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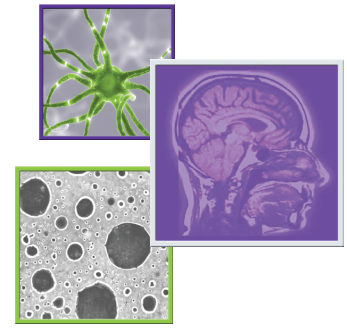

Convection-enhanced delivery for glioblastoma: targeted delivery of antitumor therapeutics

Timothy H Ung*[1], Hani Malone[1], Peter Canoll[2] & Jeffrey N Bruce[1]

Practice points

- Convection-enhanced delivery (CED) bypasses the blood–brain barrier and allows for targeted cerebral drug delivery.
- CED is a safe and effective drug delivery method for glioblastoma.
- CED increases local concentrations of antitumor agents while minimizing systemic toxicity.
- CED for glioblastoma provides increased flexibility for future therapeutic drug design, as a diverse group of agents can be delivered.
- Advancements in implantable catheter systems and catheter design will increase the integrity and efficacy of drug delivery.

SUMMARY Glioblastoma is the most common primary brain tumor in adults and carries a dismal prognosis despite advancements in treatment. Diffuse tumor infiltration precludes curative surgical resection and necessitates advancements in drug delivery mechanisms. Convection-enhanced delivery (CED) enables continuous local drug delivery for a diverse population of antitumor agents. Importantly, CED circumvents therapeutic challenges posed by the blood–brain barrier by facilitating concentrated local therapeutic drug delivery with limited systemic effects. Here, we present a concise review of properties essential for safe and efficient convection-enhanced drug delivery, as well as a focused review of clinical studies evaluating CED in the treatment of glioblastoma.

KEYWORDS
• convection-enhanced delivery • glioblastoma • glioma • high-grade glioma • targeted delivery of therapeutics for glioblastoma

Glioblastoma (GBM) is a WHO grade IV malignant CNS neoplasm and is the most common primary brain tumor in adults. Overall incidence of GBM is three cases per 100,000 in the USA with an average age of 64 years at diagnosis [1]. Advances in treatment have improved 2-year survival from 5% (1989–1994) to 15% (2006–2010), but overall patient prognosis remains dismal [2,3].

The current standard of care for GBM includes maximal safe surgical resection of contrast enhancing disease on MRI, followed by adjuvant treatment with temozolamide and fractionated radiotherapy [4]. However, the diffuse infiltration of tumor cells beyond the borders of contrast enhancement gives rise to treatment failure, as tumor recurrence is often within 2–3 cm of the original tumor margin [5,6]. The surgical limitations inherent to GBM confer great potential to local drug delivery systems capable of infusing therapeutic agents to tumor-infiltrated brain parenchyma.

Convection-enhanced delivery (CED) platforms are implantable catheter systems that employ a pump to provide continuous positive pressure for local drug delivery. CED offers significant

[1]Department of Neurological Surgery, Columbia University Medical Center, New York, NY 10032, USA
[2]Department of Pathology & Cellular Biology, Columbia University Medical Center, New York, NY 10032, USA
*Author for correspondence: Tel.: +1 212 851 4744; TU2142@columbia.edu

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advantages over systemic chemotherapy by overcoming the challenges posed by the blood–brain barrier (BBB) and facilitating concentrated local therapeutic drug delivery with limited systemic toxicity [7]. Optimal systems for CED possess the capacity to:

- Deliver a diverse range of therapeutic agents;
- Efficiently and safely infuse drug in a continuous manner;
- Monitor the volume of distribution (Vd) of the administered agent;
- Target radiographic lesions with high spatial fidelity;
- Minimize systemic toxicity.

Optimal drug characteristics for CED include: tumor cell specific cytotoxicity, limited toxicity to normal brain, long therapeutic half-life and low BBB permeability to limit systemic toxicity. In this paper, we will first describe the pertinent properties of CED that have been delineated in preclinical studies and although previous clinical trials exist investigating the technical properties of CED, these will not be reviewed. Second, we will present relevant information from recent and ongoing clinical trials including infusate agent, preclinical studies and phase results.

CED: an overview

Originally pioneered by Bobo *et al.,* CED was found to facilitate the simple diffusion of macromolecules in the brain while accomplishing target tissue drug concentrations several orders of magnitude greater than systemic levels [8]. This work began to highlight the benefits afforded by CED over existing local drug delivery mechanisms, such as carmustine wafers and other diffusion-based drug delivery methods. Comparatively, CED allows for larger Vd without relying on concentration gradient-dependent mechanisms for diffusive drug delivery [8].

CED offers direct access to the tumor bed and bypasses the BBB permitting therapeutic drug delivery regardless of molecular size and charge. Early CED clinical trials using diphtheria toxin for recurrent malignant gliomas revealed these specific advantages, as regional perfusion of transferrin-CRM107 (Tf-CRM107) and a genetic mutant of diphtheria toxin produced local tumor responses without systemic toxicity [9]. This initial work validated the unique abilities of CED to deliver large toxic molecules with regional specificity and limited systemic toxicity.

Parameters in CED

A set of important parameters can dramatically impact the safety and efficiency of CED, including: infusion flow rate, cannula size, infusion volume, extracellular space/architecture and drug molecular size/charge. Important variables in determining infusion rate are cannula size and flow rate. Infusion studies have established acceptable critical flow rates and cannula sizes, outside of which backflow of infusate will occur secondary to decreased pressure of the cannula tract [10]. Variations in flow rate impact the location of infusate distribution. Lower infusion rates are associated with distribution localized primarily to the target tissue whereas higher infusion rates result in increased distribution into the surrounding parenchyma.

Cannula size has been found to have no effect on Vd; however, larger bore cannulas cause more tissue trauma on implantation and produce decreased resistance pathways along the brain parenchyma-catheter interface that are associated with increased rates of infusate reflux. Reflux of therapeutic drug increases the risk of leakage into subarachnoid spaces and chemical meningitis [10–12]. Current advancements in catheter design have been targeted toward development of a CED system that allows for high-flow diffusion without reflux. In particular, the introduction of the 'stepped' catheter that integrates an abrupt transition from large to small catheter tips [12,13].

Vd is the product of a direct and linear relationship with the volume infused (Vi) and is independent of catheter size. Important aspects influencing Vd are tissue extracellular space and therapeutic molecular size. Molecular size influences Vd/Vi as smaller particles have a higher Vd/Vi when compared with those with a larger molecular weight [8,11]. Furthermore, infusion into more compact target tissue with minimal extracellular space yields a higher volume of drug distribution when compared with target tissue with more diffuse extracellular space. Primate studies have demonstrated this inverse relationship, as CED of gadolinium bound albumin into pontine regions of the brainstem yielded higher Vd/Vi when compared with studies of other less dense regions of the brain [14].

Tissue-specific considerations

The dynamics of fluid flow through interstitial space is a critical component of convection-enhanced delivery in the brain. Regional differences in distribution exist between gray and white matter. With gray matter, there tends to be a more spherical distribution of infusate secondary to the isotropic nature of gray matter. This is contrary to observations seen within white matter, where distribution of infusate tends to parallel fiber tracts within the surrounding target tissue [14,15]. Drug distribution via CED also has an intimate relationship with cerebral vasculature and perivascular spaces. Experiments done by Hadaczek *et al.* illustrated that therapeutic distribution is largely dependent on fluid circulation within perivascular spaces, which is driven in part by cardiovascular properties. Most notably, cardiovascular pulse pressure was found to be highly correlative with distribution of convection-enhanced delivered agents [16].

Tumor-specific considerations

Tumor-specific considerations must be addressed when applying principles of CED to the treatment of GBM. Normal brain interstitial fluid pressure typically ranges between 1 and 2 mmHg. In the setting of various brain tumors, the interstitial pressure may be elevated to 50 mmHg and may also contain heterogeneous areas of focal elevations in interstitial pressure [17,18]. The higher intestinal pressure observed within GBMs compared with surrounding brain tissue produces an interstitial pressure gradient that alters the normally observed Vd. This pressure difference actively transports infusate out of the high-pressure areas of the tumor into the lower pressure areas, such as adjacent areas with less tumor infiltration and necrotic regions of malignant glioma.

Experiments with CED of C^{14} sucrose into RG-2 subcutaneous tumors in rats revealed that solute tended to collect in the tissue surrounding the tumor where interstitial pressure was lower. Further experiments infusing of 2 µl/min of C^{14}sucrose followed by tissue examination revealed minimal amounts of C^{14} present within large areas of tumor where interstitial pressure was higher [17]. Analogous results were observed when CED infusions were similarly applied to intracranial RG-2 xenografts. Autoradiography of xenographs 30 min after infusion showed very little C^{14} isotope retention [17].

The pressure gradients observed in malignant glioma may promote efflux of infusate out of the CED target. Importantly, such efflux shortens the window for therapeutic absorption, as water-soluble molecules have less time to enter the cellular membrane and receptor mediated therapeutics have a diminished opportunity to interact with their respective receptors [15]. Given the diffuse nature of GBM, some efflux of drug into adjacent parenchyma that has been invaded by tumor cells may be beneficial. Nevertheless, CED in GBM requires more concentrated infusate and increased treatment periods in order to accurately deliver antitumor agents [10].

Resection cavity considerations

Patient-specific post-resection anatomical variations in resection cavity location and size raise additional factors that must be considered when determining catheter placement. Protocol guidelines from previous trials endorse distal catheter tip placement at least 2 cm from the margin of resection along the anticipated direction of tumor progression [19]. US FDA-approved computerized software available from BrainLAB (Feldkirchen, Germany) allow for presurgical planning that utilizes patient specific MRI brain tissue characteristics to achieve an estimation of Vd, catheter placement and the total number of catheters needed. Placement of multiple catheters tips are to be separated by 2–4 cm and positioned into any region with suspected disease [19]. Furthermore, a balloon-tipped catheter system for CED has been developed and tested in a canine model. Inflation of the balloon to fill the resection cavity permits infusate into the tumor parenchyma with minimization of reflux. Infusate containing gadolinium showed superior cerebral penetration with inflated balloons when compared with uninflated balloons [20].

Prolonged CED via a subcutaneous catheter

Many trials have employed CED systems that utilize an external catheter to deliver antitumor therapeutics in the treatment of malignant glioma. However, use of externally positioned catheters prolongs required time spent in intensive care settings and exposes patients to serious infectious risks, effectively restricting total infusion time. In our experience, intracranial CED with an external catheter should be limited to 4 days to mitigate the risks of CNS infection [21]. However, our preclinical and clinical studies have demonstrated important advantages to prolonged infusion [21–23]. Accordingly, we have

developed an experimental system using a pig model that employs an implantable subcutaneous pump (Synchromed II, Medtronic, MN, USA). Subcutaneous pump implantation into the pig's back, followed by subcutaneous tunneling of a silastic catheter and targeted insertion into the frontal white matter offers a viable model for assessing the prolonged CED of infusate (Figure 1).

Our initial investigation involved the delivery of a mixture of topotecan and/or gadolinium for a period of 10 days into a nonglioma bearing pig. Initial results demonstrate the safety and feasibility of prolonged CED into targeted regions of the brain using an FDA approved subcutaneous implantable pump and catheter system (Figure 2A) [24]. Subsequent experiments with prolonged CED for up to 1 month in our porcine model demonstrated maximal volumes of distribution achieved at 1–3 days followed by a steady state of Vd (Figure 2B). The pig model offers distinct advantages over rodent models, as the larger brain size and analogous gray and white matter composition allows for clinically relevant investigations. These promising preliminary results support the feasibility of prolonged CED via a FDA approved subcutaneous catheter and pump, which could be (re)filled for extended drug delivery in an outpatient neurosurgery or neuro-oncology clinic.

CED of antitumor agents: a focused review of clinical trials

• Topotecan

Topotecan is derived from alkaloid camptothecin and is a topoisomerase I-inhibitor that causes single-strand DNA breaks during DNA replication. It exhibits its cytotoxic antitumoral effects against the essential human enzyme topoisomerase I during mitotic activity. It is an ideal agent for environments where there is increased cell cycle activity in the setting of a mitotically quiescent environment [25]. The ability to target all mitotically active cells supports the use of topotecan as an antiglioma agent, as it is able to target the large population of heterogenetic cells observed within GBM.

The systemic application of topotecan for GBM has historically been limited by poor pharmacological penetration across the BBB and systemic toxicities associated with dose escalation. Phase II studies centered on the systemic administration of topotecan for recurrent glioma failed to show substantial antitumor activity, though patients experienced severe side effects. Greater than 20% of patients experienced grade 4 leukopenia, with two patients dying secondary to infection related complications, and 27% of patients experienced grade 3–4 thrombocytopenia [26].

Our investigations into topotecan as a potential CED treatment for GBM began with preclinical testing in a PDGF-B glioma rat model. This model was developed using a PDGF-B expressing retrovirus stereotactically delivered into white matter of adult rats that infects glial progenitors and produces a glioma model histologically resembling GBM in humans [27,28]. Using an implantable osmotic pump connected to an intercerebral infusion cannula (Alzet, CA, USA), targeted delivery of topotecan was administered to the tumors. Results from this initial experience showed substantial survival

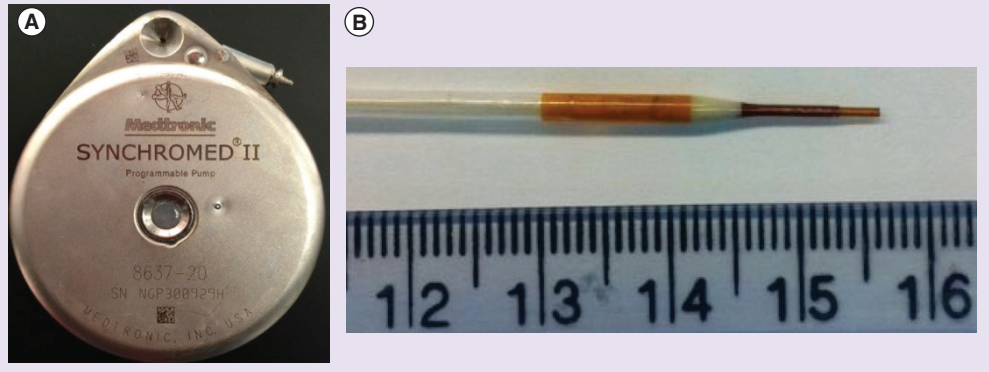

Figure 1. Implantable subcutaneous convection-enhanced delivery system. (A) Image of an experimental system using a pig model that employs an implantable subcutaneous pump that is implanted into the back of a pig (Synchromed II, Medtronic, MN, USA). **(B)** Image of a stepped catheter for convection-enhanced delivery.

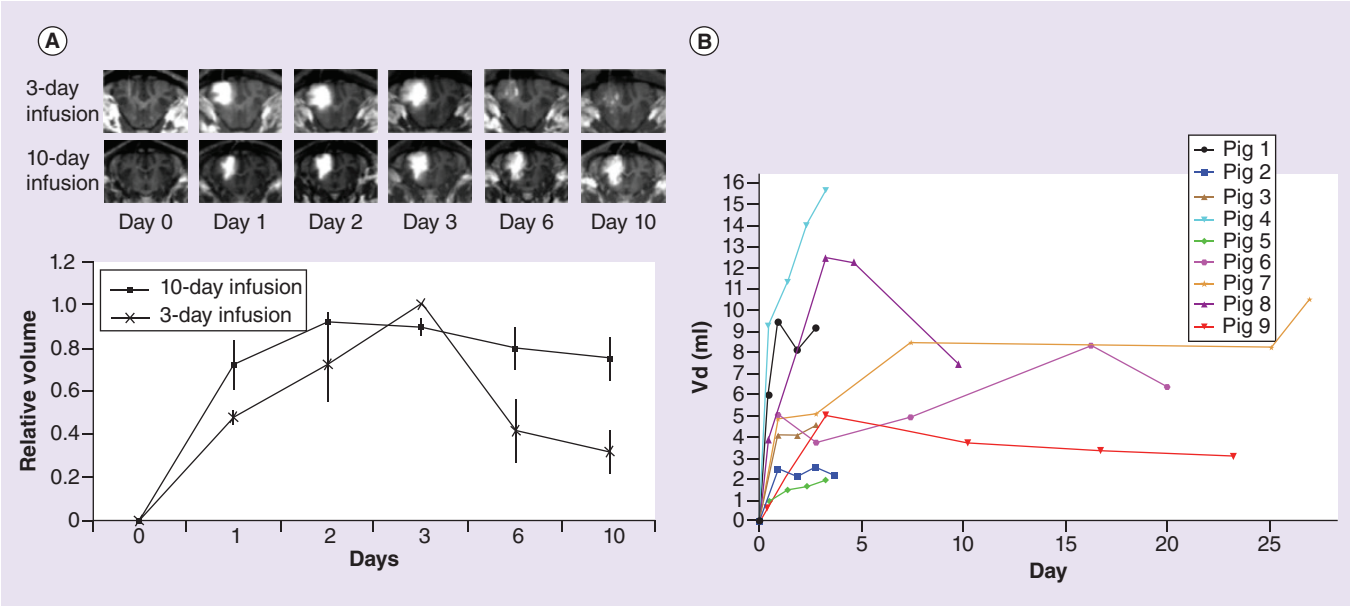

Figure 2. Convection-enhanced delivery into a porcine model: long- and short-term investigations. (A) Convection-enhanced delivery (CED) of a mixture of topotecan and/gadolinium into a nonglioma bearing pig for 10 days via a subcutaneous pump resulted in stable volume of distribution. Maximum volumes were achieved 2–3 days after infusion was initiated. **(B)** CED of a mixture of topotecan and/gadolinium into nine nonglioma bearing pigs for up to 1 month via a subcutaneous pump. Subsequent experiments with prolonged CED for up to 1 month in our porcine model demonstrated maximal volumes of distribution achieved at 1–3 days followed by a steady state of volume of distribution.
Vd: Volume of distribution.
(A) Reproduced with permission from Sonabend *et al.* [24].

advantages in rats with glioma, with additional survival benefits observed in animals receiving prolonged treatments. Notably, no adverse effects were observed in any animals receiving topotecan [23,28].

Our preclinical studies led to a Phase Ib dose escalation clinical trial of CED with topotecan, involving patients with confirmed recurrent GBM **(Figure 3)**. In this trial, 69% of patients demonstrated radiographic tumor regression when treated with drug dosages nontoxic to normal brain parenchyma. A smaller cohort (four of 16, 25%) of early responders experienced a more than 50% reduction in enhancing tumor volume through the first 3–6 months after therapy **(Figure 4)**. Additionally, minimal drug-associated toxicities were observed in patients receiving CED when compared with prior systemic studies of topotecan [21,26].

• Carboplatin

Platinum-based chemotherapeutic agents, including cisplatin and carboplatin, cause cross-linking of DNA, which inhibits DNA repair and synthesis in mitotically active cells. Although cisplatin has been widely used to treat various extracranial malignancies, poor CNS penetration and dose-limiting toxicities have limited the application of this drug for malignant glioma. The range of cisplatin-associated toxicities, including severe emesis, peripheral neuropathy, hearing loss and nephrotoxicity, has prompted the development of second-generation platinum-based chemotherapeutics, such as carboplatin [29]. Preclinical studies investigating carboplatin as a potential antiglioma agent supported use of systemically administered carboplatin for recurrent high-grade glioma [30–32]. However, multiple Phase I and II clinical trials assessing systemically administered carboplatin in the treatment of recurrent glioma have found only modest benefit with minimal penetration into the CNS and concurrent dose-limiting toxicities [33,34].

Paradoxically, the hydrophobic drug properties that minimize the diffusibility of carboplatin across the BBB also make carboplatin an excellent drug for CED and allow for compartmentalization of the drug with limited systemic toxicity. Initial attempts to increase intracranial drug concentrations of carboplatin involved

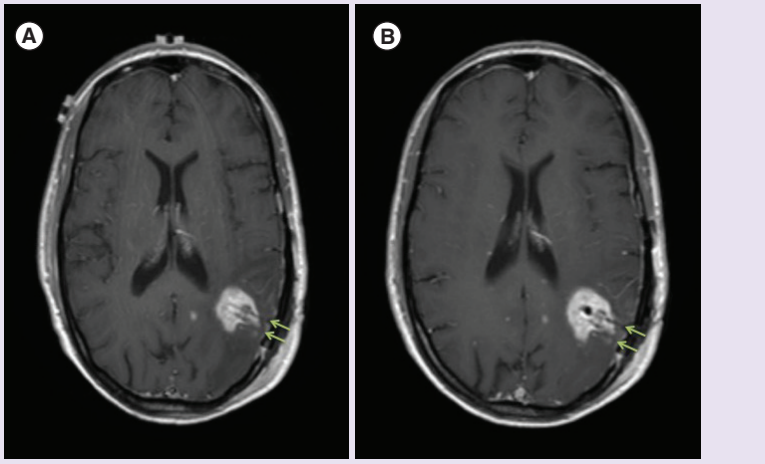

Figure 3. (A) MRI demonstrating convection-enhanced delivery catheter placement in a patient with recurrent glioblastoma. Two individual catheter tracts are visualized in a patient with recurrent GBM. (B) An additional representative axial MRI of catheter placement in the same patient.

intra-arterial administration [35–37]; however, recent Phase I study efforts have been aimed at establishing the safety of CED of carboplatin in patients with recurrent GBM [38,39].

CED of immunotoxin conjugates

Receptors for IL-13R α2, a Th-2 derived cytokine, have been demonstrated to be highly overexpressed in many human cancers, including malignant glioma [40]. Puri and colleagues have aimed to utilize the overexpression of IL-13R in malignant glioma by developing a recombinant fusion protein composed of the IL-13 ligand and a mutated form of the pseudomonas exotoxin (IL13-PE39QQR) [40]. This fusion protein was found to be highly selective for GBM cells with sparing of nonmalignant cells *in vitro* using human glioma cell lines. Moreover, significant antitumor activity was observed with intravenous and intraperitoneal administration of IL13-PE39QQR in animals with human glioma xenografts. The high molecular weight of IL13-PE39QQR necessitates direct drug delivery to the brain in order to bypass the BBB. CED experiments with continuous infusion of the fusion protein to xenograft glioma models in mice demonstrated drug efficacy and safety. Further safety and toxicity profiles were established in rats and monkeys prior to the initiation of human clinical trials [41–43].

A Phase I clinical trial assessing IL13-PE39QQR delivered via CED in patients with recurrent GBM demonstrated promising results. The study protocol included placement of a single intratumoral catheter with CED of IL13-PE39QQR over 48 h followed by tumor resection and additional placement of two to three catheters into the region adjacent to the resection bed and CED of IL13-PE39QQR for an additional 96 h. Patients enrolled experienced dose-limiting toxicities at 1.0 μg/ml with radiographic and histopathological evidence of necrosis and inflammation. The maximum tolerated infusate concentration was determined to be 0.5 μg/ml. Patients with >two catheters were found to have an overall survival advantage when compared with patients receiving <two catheters in the adjacent postresection region [44]. These optimistic Phase I results led to the PRECISE trial; a randomized trial of CED of IL13-PE39QQR versus GLIADEL wafers for recurrent GBM.

The PRECISE trial marks the first Phase III trial for antiglioma drugs delivered via CED. PRECISE trial patients were randomized 2:1 to either receive IL13-PE39QQR (0.5 μg/ml via two to four catheters 96 h postresection) or GLIADEL wafers (3.85%/7.7 mg carmistine per wafer, 8 wafers maximum). A total of 296 patients from 52 different centers were enrolled. No difference was observed in median overall survival between the two treatment arms and adverse event profiles were similar between groups. Patients receiving IL13-PE39QQR had an increased rate of pulmonary embolism that was attributed to longer hospitalizations [44].

Additional clinical trials of CED for GBM

Replication-competent adenovirus (Delta-24-RGD) is an adenovirus that has been engineered to infect only cells lacking the retinoblastoma protein (Rb) tumor suppressor gene, a common neoplastic phenotype. Adenovirus Delta-24-RGD replicates selectively in malignant cells and is capable of interrupting cellular replication after expression of an early protein called EA1. CED of Delta-24-RGD facilitates regional distribution of virus into parenchyma where malignant cell densities are the highest [45,46]. Similarly, a cytotoxic poliovirus (PVS-RIPO) has been engineered to selectively infect cells with the adhesion molecule nectin-like molecule 5, which is highly overexpressed in malignant glioma. After transfection, PVS-RIPO disrupts cancer cell RNA translation by manipulating the internal ribosomal entry

site [47]. Phase I trials of CED of PVS-RIPO for recurrent GBM have demonstrated drug safety, established optimal dosing and shown encouraging initial results [48].

Table 1 summarizes recent and current clinical trials investigating CED for the treatment of GBM.

Conclusion & future perspective

CED effectively circumvents the therapeutic challenges posed by the BBB through direct local drug delivery with limited systemic toxicity. This is particularly important in the treatment of GBM, as the diffuse and infiltrative nature of GBM precludes a surgical cure. Preclinical studies have highlighted the importance of determining optimal infusion flow rate, infusion volume and cannula size, specific to the microenvironment of the tumor under treatment and the molecular size and charge of the delivered drug. This preclinical work has translated into multiple Phase I trials that have demonstrated the safety of CED; however, there are currently no Phase III trials of CED for GBM that have demonstrated improved survival.

The next decade promises to be an exciting time for CED clinical trials, as many Phase I/II clinical trials will begin to transition into Phase III and IV. For the first time, we may observe Phase III/Phase IV clinical trials with improved patient survival. Furthermore, continued research efforts aimed at characterizing the nonenhancing portions of GBM are essential for the development of newer CED antiglioma agents. This heterogenetic tissue contains microinfiltrative disease that ultimately leads to treatment resistance and tumor progression. Identification of novel therapeutic targets within this tumor parenchyma will lead to the development of new and improved CED agents able to target GBM at the infiltrative margin.

We anticipate continued improvement in catheter design that will optimize drug delivery

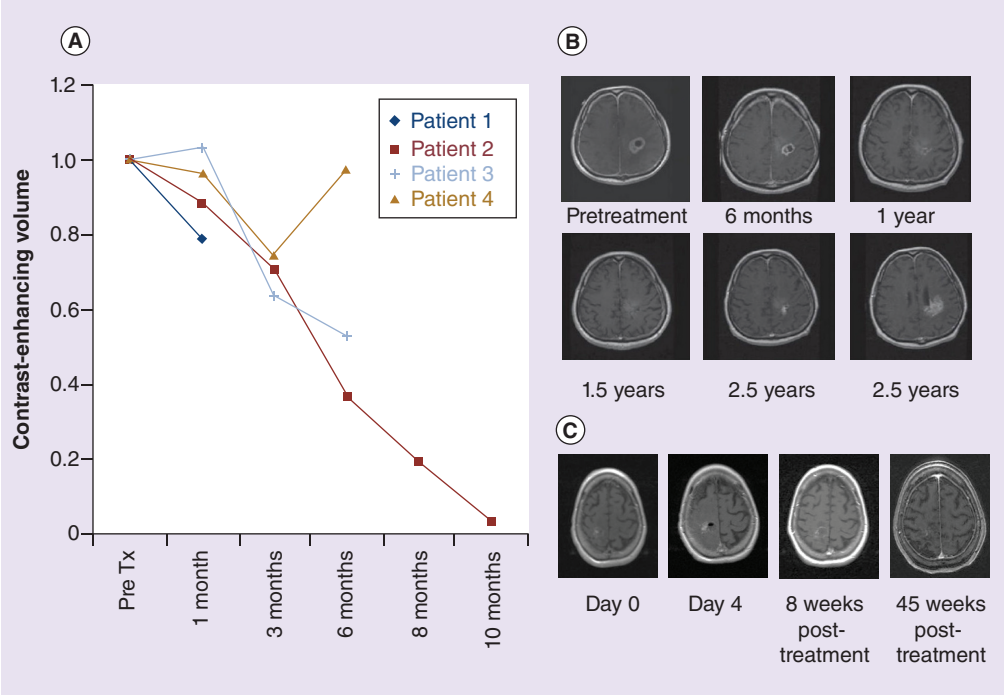

Figure 4. Dose escalation clinical trial of convection-enhanced deliverywith topotecan. (A) Early responders: four of 16 patients treated with convection-enhanced delivery of topotecan for recurrent glioblastoma demonstrated a dramatic response, shown here as contrast-enhancing volume plotted over time. **(B)** Serial MRI (T1 + gadolinium) from the patient with the greatest response demonstrates near complete resolution of enhancing tumor at 1.5 years post-convection-enhanced delivery, prior to eventual disease recurrence at 2.5 years post-treatment. **(C)** Serial MRI (T1 + gadolinium) from a patient with response and no MRI evidence of recurrence at 45 weeks post-treatment.
(B) Reproduced with permission from Bruce *et al.* [21].

Table 1. Summary of recent and current clinical trials utilizing convection-enhanced delivery.

Trial	Investigators (year)	Agent	Phase	Target disease	Current status	ClinicalTrials.gov identifier [49]
An open-label dose-escalation safety study of convection-enhanced delivery of IL13-PE38QQR in patients with progressive pediatric diffuse infiltrating brainstem glioma and supratentorial high-grade glioma	Heiss *et al.* (2009–present)	IL13-PE38QQR	I	Diffuse intrinsic pontine glioma high-grade glioma	Recruiting	NCT00880061
IL13-PE38QQR infusion after tumor resection, followed by radiation therapy with or without temozolomide in newly diagnosed malignant glioma	Kunwar *et al.* (2004–2007)	IL13-PE38QQR	I	Glioblastoma anaplastic astrocytoma oligoastrocytoma	Completed	NCT00089427
The PRECISE Trial: study of IL13-PE38QQR compared to GLIADEL wafer in patients with recurrent glioblastoma multiforme	Kunwar *et al.* (2004–2007)	IL13-PE38QQR	III	Glioblastoma	Completed	NCT00076986
Histologic effect/safety of pre/postoperative IL13-PE38QQR in recurrent resectable supratentorial malignant glioma patients	Kunwar *et al.* (2001–2007)	IL13-PE38QQR	I	Malignant glioma, grade III, IV	Completed	NCT00024557
Interstitial infusion of IL13-PE38QQR cytotoxin in recurrent malignant glioma	Kunwar *et al.* (2000–2007)	IL13-PE38QQR	I II	Malignant glioma, grade III, IV	Completed	NCT00024570
Carboplatin in treating patients with recurrent high-grade gliomas	Elder *et al.* (2012–present)	Carboplatin	I	Anaplastic astrocytoma oligodendroglioma	Recruiting	NCT01644955
Dose-escalation study of carboplatin administration into the brain for glioblastoma multiforme	Gill *et al.* (2015–present)	Carboplatin	I	Glioblastoma	Not yet recruiting	NCT01317212
Safety study of intracerebral topotecan for recurrent brain tumors	Bruce *et al.* (2004–present)	Topotecan	I II	Malignant glioma	Completed Not yet recruiting	NCT00308165
Phase IIb clinical trial with TGF-β2 antisense compound AP 12009 for recurrent or refractory high-grade glioma	Bogdahn *et al.* (2003–2009)	TGF-β	II	Glioblastoma anaplastic astrocytoma	Completed	NCT00431561
Phase I study of cellular immunotherapy for recurrent/refractory malignant glioma using intratumoral infusions of GRm13Z40–2, an allogeneic $CD8^+$ cytolitic T-cell line…	Badie *et al.* (2010–2013)	GRm13Z40–2 CTL	I	Brain tumors	Completed	NCT01082926
Safety and efficacy study to treat recurrent grade 4 malignant brain tumors	Kreitman *et al.* (2004–2007)	TP-38	II	Glioblastoma	Completed	NCT00104091
Study of immunotoxin, MR1–1	Bigner *et al.* (2006–2012)	MR1–1KDEL	I	Supratentorial malignant brain tumor	Terminated	NCT01009866
Efficacy and Safety of AP 12009 in Patients With Recurrent or Refractory Anaplastic Astrocytoma or Secondary Glioblastoma (SAPPHIRE)	Del Maestro *et al.* (2008–2014)	Trabedersen	III	Anaplastic astrocytoma glioblastoma	Terminated	NCT00761280
Study of convection-enhanced, image-assisted delivery of liposomal-irinotecan in recurrent high-grade glioma	Butowski *et al.* (2014–present)	Nanoliposomal irinotecan	I	High-grade glioma	Enrollment by invitation	NCT02022644
Poliovirus vaccine for recurrent glioblastoma multiforme (PVS-RIPO)	Friedman *et al.* (2012–present)	PSV-RIPO	I	Recurrent supratentorial glioblastoma multiforme glioblastoma	Recruiting	NCT01491893

CED clinical trials summarized from [49].

and facilitate prolonged therapeutic delivery with subcutaneous CED systems. These improvements will minimize hospitalizations and allow for outpatient management with minimally invasive means of CED parameter manipulation and therapeutic refill. Paralleled advancements in computer software and MRI interpretations will improve catheter placement and provide essential information into the Vd of specific infusates with different chemical compositions and molecular weights. Continued optimization of CED will establish this drug delivery technology as a safe and reliable method in the precise delivery of current and future antiglioma agents.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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