Convection-enhanced drug delivery: prospects for glioblastoma treatment

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“...the development of targeted therapies, which when combined with appropriate convection-enhanced drug delivery technology, raise the hope of personalized neuro-oncological treatments that can be safely and repeatedly administered for the lifetime of a patient.”

Despite intense research focus the prognosis for patients with glioblastoma (GBM) remains poor. Median survival with maximal intervention comprising surgical resection, radiotherapy and systemic chemotherapy is reported to be less than 15 months, and only a proportion of patients are suitable for this aggressive treatment strategy [1].

The diffuse and infiltrative nature of GBM confers a number of challenges to effective treatment. Traditionally, cytoreductive surgery has been targeted to the areas of macroscopic abnormality on MRI scans, guided by the operating microscope and limited by the eloquence of surrounding brain structures. The combination of fluorescence-guided surgery with intraoperative neurophysiological mapping can improve the rate of gross total resection without increasing neurological morbidity [2]. However, tumor recurrence is inevitable even when complete resection of enhancing tumor is achieved. Analysis of the patterns of tumor recurrence after radiotherapy has revealed substantial heterogeneity with up to 30% of recurrent tumors arising outside or distant to the original radiation field. This emphasizes the need to effectively

treat both the primary tumor site, as well as the distant sites of tumor infiltration in order to improve long-term prognosis [3].

The blood–brain barrier (BBB) represents a second challenge to the effective treatment of GBM. The failure of systemically administered chemotherapies, other than temozolomide, to improve prognosis may result from inadequate penetration of the BBB and subtherapeutic drug concentrations within the tumor mass and infiltrated peritumoral tissue [4]. Increasing the concentration of a systemically administered chemotherapy can result in improved penetration of the BBB; however, this strategy risks significant side effects and systemic toxicity. Convection-enhanced drug delivery (CED) has emerged as a novel method of drug delivery to the brain, which has the potential to address these challenges by bypassing the BBB and targeting drugs to large and clinically relevant brain volumes.

First described in the early 1990s [5], CED describes the direct infusion of drugs into the brain through intraparenchymal microcatheters. By establishing a pressure gradient at the tip of an infusion catheter, CED exploits bulk flow through the

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interstitial spaces of the brain, effectively distributing macromolecules that could not penetrate the BBB if delivered systemically. CED differs in technique and technology from traditional methods of intratumoral drug delivery, which usually involve the injection of agents into a tumor or comprise a drug-eluting matrix such as Gliadel (Eisai, Tokyo, Japan), which is used to line a resection cavity [6]. These traditional methods rely upon simple diffusion into adjacent tissue along a concentration gradient, resulting in limited drug distribution beyond the point source. The ‘convective’ description of CED arose from the observation that infusates carried by a pressure gradient will reach distances approximately proportionate to the duration of infusion, whereas an agent carried by diffusion will reach distances proportional to the square root of the time elapsed.

Early enthusiasm for this technique led to a number of clinical trials for the treatment of GBM. CED trials in neuro-oncology have used conventional chemotherapies (paclitaxel and topotecan), targeted toxins (IL13-PE38QRR, TP-38 and PRX321), oligonucleotides and TGF- β 2 inhibitors [6–10]. The results of these clinical trials have been largely disappointing and CED is yet to fulfil its potential as a mainstream treatment for GBM. In-depth analyses of failure modes in previous clinical trials have identified two major factors that have consistently compromised outcomes – poor drug distribution and infusate reflux (or backflow) along the brain/catheter interface resulting in off-target side effects and subtherapeutic drug concentrations within the tumor target. Some trials have also reported unacceptably high device-related complication rates.

Substantial research effort has been dedicated to optimizing the technology for CED and identifying the parameters that govern successful drug distribution. Extensive preclinical and early clinical studies have demonstrated that effective CED depends upon a number of parameters – the diameter and design of the catheter, the method of catheter implantation, the rate of infusion and infusion regimen, the physicochemical characteristics of the infusate, and the cytoarchitecture of the targeted brain tissue or structure, in particular proximity to perivascular spaces [11]. Equally important for the success of CED is effective tracking of drug distribution in real time. Determining the volume of drug distribution has proved challenging, with a range

of MRI modalities and drug-tagging methods under investigation [12]. The application of CED to the treatment of GBM adds another layer of complexity due to the heterogeneity of tumor architecture, the presence of necrosis and resection cavities and the diffuse and infiltrative nature of the disease process.

In Bristol (UK) we have developed a robot-guided method for implantation of a permanent CED catheter system with transcutaneous bone-anchored port. The neurosurgical robot provides a stable platform for minimally traumatic and accurate catheter placement, allowing implantation of catheters away from vasculature, necrotic areas and postresection cavities. The accuracy of catheter targeting can be verified with intra-operative imaging, allowing suboptimally placed catheters to be repositioned. Up to four catheters can be implanted per port, with each catheter functioning as an independent infusion channel conferring the flexibility to individualize infusion regimens for a particular tumor morphology. The use of multiple catheters allows drugs to be distributed through large volumes of brain tissue. The implanted catheters incorporate a ‘recessed-step’ feature, which effectively inhibits reflux at high flow rates [13]. The facility to perform high flow rate infusions is of paramount importance for clinical translation as the volume of a GBM can exceed 300 cm³ at the time of presentation and high flow rates are required to achieve therapeutic infusion volumes within a timescale that is acceptable to patients. The transcutaneous port allows repeated drug administration at predetermined intervals, thus allowing systemic chemotherapy regimens to be replicated without repeated surgical intervention [14]. The catheter system is MRI compatible, which facilitates real-time imaging of drug distribution during infusions, and allows the treating physician to alter and optimize an infusion regimen based on catheter performance.

Early experience of intermittent CED of carboplatin, a drug with physicochemical characteristics suitable for CED, in patients with recurrent GBM has yielded promising results with patients tolerating high flow rate, high volume infusions in excess of 25 ml per day [14]. When treating these patients, our strategy has been to target the sites of enhancing recurrent tumor, as well as the infiltrated peritumoral penumbra, a strategy that has resulted in radiological evidence of tumor regression. Based on real-time T2-weighted MRI, the infusate effectively

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encompassed the sites of tumor enhancement, as well as a 2-cm peritumoral margin.

Recent advances in understanding the aberrant molecular pathways, upregulated receptors and genetic abnormalities implicated in the pathogenesis of GBM have led to the evaluation of a number of targeted molecular therapies delivered by CED. Toxins targeted to IL-13 receptors and antiangiogenic immunotoxins have shown promise when administered by CED in preclinical GBM models [15,16]. Advances in nanoparticle formulation, such as liposomes encapsulating siRNA targeting O⁶-methylguanine DNA methyltransferase and drug-loaded nanocarriers, have also been combined with CED in experimental models with variable success [17,18]. The administration of virotherapies by CED is a particularly exciting field of investigation. A retroviral replicating vector delivering cytosine deaminase administered in combination with oral 5-fluorocytosine [19] and an oncolytic adenovirus dependent on the human transcription factor YB-1, which is upregulated in glioma stem-like cells [20], have both shown therapeutic efficacy in experimental glioma. The application of CED to GBM virotherapy offers the particular advantages of bypassing the BBB and allowing highly accurate anatomical targeting of therapies. If clinical trials confirm long-term cell transduction, virotherapies offer the possibility of effective single or intermittent infusion strategies.

Effective clinical translation of CED of novel therapies for the treatment of GBM will be dependent on the adoption of suitable catheter technology and implantation methods, used in combination with therapeutic agents that have appropriate physicochemical properties. Extensive preclinical studies correlating infusate distribution with neuropathological,

neurotoxicological and neuroradiological findings are also required to maximize the chances of success in clinical trials. These analyses are of particular relevance to viral vector-mediated therapies where transgene expression and viral load must be accurately targeted and predictable in order to optimize safety and efficacy.

CED has significant potential to improve the prognosis of patients with GBM by facilitating targeted drug delivery to the tumor, as well as the peritumoral sites of tumor recurrence, provided the lessons from past failures are learnt and rectified. The theoretical advantages of CED are multiple and include bypass of the BBB, limitation of systemic side effects, delivery of therapeutic drug concentrations, and distribution through clinically relevant brain volumes. The technology to achieve repeatable, reflux-free infusions performed with real-time MRI guidance now exists and may represent a significant step forward for effective clinical translation. Advances in defining aberrant molecular pathways in GBM pathogenesis, genetic profiling and nanoparticle technology have led to the development of targeted therapies, which when combined with appropriate CED technology, raise the hope of personalized neuro-oncological treatments that can be safely and repeatedly administered for the lifetime of a patient.

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