Chemotherapy drug reaches brain in humans for first time

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A major impediment to treating the deadly brain cancer glioblastoma has

been that the most potent chemotherapy can't permeate the blood-brain barrier to reach the aggressive brain tumor.

But now Northwestern Medicine scientists report results of the first in-human clinical trial in which they used a novel, skull-implantable ultrasound device to open the blood-brain barrier and repeatedly permeate large, critical regions of the human brain to deliver chemotherapy that was injected intravenously.

The four-minute procedure to open the blood-brain barrier is performed with the patient awake, and patients go home after a few hours. The results show the treatment is safe and well tolerated, with some patients getting up to six cycles of treatment.

This is the first study to successfully quantify the effect of ultrasound-based blood-brain barrier opening on the concentrations of chemotherapy in the human brain. Opening the blood-brain barrier led to an approximately four- to six-fold increase in drug concentrations in the human brain, the results showed.

Scientists observed this increase with two different powerful chemotherapy drugs, paclitaxel and carboplatin. The drugs are not used to treat these patients because they do not cross blood-brain barrier in normal circumstances.

In addition, this is the first study to describe how quickly the blood-brain barrier closes after sonication. Most of the blood-brain barrier restoration happens in the first 30 to 60 minutes after sonication, the scientists discovered. The findings will allow optimization of the sequence of drug delivery and ultrasound activation to maximize the drug penetration into the human brain, the authors said.

"This is potentially a huge advance for glioblastoma patients," said lead

investigator Dr. Adam Sonabend, an associate professor of neurological surgery at Northwestern University Feinberg School of Medicine and a Northwestern Medicine neurosurgeon.

Temozolomide, the current chemotherapy used for glioblastoma, does cross the blood-brain barrier, but is a weak drug, Sonabend said.

The paper will be published May 2 in *The Lancet Oncology*.

The blood-brain barrier is a microscopic structure that shields the brain from the vast majority of circulating drugs. As a result, the repertoire of drugs that can be used to treat brain diseases is very limited. Patients with brain cancer cannot be treated with most drugs that are otherwise effective for cancer elsewhere in the body, as these do not cross the blood-brain barrier. Effective repurposing of drugs to treat brain pathology and cancer require their delivery to the brain.

In the past, studies that injected paclitaxel directly into the brain of patients with these tumors observed promising signs of efficacy, but the direct injection was associated with toxicity such as brain irritation and meningitis, Sonabend said.

Blood-brain barrier recloses after an hour

The scientists discovered that the use of ultrasound and microbubble-based opening of the blood-brain barrier is transient, and most of the blood-brain barrier integrity is restored within one hour after this procedure in humans.

"There is a critical time window after sonification when the brain is permeable to drugs circulating in the bloodstream," Sonabend said.

Previous human studies showed that the blood-brain barrier is

completely restored 24 hours after brain sonication, and based on some animal studies, the field assumed that the blood-brain barrier is open for the first six hours or so. The Northwestern study shows that this time window might be shorter.

In another first, the study reports that using a novel skull-implantable grid of nine ultrasound emitters designed by French biotech company Carthera opens the blood-brain barrier in a volume of brain that is nine times larger than the initial device (a small single-ultrasound emitter implant). This is important because to be effective, this approach requires coverage of a large region of the brain adjacent to the cavity that remains in the brain after removal of glioblastoma tumors.

Clinical trial for patients with recurrent glioblastoma

The findings of the study are the basis for an ongoing phase 2 clinical trial the scientists are conducting for patients with recurrent glioblastoma. The objective of the trial—in which participants receive a combination of paclitaxel and carboplatin delivered to their brain with the ultrasound technique—is to investigate whether this treatment prolongs survival of these patients. A combination of these two drugs is used in other cancers, which is the basis for combining them in the phase 2 trial.

In the phase 1 clinical trial reported in this paper, patients underwent surgery for resection of their tumors and implantation of the ultrasound device. They started treatment within a few weeks after the implantation.

Scientists escalated the dose of paclitaxel delivered every three weeks with the accompanying ultrasound-based blood-brain barrier opening. In subsets of patients, studies were performed during surgery to investigate the effect of this ultrasound device on drug concentrations. The blood-

brain barrier was visualized and mapped in the operating room using a fluorescent die called fluorescein and by MRI obtained after ultrasound therapy.

"While we have focused on brain cancer (for which there are approximately 30,000 gliomas in the U.S.), this opens the door to investigate novel drug-based treatments for millions of patients who suffer from various brain diseases," Sonabend said.

More information: Adam M Sonabend et al, 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, *The Lancet Oncology* (2023). DOI: 10.1016/S1470-2045(23)00112-2

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