ABSTRACT

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Chronic convection-enhanced delivery of topotecan for patients with recurrent glioblastoma: a first-in-patient, single-centre, single-arm, phase 1b trial.

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BACKGROUND: Topotecan is cytotoxic to glioma cells but is clinically ineffective because of drug delivery limitations. Systemic delivery is limited by toxicity and insufficient brain penetrance, and, to date, convection-enhanced delivery (CED) has been restricted to a single treatment of restricted duration. To address this problem, we engineered a subcutaneously implanted catheter-pump system capable of repeated, chronic (prolonged, pulsatile) CED of topotecan into the brain and tested its safety and biological effects in patients with recurrent glioblastoma.

METHODS: We did a single-centre, open-label, single-arm, phase 1b clinical trial at Columbia University Irving Medical Center (New York, NY, USA). Eligible patients were at least 18 years of age with solitary, histologically confirmed recurrent glioblastoma showing radiographic progression after surgery, radiotherapy, and chemotherapy, and a Karnofsky Performance Status of at least

70. Five patients had catheters stereotactically implanted into the glioma-infiltrated peritumoural brain and connected to subcutaneously implanted pumps that infused 146 μM topotecan 200 μL/h for 48 h, followed by a 5-7-day washout period before the next infusion, with four total infusions. After the fourth infusion, the pump was removed and the tumour was resected. The primary endpoint of the study was safety of the treatment regimen as defined by presence of serious adverse events. Analyses were done in all treated patients. The trial is closed, and is registered with ClinicalTrials.gov, NCT03154996.

FINDINGS: Between Jan 22, 2018, and July 8, 2019, chronic CED of topotecan was successfully completed safely in all five patients, and was well tolerated without substantial complications. The only grade 3 adverse event related to treatment was intraoperative supplemental motor area syndrome (one [20%] of five patients in the treatment group), and there were no grade 4 adverse events. Other serious adverse events were related to surgical resection and not the study treatment. Median follow-up was 12 months (IQR 10-17) from pump explant. Post-treatment tissue analysis showed that topotecan significantly reduced proliferating tumour cells in all five patients.

INTERPRETATION: In this small patient cohort, we showed that chronic CED of topotecan is a potentially safe and active therapy for recurrent glioblastoma. Our analysis provided a unique tissue-based assessment of treatment response without the need for large patient numbers. This novel delivery of topotecan overcomes limitations in delivery and treatment response assessment for patients with glioblastoma and could be applicable for other anti-glioma drugs or other CNS diseases. Further studies are warranted to determine the effect of this drug delivery approach on clinical outcomes.

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