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Convection Enhanced Delivery of Macromolecules for Brain Tumors

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Abstract

The blood brain barrier (BBB) poses a significant challenge for drug delivery of macromolecules into the brain. Convection-enhanced delivery (CED) circumvents the BBB through direct intracerebral infusion using a hydrostatic pressure gradient to transfer therapeutic compounds. The efficacy of CED is dependent on the distribution of the therapeutic agent to the targeted region. Here we present a review of convection enhanced delivery of macromolecules, emphasizing the role of tracers in enabling effective delivery and discuss current challenges in the field.

Keywords

Convection enhanced delivery; drug delivery system; glioblastoma; surrogate markers; tracers

1. INTRODUCTION

Despite recent advances in state-of-the-art surgical resection, radiotherapy, and chemotherapy, glioblastoma multiforme (GBM) continues to have a poor prognosis [1, 2]. The ability to deliver therapeutic agents to a GBM tumor is a significant hurdle and accounts for some of the difficulty in treating this disease [3]. Since Paul Ehrlich first described the blood brain barrier in 1885 [4]_ENREF_3, it has been widely accepted that systemically applied drugs exhibit limited penetration into the central nervous system. Over 100 years later, treatment delivery options for intracerebral malignancies continue to be limited and, in their current form of non-targeted systemic or intrathecal delivery approaches, are ultimately confounded by side effects of toxicity, injury to surrounding tissues and suboptimal drug delivery to the tumor site. In addition to the challenges of navigating past the blood brain barrier, the highly invasive nature of malignant brain tumors further hinders our ability to effectively target these diseased tissues using conventional surgical resection and radiation therapy [5].

Convection-enhanced delivery (CED) targets therapies directly into the tumor thus circumventing the blood brain barrier. This is accomplished through direct intracerebral

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CONFLICT OF INTEREST

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catheter placement and often a pump that is the source of flow of fluid carrying the therapeutic agent. The fluid carries, or advects, the agents throughout the interstitial spaces [6]. If CED is applied after surgical resection of a brain tumor, then the microinfusion catheters placed under stereotactic guidance target the peritumoral region with bulk flow, supplementing intrinsic diffusivity of both small and large therapeutic compounds to greatly enhance distribution [6]. In addition, the theoretical benefit of directly applying active molecules intracerebrally is the fact that an intact blood brain barrier would conversely limit egress of therapeutic agent to extracerebral tissues, effectively enhancing drug delivery while reducing the potential risk of systemic toxicity [7]. Furthermore, because CED depends on fluid flow to carry the agent, it is possible to achieve a relatively constant concentration of drug spanning a predictable distance from the site of infusion before the drop-off [7], which provides superior localization of the therapy to the tumor upon accurate catheter placement [7, 8].

Given that the efficacy of any drug delivered by CED will be dependent on the ability to achieve sufficient concentrations of a therapeutic agent to a targeted region, much attention has been placed on the factors that dictate optimal catheter placement prior to infusion (Fig. 1) [8, 9]. If catheters are inaccurately placed, leakage of infusate into the intraventricular spaces and subarachnoid will result in poor drug delivery and distribution [9]. Currently, catheters generate a certain amount of backflow where the fluid flow in a tissue-free region created by fluid pressure along the outer surface of the catheter [9–11]. In addition, any large (millimeter sized) bubbles may redirect the flow away from the catheter tip in unpredictable ways. Thus optimization of devices and of various protocols constitute an important part of improving the delivery of CED [12]. However, in this review, we shall focus on the role of imaging, and of technologies to help determine the distribution of CED-infused drug into the brain using differing imaging modalities, in improving CED. Although there have been many imaging studies, most have been in animal models that fail to replicate the scale of drug distribution required in humans [9, 13–15]_ENREF_11.In fact, despite the rigorous use of standardized guidelines, multiple Phase III clinical trials examining CED as a delivery technique have failed to demonstrate improvement over existing therapies [16–20]. The PRECISE (Phase III Randomized Evaluation of CED of IL13-PE38QQR with Survival Endpoint) study (NeoPharm, Inc.) compared patient survival following treatment with local implantation of carmustine-impregnated wafers and direct intracerebral infusion of a *Pseudomonas*-based exotoxin, cintredekinbesudotox. A retrospective analysis of this study showed that while the original investigators reported no significant difference in overall survival between groups, suboptimal delivery may have accounted for the disappointing results [7, 8]. The catheter positioning score (hazard ratio 0.93, $p = 0.043$) and the number of optimally positioned catheters (hazard ratio 0.72, $p = 0.038$) had a significant effect on progression-free survival [21]. Thus, technologies that improve our ability to predict optimal catheter placement and provide imaging for the delivery of therapeutic agents in real-time represent technologies that will further our understanding of CED and its significance in the treatment of intracerebral malignancy.

2. *IN VIVO* IMAGING OF CED INFUSATE DISTRIBUTION

Currently, there are relatively few methods that have been developed to reliably image CED infusate distribution. Some estimate that over a 1000 patients, a majority of whom have malignant gliomas, have been treated with CED infusions without convincing evidence of efficiency [22]. Historically, mathematical models have been used to predict drug transport as a function of patient-specific parameters, though such models must be validated using techniques that allow measurement of drug localization and concentration *in vivo*. To date, approaches that have been used to track CED-infusates *in vivo* rely primarily on radiographic alterations that arise from the presence of fluid, drug-induced effects on the target tissue, or tracer molecules, but these are only indirect measures that in theory do not precisely recapitulate therapeutic infusate coverage. Recently, there have been multiple advances in our understanding with regards to our ability to radiographically validate CED-infused drug distribution to a target region, a brief review of which follows.

2.1. Radiolabels

Early attempts to validate the enhanced drug delivery offered by CED, were performed by co-infusing iodine 123-labeled human serum albumin (^{123}I-HSA)with the therapeutic agent. [23–25] The radiolabeled albumin replaced the unlabeled albumin which is usually the carrier protein for the agent. Single-photon emission computed tomography (SPECT) is used to determine the volume of distribution. However, this method has its set of draw backs-appropriate radiotracers are often difficult to develop and access and SPECT imaging is a relatively low resolution creating a paucity of anatomical information [26].

2.2. Iopanoic Acid

Iopanic acid is a nonionic contrast agent, organically bound to Iodine. It has been shown to have many favorable characteristics in validating CED-infused drug distribution including reliable imaging by CT scanning, a good safety profile even in patients intolerant to Iodine derivatives [27] and homogeneity [28]. Also, from a practical standpoint, CT scanning as an imaging modality is available in most clinical centers. While, Iopanic acid has been shown to be effective in monitoring the delivery of various low [29] and high molecular weight drugs [28], it has its limitations. Some of these are poor prediction of the distribution of small, lipophilic, or reactive drugs and concerns for adverse reactions between it and coinfused therapeutic agents.

2.3. Magnetic Resonance Imaging (MRI)T2 Imaging Changes

Preclinical models using diffusion weighted MRI for early tissue characterization have suggested that MRI signal changes may be used to estimate distribution of CED infused drug [14, 30, 31]. More recently, clinical evidence withT2-weighted MRI has been shown to accurately reflect the increase in water content in the interstitium following administration with CED. Sampson *et al.* demonstrated that this method could be used in combination with SPECT imaging to predict intraparenchymal drug coverage, showing discernable alterations following infusion even in patients with preexisting hyperintense signals on T2-weighted MRI [13].

2.4. Gadolinium Conjugated Agents

Gadolinium is a rare-earth element. Chelation with diethylenetriaminepentaacetic acid (DPTA)results in a paramagnetic metal ion used in MRI [32]. Due to its small molecular weight, gadolinium is used as a surrogate marker for infusate distribution and has been bound to albumin and liposomal constructs or used independently to reflect the coverage area of a macromolecular infusate.

2.4.1. Albumin—Albumin-linked tracers have been used in a number of studies as a surrogate marker for macromolecular distribution *via* CED in the primate brain. CED-infused albumin tracers can be linked to Gd-DTPA [14, 33–36], which can then be visualized with conventional imaging modalities like MRI.

2.4.2. Gadolinium-based Liposome Constructs—Liposomes are phospholipid nanoparticles used to carry therapeutic agents. Gadolinium–diethylenetriaminepentaacetic acid (Gd-DTPA) has been used as a surrogate tracer given that is widely available as an MRI contrast agent. Some have attempted to incorporate gadolinium-based molecules as a surrogate tracer into drug impregnated liposomes [37]. However, liposome constructs may be prohibitively difficult to manufacture and thus present a less feasible approach.

2.4.3. Small molecule Gadolinium Infusate—People have used small molecules containing Gadolinium-DTPA in various proprietary formulations known as Magnevist, Omniscan, or Prohance in a large number of animal studies. Usually the tracer distribution is indicated by a threshold on the intensity of a T1-weighted image resulting in a “volume of distribution.” More recently, a quantitative assessment of the tracer concentration has been developed [11, 38]. In conjunction with previous studies, concentration of radio-labeled tracers can now be measured [11, 14, 39, 40].

2.5. Other Tracers

Preclinical data using CED of monodispersedmaghemite nanoparticles (MNP) and MRI imaging to assess effective administration has been published [41]. This agent promises to enable the use of larger drugs and carriers previously thought inappropriate for CED and may increase the half-life of the therapeutic agent due to slow release.

2.6. Comparisons Between Tracers

2.6.1. T2 MRI Versus I^{123} Albumin Tracer—In an attempt to provide a quantitative comparison between MR signal change and drug distribution, Sampson *et al.* [13] co-infused a surrogate tracer ^{123}I-HSAand compared with T2 changes [42], revealing inherent limitations with distribution elucidated by T2-weighted MRI. First, while minor changes in hyperintense signals on T2-weighted MRI following infusion were discernable in patients with preexisting peritumoral edema, these changes were ultimately indistinguishable from edema secondary to malignant glioma [13]. In addition, T2-weighted MRI was not sufficient to assess hyperintense signal in gray matter structures due to the much lower expandability of the interstitium in such cytoarchitectures. While T2-weighted MRI signals might be useful for determining the infusate distribution to extraparenchymal regions including the interventricular space or subarachnoid space, it may be insufficient when assessing the exact

location of the infusate in the context of preexisting edema, or when visualization of distribution throughout gray matter is required.

More recently, Lonser and colleagues found that real – time T2 and diffusion weighted MRI significantly underestimated tissue volume of distribution during CED over a wide range of molecular sizes [43].

2.6.2. Gd-DTPA Versus ^{124}I Albumin Tracer—Our group has recently demonstrated the ability to define the distribution of larger molecules (in this case ^{124}I-HSA) by Gd-DTPA which is a much smaller molecule [44]. We simultaneously infused patients presenting with supratentorial recurrent malignant gliomas using an EGFRvIII-targeted immunotoxin in combination with ^{124}I-HSA (to permit PET imaging) and Gd-DTPA. As assessed by MRI and PET/CT scans, Gd-DTPA infusions provided anatomically and volume\trically accurate information about infusate distribution as well as extraparenchymal leak into CSF spaces and resection cavities.

2.6.3. Gd-DTPA Versus Gd-Albumin Tracer—Gd-DTPA's small molecular weight (938 Dalton in the Magnevist ™ formulation) initially raised concern for its ability to accurately predict the distribution of larger therapeutic molecules. Gadolinium-bound albumin (MW 72,000 D) has been recently compared in distribution with Gd-DTPA (MW 590 D) at pial and ependymal boundaries in primate models [45]. While this study demonstrated with FLAIR MR imaging that both small and large molecular weighted molecules exhibited similar distribution, this result is inconsistent with previous reports that size plays a role in the ability for drug to be distributed to a given region [46].

3. AGENTS

Although a large number of therapeutic options have been examined for CED, only a few agents have been formally studied in clinical trials. Some promising animal studies include utilization of CED for boron neutron capture therapy [47] with boronated epidermal growth factor [48], liposomal topotecan [49], adeno-associated virus thymidine kinase [50], liposomal irinotecan [49], carboplatin, and gemcitabine [51].

Some of the more prominent clinical trials studying CED have included: TP-38, cintredekinbesudotox, IL-4 pseudomonas exotoxin, paclitaxel, AP 12009, and cotara.Sampson *et al.* used CED infusion of TP-38 which is a chimeric protein that fuses TGF-α with a genetically modified Pseudomonas exotoxin. Overall survival was 28 weeks with a subset survival of 33 weeks in the 20 patients with no residual disease and 20.1 weeks in patients with residual disease [39]. There was one patient that at the time of publication had a survival of 260 weeks. The toxicities with TP-38 included 5 patients with seizures who had previous seizure disorders. Grade 3 or 4 toxicity was seen in 2 patients [24].

Cintredekinbesudotox was tested in 51 patients over the series of 3 phase I clinical trials for recurrent high grade gliomas. There was an overall survival rate of 45.9 weeks post-treatment, with 9 patients exhibiting progression free survival for 1 year and seven patients with progression free survival of 2 years [52–54]. There were grade 3 or 4 toxicities reported

with headache, convulsion, and hemiparesis; six patients developed hemiparesis [54]. A phase III trial was completed for cintredekinbesudotox that was randomized against Gliadel wafers for recurrent GBM. The median survival was comparable between CED and Gliadel wafers at 36.4 weeks and 35.3 weeks respectively. Despite no statistical significance in improved survival for CED-administered therapy, inadequate drug distribution and improper catheter placement that might have explained the results [55, 56].

A recombinant cytotoxin that is a fusion between IL-4 and Pseudomonas exotoxin was applied *via* CED in a phase I clinical trial for recurrent gliomas [19, 57, 58]. When comparing the recombinant cytotoxin to resection alone the overall median survival of recurrent GBM was 5.8 months and 5.3 months, respectively [57]. There were no noted systemic toxicities, and the most common adverse events were cerebral edema, seizures, and headaches.

On infusion of paclitaxel for recurrent grade III or IV gliomas, Lidar *et al.* demonstrated an overall median survival of 7.5 months. However, there was a significant number of treatment related adverse events including transient neurological deterioration from cerebral edema (20%), bacterial infections (15%), and chemical meningitis (30%) [31].

AP 12009, an antisense oligonucleotide that binds to TGF-β2 mRNA to inhibit translation [59], was studied through three phase I/II clinical trials for CED that demonstrated a median overall survival of 44 weeks for GBM and 146.6 weeks for patients with anaplastic astrocytoma [60]. There were 29 treatment-related toxicities, but these were mostly minor and limited to grade 2 and 3 toxicities.

Cotara, an immunotoxin with an antibody specific for histone H1-DNA complex that was labeled with ^{131}I, was studied in 51 patients enrolled in phase I and II studies. This treatment achieved a median survival in GBM patients of 37.9 weeks [18]. Eighteen patients had a grade 3 or 4 neurological toxicity, while 4 patients had grade 3 systemic toxicities [18].

These clinical trials have demonstrated the promise of convection enhanced delivery as a therapeutic option for patients with recurrent high grade gliomas with a relatively low toxicity profile associated with therapy. Further investigation using a phase 3 clinical trial and image guided therapies is needed in the future of CED clinical trials.

4. PLANNING CED

We now turn briefly to the second aspect of technologies to improve CED delivery. In analogy to the planning of radiation therapy, CED would benefit from the use of reliable computer modeling as well as the *real-time* monitoring of the catheter placement and infusion processes. We have reported on the performance of an early version of a computer planning system [25]. A detailed report on the algorithms employed, and performance in animals is forthcoming [61]_ENREF_52. As mentioned, costly failures in clinical trials involving CED may in part be attributable to failures in understanding tissue physiology (*e.g.*, the inhomogeneities in fluid pathways in brain) and in employing such information to target agent delivery. In fact, radiation therapy became mainstream only when therapists could plan the treatment before it starts. It is important that we move towards the goal of

testing the therapy, and not the delivery. We feel that only then will CED acquire success in clinical trials and become an approved procedure for drug delivery. In conjunction with this, improvements in the efficacy of the navigation and placement of the catheters are also useful. Recent renewed interest in interventional MR, together with advances in software to control the scanner to obtain rapid imaging of catheter placement during the procedure, will help CED as well as other interventional procedures.

CONCLUSION

The infusion of therapies to the intracerebal compartment offers many advantages and is a promising platform for treatment in patients with GBM. Presently, there are few established techniques for *in vivo* validation of mathematical models that predict the distribution of infusate following CED. As mentioned herein, what has previously been considered disappointing results for CED in clinical trials may reflect suboptimal catheter placement. *In vivo* imaging for CED will also weigh heavily on our ability to monitor infusate distribution and evaluate CED, as well as potential impact on outcomes, with greater precision and fidelity.

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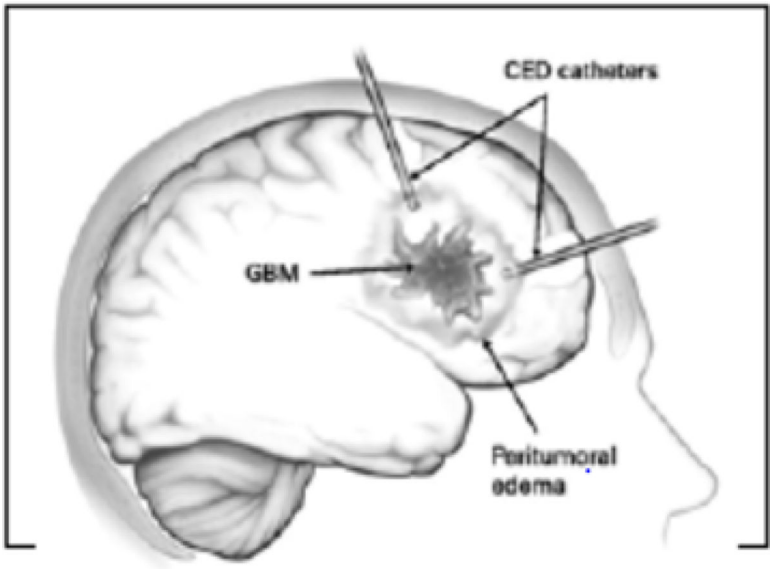

Fig. (1) –.
Diagram of CED Catheter