

the implementation of androgen receptor pathway inhibition continuation during docetaxel chemotherapy for mCRPC.

Although the PRESIDE trial reported prolonged progression-free survival with enzalutamide continuation during subsequent docetaxel chemotherapy in patients with mCRPC, a careful discussion of the risks and benefits of continuing enzalutamide during docetaxel therapy in mCRPC and further investigation on survival are needed.

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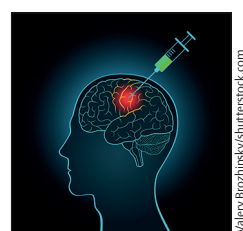
Chronic convection-enhanced intratumoural delivery of chemotherapy for glioblastoma

In *The Lancet Oncology*, Eleonora F Spinazzi and colleagues¹ present a first-in-human study of chronic convection-enhanced delivery (CED) of chemotherapy to five patients with recurrent glioblastoma.¹ CED involves stereotactic placement of catheter(s) into a tumour, followed by connecting the catheter(s) to pumps to allow intratumoural drug distribution by bulk flow via continuous, low-grade, positive-pressure microinfusion.² The rationale for CED of chemotherapies in glioblastoma is the ability of this technique to deliver high intratumoural drug concentrations throughout the tumour, bypass the blood–brain barrier, and avoid toxic effects from systemic drug administration.²

Although better catheter design and understanding of optimal catheter positioning have improved CED for glioblastoma,³ multiple CED trials have shown that intracranial drug delivery will probably need to be repeated to target tumour cells that were either not dividing or that received insufficient drug during

the initial CED, based on post-CED recurrence typically occurring outside the infused areas.⁴

Spinazzi and colleagues' study addressed this limitation of CED via chronic CED of the topoisomerase inhibitor topotecan. In this clinical trial, catheters were stereotactically implanted intratumourally and connected to subcutaneously implanted pumps that infused 146 μM topotecan at 200 μL/h for 48 h, followed by a 5–7-day washout period before the next infusion, with a total of four infusions per patient. After the fourth infusion, pumps were removed, and tumours were resected with stereotactic-guided biopsies collected. By co-infusing gadolinium with the first and fourth treatments, the authors measured the volume of drug distribution and backflow. Chronic CED produced a large stable volume of drug distribution, with only 8.8% (1.8 mL [mean maximum backflow volume] divided by 20.5 mL [mean maximum volume of distribution]) of the infused volume identified as backflow. Topotecan concentrations from biopsies



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were 1.1–30 µM, with topotecan identified in all but one biopsy, with µM concentrations found even 6.5 cm from the catheter tip. In post-CED resected tissue, immunohistochemistry revealed decreased Ki67 and SOX2 labelling indices compared with samples taken before CED. Similarly, [¹⁸F]fluorodeoxyglucose uptake was decreased after CED. Tumour tissue samples taken after CED showed upregulated apoptosis genes, macrophages, and pro-inflammatory cytokine genes compared with samples taken before CED. Unchanged neuronal markers confirmed the clinical observation of no adverse events.

Spinazzi and colleagues' trial advances on previous studies completed by their team and others. Previous work revealed topotecan to be the most effective and safest drug for CED in glioblastoma.⁵ This finding led to a phase 1 trial of topotecan CED in 16 patients with recurrent glioblastoma multiforme, with some findings of tumour regression but insufficient durability suggesting a need for repeated infusions.⁶ This result led the group to pursue porcine studies to develop chronic CED of topotecan. First, CED was done for 10 days in pigs with US Food and Drug Administration-approved subcutaneous Synchromed II pumps (Medtronic; Dublin, Ireland) attached to intracranially implanted catheters.⁷ This study was followed by a longer study of intracranial CED of topotecan for 32 days in the same porcine model.⁸ In that study,⁸ the authors used a single proximal ventricular catheter connected via a silastic lumbar catheter to a microinfusion Synchromed II pump implanted subcutaneously in the flank. They found that high flow rates up to 4 mL/day led to a large and stable volume of drug distribution throughout the treatment, without toxic effects. Notably, the group also observed no toxic effects 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 multiple catheters and modification of catheter locations over time. Embedding chemotherapy in liposomes could be considered, allowing for slower agent release and increased time between treatments, as we investigated with another topoisomerase inhibitor, irinotecan (CPT-11; NCT02022644). Future

catheter refinement to minimise scar formation and achieve higher infusion rates without reflux could further improve lesion targeting and drug delivery with chronic CED. Implementing chronic CED will also require an understanding of whether it is associated with treatment-related imaging changes, as occurs with other treatments.⁹ Furthermore, we must determine whether catheters should also target non-enhancing fluid attenuated inversion recovery bright regions, which are known to contain infiltrating tumour cells,¹⁰ and that might be well served by intratumoural chemotherapy given the intact blood-brain barrier in these regions. Additionally, the optimal agent(s) for chronic CED remains undetermined, and the choice of agent(s) might need to account for drug stability at body temperature or be patient-specific in a precision medicine manner.

Answering these and other questions in preclinical studies and future human studies of chronic CED could allow this technique to reshape glioblastoma multiforme treatment. This study by Spinazzi and colleagues constitutes a meaningful step towards that objective.

We declare no competing interests.

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