrations increase proportionally to albumin-bound paclitaxel dose,[22] our results indicate that use of LIPU-MB with concomitant albumin-bound paclitaxel infusion leads to paclitaxel concentrations that are cytotoxic for half of human glioma cell lines.

Our results provide insight into the rate of restoration of blood–brain barrier integrity after LIPU-MB. Previous studies in humans reported restoration of blood–brain barrier integrity by 24 h after sonication,[23–25] and preclinical studies showed that blood–brain barrier repair starts shortly after LIPU-MB and is completed within 6 h.[26,27] By contrast, our analyses suggest that most blood–brain barrier integrity is restored within 1 h after LIPU-MB. This finding is important because it shows that a delay in drug administration after LIPU-MB is likely to lead to a peak in drug plasma concentrations when the blood–brain barrier is largely restored, limiting penetration of the agent into the brain. The temporal dynamics of blood–brain barrier repair are complex and vary depending on the LIPU-MB technology (eg, sonication parameters used)[27] and on the molecular characteristics of the drug.[28] Thus, animal modelling studies might be unreliable to optimise the timing of the LIPU-MB procedure relative to drug infusion in human patients.

There are several limitations of our image-based temporal analysis of blood–brain barrier closure. Enhancement might not have a linear association with gadolinium concentration, and permeability of gadolinium might not be representative of that of other molecules. Additionally, we did not characterise the decay in post-sonication enhancement past 150 min.

The SC9 can target a brain volume of approximately 53 mL. Although this volume is considerably larger than that targeted by other skull-implantable devices reported previously,[10] it might not be sufficient to be efficacious in the treatment of large tumours because sonication coverage of a large portion of peritumoural brain is required. Other limitations of the SC9 device include the fixed field of sonication and the need for percutaneous connection of the device, which might limit the frequency of LIPU-MB.

Important pharmacokinetic questions remain un-answered. The temporal and spatial dynamics of drug

accumulation, dispersion, and clearance in the human brain following LIPU-MB, and characterisation of the effect of this procedure on drug concentrations in tumour tissue, remain largely unexplored. Preclinical studies in rats suggest that LIPU-MB can enhance the delivery of drugs into the tumour core and stabilise drug concentrations for longer in this compartment.[29]

Our trial results have led us to investigate LIPU-MB for the delivery of albumin-bound paclitaxel plus carboplatin for glioblastoma in an ongoing phase 2 clinical trial (NCT04528680). Along with several other reports, our findings support the feasibility of LIPU-MB to effectively bypass the blood–brain barrier and treat diseases in the brain, an organ that is beyond the reach of many pharmacological agents.

Contributors

AMS and RS conceived and designed the trial, had access to the data, and verified the results presented in the manuscript. AMS did the surgery for resection, intraoperative pharmacokinetic experiment including sonication and biopsy, and SC9 implant. AG did the sample collection, cataloguing, and annotation. AC, the principal investigator for the LIPU-MB and carboplatin trial (NCT03744026), did the pharmacokinetic analysis with carboplatin as a collaboration. MRI analysis was done by BL, DYZ, GB, MC, and AMS. JFB did the neuroanaesthesia related to the intraoperative pharmacokinetic study. MM quantified haemoglobin, paclitaxel, carboplatin, and fluorescein concentrations. CA, KS, AMS, PK, RVL, and RS did the sonications. AMS, RS, RVL, PK, KD, CA, RW, KS, and CG provided care related to trial procedures and assessments. IBH and HZ contributed to the statistical design and analyses and had access to the data. AMS, CA, and RS accessed and verified the underlying study data and confirmed the accuracy of the results presented in the manuscript. VAA helped generating graphs for figures. CA and CG provided trial oversight and data management. AMS and RS wrote the manuscript. MSL, VAA, CD, MC, RVL, GB, and CA revised the manuscript.

Declaration of interests

AMS and RS have received in-kind (drug) support from Bristol-Myers Squibb, in-kind (ultrasound devices) and research support from and Carthera, and in-kind (drug) and research support from Agenus. AMS, DYZ, VAA, and RS are co-authors of intellectual property filed by Northwestern University related to therapeutic ultrasound. RS has acted or is acting as a scientific advisor or has served on advisory boards for the following companies: Alpheus Medical, AstraZeneca, Boston Scientific, Carthera, Celularity, GT Medical, Insightec, Lockwood (BlackDiamond), Northwest Biotherapeutics, Novocure, Syneos Health (Boston Biomedical), TriAct Therapeutics, and Varian Medical Systems. RVL is on the scientific advisory board and speakers' bureau for Merck and on the speakers' bureau for Novocure; has obtained research support from Bristol-Myers Squibb; and has received honoraria for editing from EBSCO INFORMATION services, Medlink, Neurology, and Elsevier. PK participates in advisory boards for Novocure, Janssen, SDP Oncology, Affinia, Sintetica, Mirati; has done consulting for Biocept, Enclear Therapies, Affinia Therapeutics and Bioclinica; and has received research support from Genentech and Novocure. MC, CD, GB, and AC are employees of Carthera, inventors of patents related to the technology, or have stock ownership in Carthera. AC has received funding support from Horizon 2020 European Innovation Council; is a paid consultant of Carthera; and is part of the Board of Directors of Carthera. JB is vice chair of the Neuro Education Track Subcommittee from the American Society of Anesthesiologists.

Data sharing

The trial protocol is provided in the appendix. De-identified data from this study can be made available upon request and approval by the study management committee and subject to appropriate data transfer agreements. Requests should be directed to AMS.

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