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5-Aminolevulinic acid sonodynamic therapy in recurrent glioblastoma: A first-in-human phase 0/1 clinical trial

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Background

5-aminoleveulinic acid sonodynamic therapy (5-ALA SDT) is a drug-device strategy that exploits the metabolic liabilities of cancer. Following systemic administration of 5-ALA, incomplete tumor metabolism leads to accumulation of a photosensitive intermediary, protoporphyrin-IX (PpIX). Activation of PpIX by non-invasive, non-ablative magnetic resonance-guided focused ultrasound (MRgFUS) induces cytotoxic reactive oxygen species and tumor cell death. This first-in-human phase 0/1 study investigates the feasibility, safety, and biological effects of 5-ALA SDT in recurrent glioblastoma patients (GBM).

Methods

Ascending energy doses of 5-ALA SDT are tested in adult patients with recurrent GBM undergoing planned re-resection. In a Dose-Escalation Arm, 9-18 patients are assigned to one of three dose levels of MRgFUS (200J, 400J, and 800J), followed by a four-day interval to tumor resection. In each patient, half the tumor volume, including Gadolinium-enhancing and nonenhancing tumor, is targeted with MRgFUS and the other half is an internal control. Using tumor pharmacodynamic endpoints, the Minimum Biological Dose (MBD) associated with 5-ALA SDT response is identified. In a subsequent Time-Escalation Arm, 12 patients are treated at the MBD and assigned to one of two time-intervals (two-days vs. six-day) between SDT and resection.

Results

As of May 1, accrual to the 200J dose level was completed (n=3) without significant drug- or device-related adverse events. No cellular or radiographic changes to non-targeted tissue were observed. Following 5-ALA infusion, the median Cmax for 5-ALA and PpIX were 307 μM and 319 nM, respectively. For all patients, the oxidative stress biomarkers 4-hydroxynonenal , glutathione, cysteine, and thiol were elevated in treated tissue vs. internal control. Similarly, the apoptosis biomarker cleaved caspase-3 was increased in treated tumor vs. control (median, 48.6% vs. 29.6%, p=0.05).

Conclusions

This initial, first-in-human experience with a new therapeutic modality for recurrent glioblastoma indicates that 5-ALA SDT is well-tolerated and safe at 200J. Sonodynamic therapy leads to targeted oxidative stress and accompanying cell death in human glioblastoma tissue.

Clinical trial identification

NCT04559685.

Legal entity responsible for the study

Neurotrials LLC.

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Disclosure

All authors have declared no conflicts of interest.

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