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# Chronic Convection-Enhanced Intratumoral Delivery of Chemotherapy for Glioblastoma

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In “Chronic convection-enhanced delivery of topotecan for patients with recurrent glioblastoma: a first-in-patient, single-center, phase 1b trial,” Spinazzi et al. present the first in human study of chronic convection-enhanced delivery (CED) of a chemotherapeutic agent to five recurrent glioblastoma (GBM) patients.[1] CED involves the stereotactic placement of catheter(s) into a tumor, followed by connecting the catheter(s) to pumps to allow intratumoral drug distribution by bulk flow via continuous, low-grade positive-pressure microinfusion.[2] The rationale for CED of anticancer drugs in GBM is its ability to deliver high intratumoral drug concentrations, simultaneously bypassing the blood-brain barrier, achieving diffuse coverage throughout the tumor, and avoiding toxicity from systemic drug administration.[2]

While better catheter design and improved understanding of optimal catheter positioning have improved results with glioblastoma CED,[3] multiple CED trials have revealed that successful intracranial drug delivery will likely need to be repeated to target tumor cells that were either not dividing or failed to receive sufficient drug during the initial CED, as evidenced by studies in which post-CED recurrence typically occurred outside infused areas.[4]

This study addressed this limitation of CED by investigating chronic CED of the topoisomerase inhibitor topotecan (TPT) in five patients. In this phase Ib clinical trial, catheters were stereotactically implanted into glioma-infiltrated peritumoral brain and connected to subcutaneously implanted pumps that infused 146 μM topotecan at 200 μL/hour over 48 hours followed by a 5-7-day therapy holiday before the next infusion for four total infusions per patient. After the fourth infusion, the pump was removed and the tumor was resected with stereotactic-guided biopsy samples collected. Co-infusion of gadolinium with the first and fourth treatments was performed to determine volume of drug distribution (Vd) and backflow. Chronic CED resulted in large and stable Vd with only 8.8% of the total infused volume identified as backflow. Average TPT concentrations from the biopsy samples ranged from 1.1-30 μM. In post-CED resected tissue, immunohistochemistry revealed decreased Ki67 and SOX2 labeling indices. Similarly, $^{18}$FDG uptake was decreased after CED. RNA-sequencing of tumor tissue post-CED showed upregulated

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Declaration of Interest

We (J.S.Y. and M.K.A.) declare no competing interests.

DNA damage and apoptosis genes relative to pre-treatment samples. Finally, the $CD68^+$ macrophage population increased and pro-inflammatory cytokine genes were upregulated after CED treatment. No change was observed in neuronal markers, confirming their clinical observation of no adverse events and suggesting chronic CED of TPT is not neurotoxic.

This trial builds on several preclinical and clinical investigations completed by this team and others. The choice of TPT emerged from preclinical CED investigations showing safety and efficacy,[5] which led to a phase I trial of TPT CED in 16 recurrent GBM patients. This trial showed some examples of tumor regression, but there was a lack of response durability suggesting a need for repeat infusions.[6] The group then began investigating chronic CED with porcine models where CED of TPT was done for 10 days in pigs with Food and Drug Administration (FDA)-approved subcutaneous Synchromed-II pumps attached to intracranially implanted catheters.[7] This was followed by a longer study where intracranial CED of TPT for 32 days was performed with a single proximal ventricular catheter connected via a silastic lumbar catheter to a microinfusion Synchromed II pump that was implanted subcutaneously in the ipsilateral flank.[8] The authors found that high-flow rates up to 4 mL/day led to large and stable Vd without toxicities. Of note, the group also observed no toxicities from gadolinium mixed with the infusion, validating the chronic use of this previously described technique for monitoring infusions with MRI.[3]

The authors are to be commended for this trial, which constitutes a major advance for CED. Future development of this technique will hopefully allow for revision of the catheter location as the tumor target changes over time. Another modification to consider for chronic CED is embedding the chemotherapy into liposomes, to delay the agents release and increase time between treatments, as we have investigated with another topoisomerase inhibitor irinotecan (CPT-11) (NCT02022644). Future catheter refinement to minimize scar formation and achieve higher infusion rates without reflux could further improve lesion targeting and drug delivery with chronic CED. Furthermore, neurosurgeons will need to determine whether catheters should also target non-enhancing FLAIR bright regions known to contain infiltrating tumor cells,[10] that might be well served by intratumoral chemotherapy given that intact blood-brain barrier in these regions. Finally, the optimal agent(s) for chronic CED remains undetermined and may be patient specific in a precision medicine manner.

Answering these and other questions in preclinical studies and in future human studies of chronic CED could allow this technique to meaningfully reshape how GBM is treated.

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