Expert Opinion

Convection-enhanced delivery of targeted toxins for malignant glioma

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Malignant gliomas represent a difficult treatment challenge for the neuro-oncologist and the neurosurgeon. These tumours continue to be refractory to standard therapies, such as surgery, radiotherapy and conventional chemotherapy, and new therapeutic options are clearly needed. Therefore, investigators have recently taken a new direction and started to engineer compounds such as recombinant cytotoxins, antiangiogenesis factors and genetic delivery vectors. However, these promising new agents are all dependent on an effective distribution method in order to bypass the blood–brain barrier. Convection-enhanced delivery (CED) allows for the administration of targeted toxins and other agents directly into the brain at the site of a tumour via catheters placed with the aid of stereotactic or image-guided surgery. The use of this technique is gaining momentum as a newly accepted treatment modality where little else has produced durable results in the fight against gliomas. Direct intratumoural infusion was first performed in nude mouse flank tumour models of human malignant glioma. After significant testing in preclinical animal studies, this method of delivery was followed by the successful demonstration of *in vivo* efficacy in Phase I and II clinical trials. Currently, this technique is being used in the investigational setting at academic medical centres where investigators are starting to define the best practice for CED. Fundamental issues in this method of delivery such as rate of infusion, cannula size, infusate concentration and tissue-cannula sealing time shape the current discussion in the literature. Targeted toxin therapy represents one of the newest and most promising treatments for this unfortunate patient population, with proven clinical efficacy administered through CED, which is a novel approach to drug delivery.

Keywords: brain neoplasm, convection-enhanced delivery, glioma, targeted toxin

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1. Introduction

The term glioma refers to a wide spectrum of tumours of the CNS, including the most aggressive forms: anaplastic astrocytoma and glioblastoma multiforme. Almost all of these diseases have long been associated with devastating and usually fatal clinical outcomes. In fact, most malignant glioma patients measure their survival in months instead of in years. Their physicians struggle with the impediments of dose-limiting toxicities and detrimental side effects that significantly impact quality of life when aggressive treatment is rendered. Although a near-radiographically complete surgical resection can provide a statistically significant survival benefit, the long-term prognosis for malignant gliomas is still limited because of their diffusely infiltrative nature. Once the disease has been diagnosed, neurosurgeons consider the 'whole organ diseased' [1].

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Circumventing the blood–brain barrier (BBB) is one of the most important challenges for new therapy development. Two techniques that are capable of accomplishing this task are radiation therapy and direct-targeted toxin infusion into the brain after surgical resection. Other techniques that bypass the BBB are osmotic or pharmacological disruption prior to chemotherapy administration and intra-cavitary chemotherapy. Another challenge that is associated with the BBB is the size of the molecules that will pass into the brain [2]. Large (often > 180 kDa), exquisitely engineered fusion proteins are then simply rendered ineffective when administered through traditional intravascular routes because of their inability to cross the BBB. Alternatively, the physician may consider treating their patient with radiation therapy, which is not influenced by the BBB. Although there have been recent advances in radiation oncology that are intended to diminish toxic side effects, there are still significant risks such as radiation-induced necrosis, leukomalacia as well as pituitary and hypothalamic dysfunction. New, different and potentially less-toxic treatment options with fewer long-lasting side effects are in development, which include the convection-enhanced delivery (CED) of targeted toxins.

Among the targeted toxins that have been used clinically are Tf-CRM107, TP-38, IL4-PE38KDEL and IL13-PE38QQ3R; an exotic list of exciting agents that merit a more complete description herein. These targeted toxins all have had proven efficacy in decreasing, or in some cases even causing, complete regression of human malignant brain tumours in animal models [3]. Significant energies have been expended in carefully designing the targeted toxins themselves. Now, an equally substantial effort is needed to perfect their accurate delivery to the target tumour.

2. Convection-enhanced delivery

When considering the steps that are necessary to treat a patient through CED, this delivery technique might seem too complex for most healthcare providers. After all, performing CED does involve several imposing components that include careful pharmacological/oncological planning, complex neurosurgery, multiple in-patient hospital days and skilled nursing support. Furthermore, there is a significant preoperative time commitment for accurately assessing patients and choosing those that are most appropriate for such a rigorous regimen. In order to qualify for these on-going study treatments, patients usually need to have a histologically verified, supratentorial, single tumour recurrence and must be between 18 and 70 years of age with a Karnofsky performance score of ≥ 60 (70 in some studies) [4,5]. Clearly, the treating physician will need both a sophisticated healthcare facility and a team of dedicated, interested colleagues to address all of the details included in the evaluation and at each sequential follow-up step.

2.1 Fluid dynamics

Once the patient qualifies for one of the trials, surgical planning can commence. In some reports, only a single drug-infusion catheter is described as the conduit for delivery [4]. In general, the study protocol defines the exact number (usually one to four) of catheters that can be placed for drug delivery with very specific guidelines for where they can be placed (within or outside) with respect to the tumour. However, an evolving preferred method for drug delivery is to stereotactically place two to three catheters around the border of the resection cavity after image-guided tumour resection has been accomplished. Whether intratumoural or peritumoural catheter placement is more advantageous is the focus of debate and further investigation. If the tumour is considered inoperable because it is located in eloquent neural tissue, two catheters are placed stereotactically directly within the target. Although most tumours recur within 2 cm of the resection margin, the aim is to achieve a homogenous drug distribution that is circumferentially away from the point of infusion to the greatest extent, given the infiltrative nature of these tumours [2]. In fact, carefully choosing the locations for the catheter tips has become a crucial question, particularly given the fact that each trial specifies a required number of catheters. Investigators have discovered that there is another barrier to treatment that alters the fluid dynamics within certain regions of the tumour-infiltrated brain. At a recent national meeting on CED held at the Cleveland Clinic, two major physical challenges were identified as critical for accomplishing proper convective drug delivery: i) understanding the influence of brain tumour tissue density and character on the volume of drug distribution and; ii) the residence time, or time course of drug distribution, in the setting of tumour-altered fluid dynamics [6].

The achievable volume of drug distribution via CED in tumour tissue is very different from the volume of distribution that is possible in normal neural tissue. This finding is most likely due to the dramatic increase in interstitial fluid pressure that results in the setting of a brain tumour. Interestingly, areas of normal interstitial pressure (1 – 2 mmHg) are interposed with peritumoural areas where interstitial fluid pressure may be as high as 50 mmHg or greater. Naturally, this difference creates counterproductive pressure gradients that redirect any infusing chemotherapy away from diseased brain tissue, back into normal tissue and soon out of the cerebrum entirely [6]. Although the interstitial pressure within a tumour has been posed as an explanation for poor drug distribution, breakdown of the BBB (as evidenced by the contrast enhancement seen within a tumour) allows drugs to be washed out by the circulation.

The mixed density of collagen/elastic fibre stroma and cystic/necrotic areas found in tumours are likely to be the basis for much of the difficulty that is encountered during drug distribution. This problem was suspected during the early prepump infusion experiments where rapidly rising serum drug levels were observed in glioma patients. The mixed tissue environment creates abnormal pressure gradients, leading to a relatively faster efflux of the drug out of the brain. This occurrence will in turn reduce the residence time

for the drug below that which is needed for proper receptor binding and uptake by the cancerous cells. The proposed solution, studied first in animal models, was to use an infusion pump that will maintain a constant pressure in order to maximise the effect of the natural bulk fluid flow through the interstitium of the brain [7,8]. This capability would require careful laboratory confirmation in order to allow for the proper selection of the infusion parameters, which would optimise the resident time and volume of distribution.

2.2 Basic science

Basic science research has been essential for streamlining fundamental issues that have arisen as CED matured. For example, early, time-consuming and complex animal studies were required to explore even the most basic questions, such as simple diffusion differences in brain white matter versus grey matter [9,10]. In response, Chen *et al.*, at Virginia Commonwealth University, pursued the development of 'brain phantom gels' that mimic neuronal tissue [4,11-13]. These gel models are quickly replacing animal studies as the best way to initially design a new catheter or study a new proposed diffusion pattern. Most importantly, the group is using the synthetic brain tissue to mathematically model a 'poroelastic theory' of CED, whereby infusion line-pressure measurements and video-microscopy determinations of infusate volume of distribution within the gel demonstrate a good match between the theory and experiment over a wide range of flow rates (0.5 – 10.0 µl/min) [12]. This model may even hold the promise of eventually moving the research out of the laboratory and into a shared, accessible computing algorithm.

The actual mathematics behind the current clinical protocols can be summarised by briefly considering the core variables that are required to create bulk flow. Diffusion of targeted toxins is dependent on their concentration, molecular weight, polarity and their avidity for the target antigen [2]. Calculating the time required for an immunotoxin to travel in the tissue of a distance (L) can be approximated by the formula:

$$\frac{L^2}{4D}$$

where D is the diffusion coefficient for that drug. Finally, the task of choosing the most appropriate rate of infusion that achieves the widest possible homogenous dose distribution must be considered. Until recently, animal studies were the only reliable way to evaluate a set of prospective infusion variables. Clearly, such studies are still essential for true preclinical drug preparation as issues, such as dose toxicity, cannot be mathematically modelled. In the past, several animal dosing trials were undertaken and have proven to have been invaluable in determining the settings for rate and dosing in the initial human subjects [7,9,14-16]. The limiting factor in choosing a maximum dose and how rapidly we can infuse a drug is the onset of neurotoxicity, as seen in these animal trials [17,18]. Therefore, work must proceed carefully to adapt these regimens safely to the human patient population where such toxicity cannot be tolerated.

Recently, Macaca monkeys and rats were used to prove that CED is safe and efficacious, even for the exquisitely sensitive and very dense pons of the brain stem [16,19]. In these experiments, scientists are opening the doors for clinicians to consider treating this area of the brain that was previously thought to be untouchable. Undoubtedly, excellent collaboration between basic and clinical science is essential for this field to progress and should enhance drug development in the future.

2.3 Imaging

One difficult question remains: how do we truly know that all of this preparatory work is really allowing us to infuse the tumour bed in the novel and therapeutic way that we are envisioning and what proof do we have? An exceedingly important facet of this advancing field is the increasing involvement of imaging. MRI can be used to visually track the convective process; however, there are new imaging techniques that may be more accurate. Early studies infusing paclitaxel into a glioma followed by diffusion-weighted MRI showed a hyperintense signal within the tumour tissue [20]. Experts in the field are still unsure whether this appearance truly represented the actual drug distribution or whether this was just water being displaced from the tumour [6]. In the case of the TP-38 studies, single photon-emission computed tomography scanning has been performed in combination with MRI to give a better real-time estimate of the effect [6]. Excellent studies performed by Croteau *et al.* [21] and Lonser *et al.* [19] at the National Institutes of Health aimed to develop and refine the use of radio-opaque tracers that could be intermixed with the targeted toxin solution. These recent experiments that were completed in primates attest to the usefulness of substances such as iopamidol, which is a low molecular weight iodine-based tracer. Administered with the infusate, the addition of an iodine-based tracer allows for the real-time, *in vivo* and postinfusion evaluation of the treatment distribution with a simple CT scan [21,22]. Other work has focused on MRI and gadolinium-based tracers [19].

Preoperatively, the surgical planning for accurate catheter placement has also come to heavily rely on imaging. Voges *et al.* describe one practice for integrating MRI and positron-emitting tomography scanning into the treatment plan [23]. These studies commenced by performing baseline-imaging studies for localising both soft tissue margins and visualising the metabolically active areas in real time. These scans are then merged and uploaded into a stereotactic, computer-assisted trajectory system for use intraoperatively during the catheter placement.

Follow-up serial MRI scans are, of course, obtained at future clinic visits for the management of any tumour patient after surgery [6]. These techniques allow the treating physician to understand and adjust for almost every facet of this complex drug delivery system, which may in fact represent one of

the few fully monitored and dynamic treatment regimens that are currently available. The precision of CED is as yet unknown and is under investigation because of an inability to precisely monitor it in real time.

2.4 Current toxins

The basic concept of a targeted toxin is relatively simple. The carrier ligand is usually a basic cellular substrate that is needed by the dividing tumour cells and is coupled to a known protein toxin. For example, Tf-CRM107 is a conjugation of iron-loaded human transferrin (Tf) to a genetically modified diphtheria toxin (crossreacting material [CRM] 107) that is currently in a Phase III clinical trial [1,24]. Among those subjects that were treated in the Phase II trial, there were two complete tumour responses, and 60% of those who were treated in the study experienced a reduction of their tumour volume by ≥ 50% on serial MRI. IL13-PE38QQR is the fusion product of IL-13 and is a mutated form of the *Pseudomonas* exotoxin. This fusion protein is potent at nanomolar concentrations (0.5 – 2.0 µg/ml), as confirmed by post-treatment histopathology analysis. In exploring the maximal limits of dosing, one study compared bolus injections with CED administration. In fact, CED allows for doses as high as 10 µg/ml to be administered, whereas the bolus method was more toxic and allowed for only 4 µg/ml [25]. This potent therapy had the ability to prolong survival in the 46 patients who were enrolled in the initial Phase I trial [26]. DAB389EGF, an EGF combined with a mutant diphtheria toxin, has also been evaluated as a candidate for future targeted toxin therapy [1,27]. DAB389EGF and TP-38 both target the EGFR. At present, there are plans to simultaneously use DAB389EGF in conjunction with IL13-PE38QQR in dosing studies to hopefully achieve synergistic tumour killing ability. The anticipated synergy between DAB389EGF and IL13-PE38QQR is due to their ability to target different receptors that are expressed by glioblastoma multiforme. Because they possess different protein toxins, there should be no additive toxicity that would be associated with having the same toxin moiety.

TP-38 is a protein that is composed of TGF-α and a mutated form of the *Pseudomonas* exotoxin called PE38. This compound functions by binding to the EGFR, which is amplified in ~ 50% of the occurrences of human glioblastomata. The EGFR is often found on the cell surface of tumour tissue but is not usually expressed on normal brain tissue [1]. Initial dosing studies started with a constant infusion lasting 50 h at a rate of 0.4 ml/h, which represents a relatively small dose. Each catheter was used to infuse 20 ml of TP-38 for a total infusion volume of only 40 ml [28]. This infusion regimen is intended to avoid toxicity by using such small volumes whilst simultaneously demonstrating therapeutic efficacy.

IL4-PE38KDEL also employed a mutant *Pseudomonas* exotoxin to kill tumour cells by blocking protein synthesis. IL-4 receptors have been demonstrated on the cell surface of human gliomas [29]. As mentioned above, some receptors are clearly upregulated in these tumours and most likely confer some survival advantage. Conversely, these receptors may also provide the best opportunity to specifically target cancer cells by designing targeted toxins to which they will bind. No IL-4 receptors were detected on normal brain tissue by immunohistochemistry, which should prevent treatment-related neurotoxicity [30]. In a recent multi-centre, dose-escalation trial, infusion of the drug was not proven to be safe and further investigation of the drug has been discontinued. MRI after treatment did demonstrate significant areas of tumour necrosis in many patients. These initial results were encouraging and hold great promise for one day being able to potentially control malignant gliomas [5].

2.5 Other uses

With the advent of CED, researchers have realised that they are no longer limited to infusing immunotoxins alone into the brain. Viral vectors, receptor antagonists, antiviral agents against HIV, traditional chemotherapy and even radioactive molecules are under consideration for CED [14,31]. Three different groups have experimented with infusing a radiotoxic vector into glioma tissue as a form of localised brachytherapy [24,32,33]. One additional benefit of using radioactive agents is that the radiological monitoring in these patients can be easily accomplished with scintigrams. As with the other techniques, research continues in order to determine safe drug doses for administration and to establish therapeutic efficacy. Viral vectors that transport gene sequences to the replicating cells may also rely on CED in order to bypass the BBB. Human adenovirus, human herpes simplex virus and mouse-related retroviruses are loaded with one therapeutic, gene-based intervention and directed towards tumours. Unfortunately, there seems to be a deficiency in the degree of infectivity of glioma cells and a recent Phase III trial failed to show any evidence of clinical effectiveness. Another problem that was encountered was that higher viral doses produced malignant brain oedema and inflammation [34]. Similar concerns have been seen in other abandoned therapies such as monoclonal antibodies that are directed against EGFR [35]. Because of these findings, there is a new sense of caution among investigators towards pursuing viral-based therapy. Theoretically, viral vectors have shown great promise, but are likely to require further development before they demonstrate a therapeutic response comparable to that which is associated with targeted toxins.

Antiangiogenesis factors represent a new therapeutic direction for pursuit against both developing and established tumours. CED is being used to target the ability of the glioma to build its intricate network of blood vessels that supply the tumour with the necessary nutrients for growth. One appropriate target is the VEGF and its tumour cell surface receptor (VEGF/VEGFR) pathway. Currently, there are rational design efforts that are ongoing to create antibodies and other potent molecules that will directly interrupt this signal transduction pathway. The treatment objective is to prevent the development of the vascular supply to the nascent tumour in

the early stages [36-39]. Another potential antiangiogenic candidate is SU-6668, an engineered molecule that targets the vascular fibroblast growth factor receptor on the tumour cell. This promising new drug successfully inhibits receptor tyrosine phosphorylation and, therefore, mitogenesis in many human tumour xenografts. This drug continues to show promise in on-going clinical testing [37]. Antiangiogenesis therapy may soon serve as an adjunctive therapy for targeted toxins, if not as a powerful primary treatment on its own.

3. Conclusion

Drug delivery using pump-assisted CED has led to a number of exciting, potential treatments for malignant glioma. Some compounds that are presently in clinical trials are more refined and further developed than others. TP-38-, Tf-CRM107- and IL-13-based treatments successfully bypass the BBB through the use of CED and, given their clinical tolerance, are poised to become an alternative therapeutic option. Nonetheless, in this rapidly developing area of brain tumour research, these agents may soon be outdated. To label those targeted toxins that are currently in clinical trials as more traditional CED-based therapy may be premature. The promise of viral vectors, gene therapy, antiangiogenesis factors and even liposomal vectors or stem cell implantation ensures that there will be additional routes of investigation for future drug development [40].

4. Expert opinion

The authors routinely place the drug delivery catheters at their facility with intraoperative MRI guidance. This surgical technique provides an unrivalled finesse in deployment accuracy and allows for a greater degree of confidence that a beneficial therapeutic effect will occur after beginning the drug infusion. The authors feel that intraoperative MRI guidance is far superior to computer-assisted guidance alone because it allows for the ability to visualise the operative site in near-real time. Beyond the targeted toxins themselves, new ideas for catheter placement techniques continue to generate excitement for greater precision in drug delivery. Nonlinear magnetic stereotaxis uses externally generated magnetic fields to apply torques and forces to a magnetic tip at the distal end of the catheter [41]. This technique may make treating lesions that are deep in the brain and underlying essential structures, such as blood vessels, an attainable goal. In the future, drug delivery catheters that contain several smaller, deployable microarray catheters may allow for an even wider diffusion diameter and treatment distribution than is now possible [24]. Perhaps one day, even implantable pumps may change gliomas into a chronic disease if a therapeutic cure is not possible with current treatment modalities.

Compared with the dismal outcome that is provided by standard therapies such as surgery, chemotherapy and radiation, CED of targeted toxins seems to be the gateway towards a new era in tumour control. Multi-centre studies that have been underway since 2001 should be expanded in order to include as many clinical locations as is logistically possible. Given the exquisite range of therapies that are under evaluation, we can at least now begin to test the most promising among them without the interference of the BBB, the obstacle of adverse fluid dynamics or the fear of severe systemic reactions.

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