Clinical Cancer Research

Overcoming the Blood–Brain Barrier with an Implantable Ultrasound Device

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Ultrasound-based blood–brain barrier disruption enhances drug delivery. To bypass the human skull, an implantable ultrasound emitter was developed, and proven safe and feasible in a first-in-human trial. Next development steps aim for larger field of disruption, quantification of drug levels, use of various drugs, and ultimately a pivotal trial demonstrating improved outcome.

See related article by Idbaih et al., p. 3793

In this issue of *Clinical Cancer Research*, Idbaih and colleagues report on their phase I trial of opening the blood–brain barrier (BBB) with the use of an implantable ultrasound (1). Infiltrative gliomas and glioblastoma in particular, remain an incurable disease. As numerous novel therapeutic approaches have failed in controlled clinical trials, temozolomide remains the first-line drug in the treatment of these tumors, which is in part explained by its good penetration across the BBB. Indeed, the BBB is a major impediment to drug therapy of brain tumors, and thus, the technology evaluated on this trial overcomes such limitation.

Pulsed ultrasound, when used in combination with intravenous injection of microbubbles, transiently disrupts the BBB. This technology has been around for some time, and shown to enhance delivery of antitumoral agents to the brain in a multitude of preclinical models. However, translation of this approach into patients requires the ultrasonic waves to either penetrate or bypass the relatively thick human skull. Our French colleagues take it to a new level by implanting the ultrasound emitter into a window on the patients' skull, thus overcoming the intrinsic resistance of the skull when using conventional external systems. This system has allowed easy and repeat opening of the BBB. The ultrasound emitter activates microbubbles that are simultaneously administered intravenously. By this means, the BBB is mechanically disrupted, and diffusion of larger and polar molecules into the brain becomes feasible. The BBB opening is reversible and lasts for several hours after the sonication.

Here, Idbaih and colleagues have successfully treated 19 patients with BBB disruption using the implantable ultrasound emitter, and concomitant administration of the cytotoxic chemotherapy agent carboplatin (1, 2). They visualize the opening of the BBB as temporary extravasation of gadolinium on MRI performed immediately after each sonication. They report "successful" BBB opening in 52 of 65 sonication sessions. Overall, treatment-emergent toxicity was mild–moderate and related to the known toxicity of the chemotherapy agent used. No hemorrhage or severe neurologic symptoms were observed. Two occurrences of transient grade IV edema were attributed to the ultrasound and BBB opening, one event occurring within hours of sonication, the other only on day 15 and possibly related to tumor progression.

Idbaih and colleagues chose carboplatin as the chemotherapy agent for this first in human trial. The small number of patients does not allow for any conclusions regarding treatment efficacy, nevertheless, the trend for improved patient outcome in patients with successful opening of the BBB is encouraging. The delivery of other and potentially more effective agents will certainly have to be investigated in future trials.

Ultrasound-based BBB disruption is an emergent technology actively being investigated in gliomas in at least five separate clinical trials currently registered on ClinicalTrials.gov (Table 1). This approach to enhancing drug delivery could have an important impact on brain tumor therapy by making it possible to achieve efficacious delivery of potent drugs that otherwise would not penetrate across the BBB.

The concept of implantable ultrasound emitters is intriguing. Given that the ultrasonic waves do not penetrate across the bone, this system avoids variability of acoustic transmission secondary to irregularities in skull thickness, or metal plates that are commonly used to fixate the bone after a craniotomy in these patients. Implantable ultrasound devices can generate reproducible sound waves targeted to the brain tissue infiltrated by tumor cells. Therefore, this technology does not require complex MRI guidance or feedback systems to modulate the high-energy pulses that are required for BBB disruption by transcranial ultrasound technologies (3–5). Thus with this approach, BBB disruption promises to be simple and accessible, allowing for repetitive treatments in an outpatient setting. Potent larger molecules may be delivered to infiltrating brain tumor cells that are normally protected by the BBB. In this article the principle feasibility of this technology has been nicely demonstrated. Yet, between the proof of principle and the broad adaptation of this emergent technology, there will be several challenges to be overcome (Fig. 1). Quantification of drug levels in the tumor and in the adjacent infiltrated human brain tissue would be informative. Whereas preclinical studies demonstrate effective opening of the BBB, there are several species' differences that limit the extrapolation and complicate implementation of these approaches in humans. The acoustic pressures and the dosing regimens used in patients cannot be directly tested in small animals. Another

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Table 1. Ongoing early-phase clinical trials investigating ultrasound for BBB opening

Device/intervention	Disease/population	Phase	Pts (*N*)	Location	Status	NCT#
Implantable ultrasound "Sonocloud-1"	GBM rec	I	21	Paris, France	Completed	02253212
Implantable ultrasound "Sonocloud-9"	GBM rec	I/II	30	International	Completed	03744026
Transcranial MRI-guided focused ultrasound "Exablate"	GBM rec	I	10	Toronto, Canada	Completed	02343991
Transcranial focused ultrasound "Navi"	GBM rec	I	9	Taoyuan, Taiwan	Recruiting	03626896
Transcranial MRI-guided focused ultrasound "Exablate"	Breast cancer mets	I	10	Toronto, Canada	Planned	03714243
Transcranial MRI-guided focused ultrasound "Exablate"	High-grade glioma rec	I	20	Baltimore, MD	Recruiting	03551249

Abbreviations: GBM, glioblastoma; mets, brain metastases; NCT#, registration number in ClinicalTrials.gov; pts, patients; rec, recurrent.

requirement is expanding the volume of BBB disruption. For this study, only one single ultrasound emitter was implanted, thus providing BBB disruption to only a small field of sonication. However, as almost all primary brain tumors are diffusely infiltrating diseases with tumor cells migrating well beyond the initial visible tumor margin, larger volume BBB disruption will be important to achieve a clinical impact. A second-generation implantable device with nine ultrasound emitters is currently undergoing clinical testing by the same group of investigators. And finally, before broad adoption of ultrasound-based BBB disruption for drug delivery in general, the clinical value will need to be demonstrated for several therapeutic agents. The choice of carboplatin, an agent that is occasionally used for salvage therapy in recurrent glioma has been used for this first-in-human clinical trial, largely because the agent is established with a well-known toxicity profile. The experience with carboplatin may be

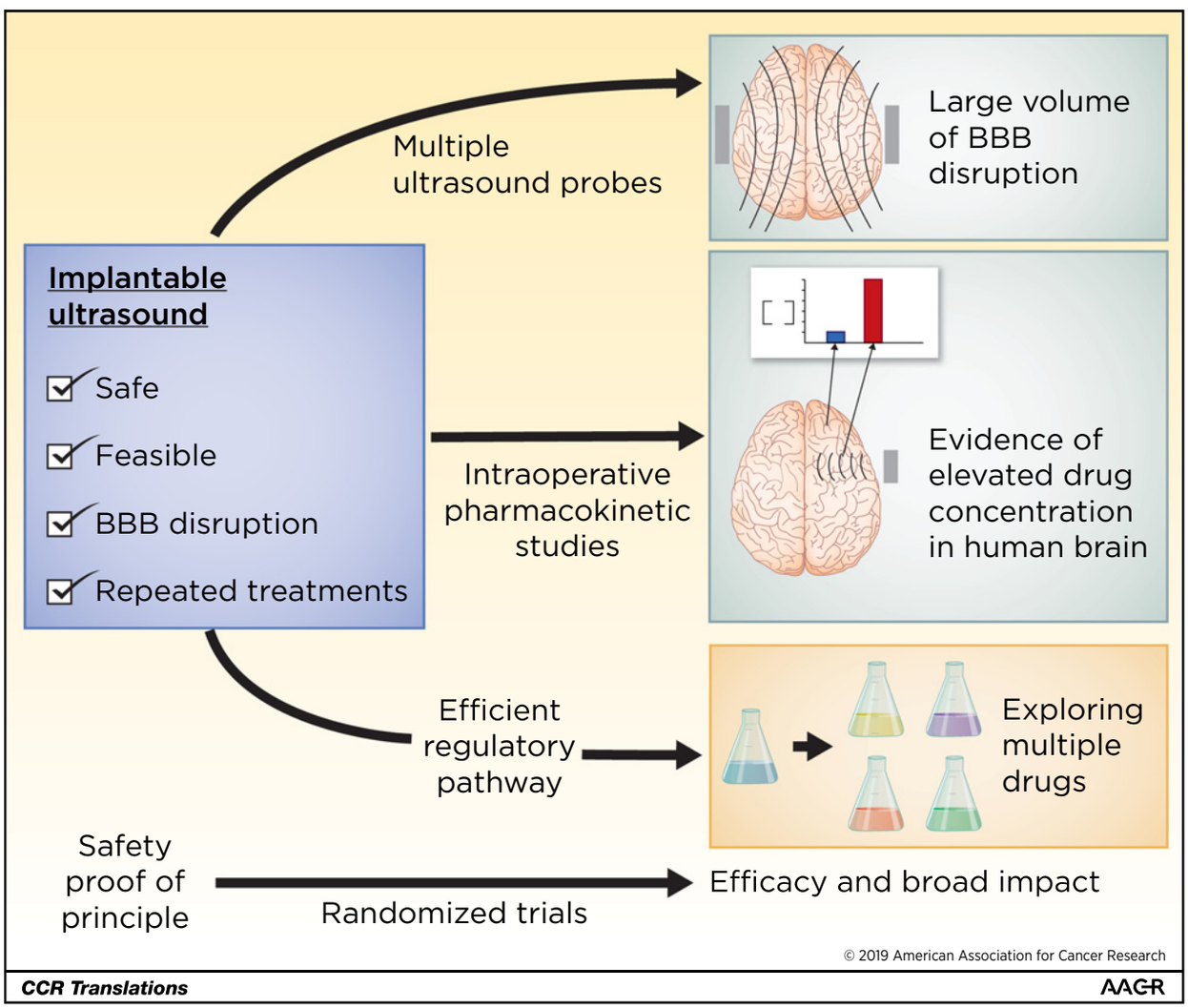

Figure 1.
Next steps in development of implantable ultrasound. Boxes represent implantable ultrasound device.

extrapolated to other potentially more active antitumor agents. It will be important to establish streamlined regulatory pathways that allow the concomitant use of various chemotherapy agents and drugs without repeating every clinical experiment. Sonication parameters can be obtained and extrapolated from prior trials. For many established and novel drugs with promising preclinical activity the limited penetration and distribution beyond the BBB has been an important cause of failure. Ultrasound-based opening of the BBB provides an opportunity for adequate regional drug delivery with limited local or systemic toxicity. And finally, it remains to be evaluated whether such a technology can also enhance drug delivery for other neurologic diseases. We commend Idbaih and colleagues for this innovative technology which opens both the BBB, as well as exciting therapeutic possibilities for gliomas, a disease beyond reach for most drugs.

Disclosure of Potential Conflicts of Interest

A.M. Sonabend and R. Stupp are inventors of a patent for combining ultrasound with albumin-bound paclitaxel for treating brain tumors (patent 47460-60). No other potential conflicts of interest were disclosed.

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