Convection-enhanced drug delivery for gliomas

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Abstract

In spite of aggressive multi-modality treatments, patients diagnosed with anaplastic astrocytoma and glioblastoma continue to display poor median survival. The success of our current conventional and targeted chemotherapies are largely hindered by systemic- and neurotoxicity, as well as poor central nervous system (CNS) penetration. Interstitial drug administration via convection-enhanced delivery (CED) is an alternative that potentially overcomes systemic toxicities and CNS delivery issues by directly bypassing the blood–brain barrier (BBB). This novel approach not only allows for directed administration, but also allows for newer, tumor-selective agents, which would normally be excluded from the CNS due to molecular size alone. To date, randomized trials of CED therapy have yet to definitely show survival advantage as compared with today’s standard of care, however, early studies appear to have been limited by “first generation” delivery techniques. Taking into consideration lessons learned from early trials along with decades of research, newer CED technologies and therapeutic agents are emerging, which are reviewed herein.

Key Words: Blood–brain barrier, convection-enhanced drug delivery, central nervous system, chemotherapy, glioma

INTRODUCTION

In spite of aggressive multi-modality treatments, patients diagnosed with glioblastoma (GBM, WHO Grade IV glioma) have median survival rates of only 14.6 months,[59] and 11.1–58.6 months if they have an anaplastic astrocytoma (WHO Grade III glioma).[13] After initial recurrence, additional conventional and investigational therapies have afforded an additional median survival of only 6–8 months.[35] Although surgical resection remains a critical component in the multi-modal regimen for these neoplasms, their infiltrative nature prevents a focal therapy like surgery to have curative benefit. This mismatch between a focal treatment modality and a diffuse disease mandates that additional modalities be used, including radiation therapy and chemotherapy. Radiation therapy has shown clear benefit, but ultimately its utility is limited by dose-dependent toxicity, which is cumulative in nature. Furthermore, the success of our current conventional and targeted chemotherapies is hindered predominately by poor drug delivery. Systemic toxicity, neurotoxicity, and poor central nervous system (CNS) penetration secondary to passive and active blood–brain barrier (BBB) mechanisms limit the efficacious delivery of chemotherapeutics to gliomas. Interstitial...
drug administration is an alternative that potentially overcomes systemic toxicities and CNS delivery issues by directly bypassing the BBB. This novel approach not only allows for directed administration but it also allows for newer, tumor-selective agents, which would normally be excluded from the CNS due to molecular size alone.

The benefit of interstitial therapy first was shown in a randomized clinical trial of carmustine administered as an intracavitary treatment following surgical resection of bulk tumor where a small but significant survival benefit was observed in a subgroup of patients.[7] This form of interstitial therapy is mediated by diffusion, a delivery mechanism that limits effective drug distribution to a narrow band around the resection cavity after which there is a steep concentration fall-off.[25] Convection-enhanced delivery (CED) methods may offer many of the same benefits as intracavitary delivery, including reduced risk of systemic toxicity. Unlike diffusion-limited treatment, however, CED provides a localized pressure gradient, enhancing interstitial drug distribution.[8] To date, randomized trials of CED therapy have yet to definitely show survival advantage as compared with today’s standard of care,[25] and this may be due to presently unreliable drug delivery technology.[50,52] Nevertheless, new CED technologies are emerging and therapeutic agents, which will rely on CED are presently in the pipeline for the treatment of brain tumors and other neurological disorders.

THE BLOOD–BRAIN BARRIER

The BBB consists of tight junctions of the CNS endothelium,[46,55] and is supported by juxtaposed astrocytic foot processes. These endothelial tight junctions exhibit few fenestrations and minimal pinocytosis,[55] mechanically preventing the passage of macromolecules, especially those exhibiting polarity or higher molecular weights.[45] Small molecules will passively diffuse (<400–500 kDa), such as certain traditional chemotherapeutics (BCNU,[66] MTX[12]), however, even these molecules tend to maintain less-than-therapeutic CNS concentrations due to high brain tissue clearance rates.[58] Another important mechanism by which molecules are excluded from the CNS is via active drug efflux pumps. Intermediate lipophilic molecules, especially, are actively exported at the level of the BBB via multidrug-resistant transporter P-glycoproteins.[55] Ideally, chemotherapeutics targeting tumor-specific genes or surface antigens will yield higher toxicity to tumor tissue while sparing normal nervous tissue. Unfortunately, however, most targeted chemotherapeutics and biologics carry much higher toxicity to tumor tissue while sparing normal nervous tissue. These phenomena have all been shown to increase BBB permeability for larger molecules, however, these techniques still lack specificity in many cases, imparting neurotoxicity along with enhanced CNS penetration.[58] Even with the directed administration of chemotherapeutics afforded by CED, local rate- and dose-limiting toxicities may still be obstacles, which will be addressed in clinical trials moving forward. New drug formulation, catheter, and imaging techniques are all presently being addressed to optimize drug delivery in future clinical trials.

FACTORS AFFECTING CONVECTION ENHANCED DELIVERY

The technique of CED still requires the consideration of many traditional variables related to pharmacology, including drug half-life and tissue clearance rates. In contrast, a number of novel considerations move to the forefront, and optimization of each of these variables is paramount to the enhancement and efficacy of CED. Factors affecting infusate distribution include (i) infusion rate, volume, and concentration; (ii) tumor tissue architecture, interstitial fluid pressure; (iii) infusate characteristics, half-life, and drug metabolism; (iv) cannula size, shape, and number (backflow); and (v) catheter position and actual volume of distribution (Vd). Each of these variables need to be modified as we optimize tumor treatment strategies.

Infusion rate, volume and concentration

The concentration gradient is the driving force of any diffusion-dependent mechanism of local drug delivery. Alternatively, CED relies on the bulk-flow of interstitial fluid, which occurs due to pressure gradients, and therefore relies less on the concentration of the infusate. When a drug interacts with the target tissue, infusate concentration likely plays a role until any binding or metabolic interactions are saturated, after which point drug distribution is less concentration-dependent.[1,24] Infusion rate and volume of infusion (V), however, are key components that impact on infusate distribution, and are also important variables to be considered in terms of risk of backflow. The Vd of an infusate will initially correlate in a linear fashion with V, even large (50 kDa) molecules.[14] However, in animal models, rates greater than 0.5–1 µl/min have resulted in significant backflow, rendering the Vd independent of V.[11] These phenomena have been seen in clinical trials as well,[50] and reducing backflow while accounting for infusate clearance and metabolism from the target tissue is necessary to optimize Vd.[50] As improvements are made to delivery methods that result in a reduction in propensity for backflow, a more linear relationship between Vd and V likely may be achieved, thereby facilitating higher rates of infusion.[4,52]

Tumor tissue structure/interstitial fluid pressure

Normal brain tissue has a complex architecture with both spatial heterogeneity and anisotropy and these
Characteristics have an impact on the ability to control convective fluid flow.\textsuperscript{[16,40,50]} Gray and white matter differ tremendously from one another. White matter exhibits less resistance to extracellular bulk flow,\textsuperscript{[16,62,65]} while gray matter exhibits more regional homogeneity, yielding more isotropic drug delivery.\textsuperscript{[50]} Both tissues vary regionally as well, in terms of both tissue architecture and the volume of extracellular space. These regional characteristics can be compared using the ratio $V_d/V_i$, where higher values may indicate more densely packed extracellular matrix.\textsuperscript{[31]} Infusion of the primate brainstem was found to have a much higher $V_d/V_i$ when compared with spinal cord or brain tissue infusions.\textsuperscript{[33]} White matter also differs greatly based upon white matter tract direction, yielding regionally dependent anisotropy.\textsuperscript{[10,31]} Anisotropy in $V_d$ occurs not only in relation to white matter tracts, but also preferentially along the axis of a delivery catheter inserted into the brain.\textsuperscript{[30]} Despite these variables, experiments involving CED to normal brain tissue have shown relatively predictable drug distribution patterns.\textsuperscript{[4,29,32]}

Variability in CED increases when it is performed in pathologic tissue. This unpredictability in $V_d/V_i$ is secondary to not only neoplasia-induced changes, but also postoperative tissue changes as well.\textsuperscript{[19,61]} In the case of newly diagnosed tumors that have not yet undergone surgery, the central area of necrosis and its poor vascularity is surrounded by a unique, heterogeneous cytarchitecture, rich in vascularity, with a complex interstitial composition.\textsuperscript{[20]} Mathematical models and tracer studies in clinical trials illustrate the preferential movement of infusate along the path of preexistent white matter edema,\textsuperscript{[65]} increased $V_d/V_i$ in regions of hypercellularity,\textsuperscript{[13]} and faster drug clearance through pathologic, “leaky”, tumor vasculature.\textsuperscript{[20,66]} Pathologic vascularity and vascular permeability coupled with the natural absence of a lymphatic system also create higher interstitial fluid pressures centrally, extending to normal brain adjacent to tumor.\textsuperscript{[20]} This outward pressure gradient conducts fluid rapidly out of diseased tissue.\textsuperscript{[20,61]} Not only must infusate from catheters placed in the tumor periphery overcome this outward driving force, but also complex pressure gradients in neoplastic tissue result in more variable $V_d$ and infusate clearance rates.\textsuperscript{[20,65]} In a subcutaneous tumor model, drug clearance was found to be up to 20 times more rapid in tumor tissue as compared with normal brain.\textsuperscript{[61]}

Postoperative tumor characteristics further complicate drug delivery. From a drug distribution standpoint, treating a cavity that has a direct communication to the subarachnoid space becomes more difficult. Recent clinical trials attempted to achieve catheter placement $>2$ cm from brain surface and $1$ cm from any cavity including the surgical resection cavity.\textsuperscript{[42]} When catheters are placed peri-tumorally, it has been hypothesized that reactive changes in postoperative regions may hinder extracellular movement of larger molecules, reducing $V_d$ in these clinically relevant scenarios.\textsuperscript{[65]} Further, when catheters are placed near the gray–white interface in the peri-tumoral area in human studies, infusate can be visualized preferentially coursing along white matter tracts.\textsuperscript{[65]} Technically, catheter placement can be more difficult with the presence of artificial dura and greater CSF space, potentially altering catheter trajectory and placement.\textsuperscript{[56]}

**Physical and chemical characteristics of infusates**

Limitations to $V_d$ also relate to the properties of the infusates themselves. Small molecular weight molecules, which tend to be favored for diffusion-driven delivery but also perform well in CED, can also be cleared from the brain more quickly than large molecular weight molecules, thereby limiting $V_d$.\textsuperscript{[59,66]} Clearance of drug from tissue is not only associated with its metabolism, but also with the rates of endocytosis, receptor binding, convection to the subarachnoid space and systemic clearance via leaky tumor vasculature. Mathematical modeling has shown that macromolecules of 180 kDa can be delivered to volumes of tissue up to 10-fold greater than the volume of infusate via a 12-h infusion with CED (6 $\mu$L/min).\textsuperscript{[38]} This $V_d$ is of course contingent upon the molecule not binding to the extracellular matrix and undergoing only slow degradation.\textsuperscript{[38]} Molecules that undergo more rapid degradation (such as growth factors) may exhibit substantially lower $V_d$.\textsuperscript{[38]} Furthermore, slowly degraded molecules may undergo additional postinfusion diffusion-driven distribution over ensuing days.\textsuperscript{[38]} Newer technologies seek to prolong the time that active drug remains in the target tissue, by lowering a drug’s clearance rate, thereby improving $V_d$ and possibly efficacy. To accomplish this goal, ongoing efforts have conjugated drugs to larger less reactive molecules,\textsuperscript{[9]} nanoparticles,\textsuperscript{[12]} or incorporated them into liposomes.\textsuperscript{[65]} As the molecular weight of the modified therapeutic is increased in order to reduce clearance, however, this benefit must be balanced against the risk that postoperative changes in the tissue architecture and extracellular matrix may hinder transit of the larger molecule through tissue.\textsuperscript{[65]}

Recent animal studies have shown that one does not necessarily need to alter drug composition in order to change its flow rate and/or retention time in tissue. For example, an increase in infusate viscosity by itself enhances convection.\textsuperscript{[35,36]} One study showed that use of a 3.0% solution of human serum albumin in saline, as opposed to the less viscous standard 0.02% solution, resulted in an increase of nearly threefold in the volume of distribution of immunotoxin PRX-321.\textsuperscript{[35]}

**Cannula characteristics – impact on backflow**

Initial work in the field of CED has focused on open-ended, straight cannulas. These cannulas are prone to backflow with relatively low infusion rates. Chen \textit{et al.} evaluated the impact of cannula diameter on propensity...
Furthermore, real time imaging even with use of these guidelines governing their use. Because these catheters were highly susceptible to backflow, they were required to be placed at least 2.5 cm into the brain and this may not have been the ideal location for infusing the target tissue. Other nuances relating to placement of these single port catheters included a requirement to limit catheter tip proximity to ependymal surface by at least 0.5 cm as these surfaces tend to be “leaky” and result in loss of infusate to the ventricles, which act as a “sink.” Also, it was felt important that these catheters do not penetrate pial surfaces of deep sulci or the ventricular system due to the same concern of loss of infusate to CSF spaces, which act as “sinks.” These guidelines for catheter placement had not been prospectively validated; they were derived from small studies that performed retrospective validation and/or used tracers in a small number of patients.

Despite highly organized efforts to train neurosurgeons regarding placement of open ended single port catheters, clinical results from the phase III NeoPharm PRECISE trial show that catheter positioning was highly variable and only considered optimal in 51% of patients and that drug distribution was likely to be adequate in less than 20%. Although the phase III study did not include the co-infusion of tracers, it was considered to be a reasonable conclusion that suboptimal placement contributed to the inadequate clinical results.

Visualization of CED in real time
To be clear, the impact of catheter placement on clinical outcome remains speculative. What is widely viewed as the single most important limitation in the field of CED is the inability to directly visualize drug delivery. Fortunately, this important limitation is being addressed. Intraoperative imaging techniques may allow for confirmation of catheter placement as well as monitoring of infusate real-time. Monitoring infusate $V_d$ has been shown efficacious using Gd-diethylenetriamine-pentaacetic acid (Gd-DTPA) or I-123-Albumin in animal models and human studies. Furthermore, real time imaging has been described in animal studies with use of Gd-enhanced liposomal delivery methods and iron oxide-loaded nanoparticles and in humans with use of Gd-DTPA or Gd-DOTA co-infusion. These methods potentially can allow the neurosurgeon to adjust flow rates, in real time, based on visualization of reflux. In the canine model, liposomal delivery methods were found to accurately reflect drug $V_d$. When using molecules with molecular weights smaller than the active agent, such as Gd-DPTA (<1 kDa), the question of whether tracer diffusion matches that of the active agent is raised. However, in human trials, the correlation between Gd-DTPA $V_d$ and target tissue response to therapy were surprisingly similar. These correlations were also observed in animal studies and computational models. Moving forward it is expected that not only will clinicians be able to track an infusion
in real time, but will also be able to predict the pattern of distribution by taking many of the aforementioned tissue architecture factors into account.\textsuperscript{130} Factoring catheter and infusate characteristics as well as magnetic resonance imaging (MRI)-determined anatomy and tissue properties, Linninger \textit{et al.} demonstrated the possibility of mathematical, patient-specific prediction models incorporating diffusion tensor imaging (DTI) data.\textsuperscript{139}

**Catheter placement in eloquent brain**

The safety of catheter placement, particularly into eloquent areas of the brain, has been evaluated in multiple studies. In animal models, catheter placement and infusion has been shown safe in normal brainstem\textsuperscript{132} and spinal cord.\textsuperscript{131} However, there are concerns that tumor-infiltrated critical structures may have less reserve and be more susceptible to injury with catheter placement and high-flow, or high-volume infusion.\textsuperscript{11,16} Reports in a pediatric patients receiving CED with intrinsic brainstem glioma describe transient neurological symptoms, reversible with cessation of therapy and steroid treatment,\textsuperscript{133} or potentially preventable with lower rates and volumes of infusion.\textsuperscript{11} Many reports exhibit neurologic changes with infusion that are transient and reversible over several days.\textsuperscript{33,56,65,67,68} A recent retrospective review of over 40 cases found that edema and hemorrhage were often present on postinfusion imaging, but in most cases these imaging findings did not lead to clinically detectable signs or symptoms.\textsuperscript{156} Seizures, infection and neurologic deterioration were also reported, although permanent sequelae (defined as reduction in Karnofsky Performance Scores by 20 points or greater) occurred in 13.8\% of patients.\textsuperscript{160} In a randomized clinical trial, complications rates were no different as compared with implantable polymers,\textsuperscript{23} however, other reports raise concerns associated with targets in eloquent areas already compromised by neoplastic infiltration.\textsuperscript{156}

### CLINICAL TRIALS

CED clinical trials have been carried out with various agents including conventional chemotherapies,\textsuperscript{8} cytotoxin-ligand conjugates targeting cell surface receptors,\textsuperscript{27,67-69} and monoclonal antibodies with\textsuperscript{122} or without\textsuperscript{30} radioactive isotope conjugates, antisense oligonucleotides,\textsuperscript{5} and liposomal vectors engineered to deliver gene therapy.\textsuperscript{161} Phase I-III trials were carried out in humans starting in the 1990s demonstrating adequate safety profiles for a number of convection-delivered agents [Table 1]. One limitation of early CED trials was likely secondary to the use of “1\textsuperscript{st} generation catheter” design. As noted above, these “off-the-shelf” catheters were considered to be prone to backflow. Despite a lack of data evaluating the delivery characteristics of the catheters in the clinical setting, and fueled by apparently promising results from the small phase I and II trials, CED trials moved forward utilizing catheters already approved for clinical usage (peritoneal and ventricular catheters). Two phase III trials were initiated in patients with brain tumors. One trial, utilizing Ti-CRM107, was aborted with the latest data published regarding

### Table 1: CED clinical trials: Targeted fusion toxins

| Drug name     | Active agent | Ligand/ domain | Study population | Recent status | Catheter description | Concentration, rate, dose | References |
|---------------|--------------|----------------|------------------|--------------|----------------------|---------------------------|------------|
| TransMID (TF-CRM107) | Mutant diphtheria toxin | Transferrin/ transferrin receptor | Refractory MG | Low efficacy in phase III, aborted | Sialastic infusion catheters (2.5 mm OD) | 0.67 mcg/mL @ 0.2 mL/h total: 40 mL | Phase I\textsuperscript{[27]} Phasell\textsuperscript{[47]} Phasell: Aborted Phase I\textsuperscript{[60,69]} |
| NBI-3001\textsuperscript{,*} (IL-4-PE, IL-4[38-37]-PE38KDEL) | Mutant pseudomonas exotoxin | Recombinant human IL-4/ IL-4 receptor | Recurrent MG | Survival benefit in phase II, multicenter trial planned | Phase I/II well tolerated Phase III no statistical survival benefit @ primary endpoint | 0.5 mcg/mL @ 0.75 mL/h for 96 h | Phase I\textsuperscript{[26]} Phase III PRECISE Trial\textsuperscript{[25]} |
| Cintredekin besudotox\textsuperscript{2} (IL-13-PE38QQR) | Mutant pseudomonas exotoxin | Recombinant human IL-13/IL-13 receptor | First GBM recurrence | Phase I well tolerated with concurrent EBRT+TMZ | Barium impregnated open ended silicon catheter (1 mm ID, 2 mm OD) | 0.5 mcg/mL @ 0.75 mL/h for 96 h | Phase I\textsuperscript{[64]} |
| Cintredekin besudotox\textsuperscript{3} (IL-13-PE38QQR) | Mutant pseudomonas exotoxin | Recombinant human IL-13/IL-13 receptor | Newly diagnosed MG | Phase I well tolerated with concurrent EBRT+TMZ | Ventricular catheter (OD 2.1 mm) (Medtronic Inc, USA) | 100 nanog/mL @ 0.4 mL/h Total: 40 mL | Phase I\textsuperscript{[69]} |
| TP-38 | Mutant pseudomonas exotoxin | TGF-α domain/EGFR | Recurrent or progressive MG or metastases | Survival benefit in phase II | | 0.67 mcg/mL @ 0.2 mL/h total: 40 mL | |
Monoclonal antibodies have also been utilized in clinical trials [Table 2]. Cotara, a radioactive isotope-conjugated monoclonal antibody was well tolerated in phase I and II trials. However, there has not yet been a phase III study completed with a monoclonal antibody used in this manner. Conventional chemotherapies have been delivered intratumorally since the 1980s via diffusion-driven, slow-release polymers, and low-flow delivery techniques. Although low flow diffusion methods work best for molecules with high diffusion coefficients, most often these are low molecular weight substances, which are also cleared from tissue rapidly. Driven almost entirely by concentration gradients, these methods are limited by local neurotoxicity in areas where the concentration is high, and lack of efficacy in nearby areas where the exponential decay in concentration results in subtherapeutic tissue doses.

Table 2: CED clinical trials: Chimeric monoclonal antibodies

| Drug               | Active agent/ mechanism | Ligand/target | Study population | Status                        | Catheter              | MTD                  | References |
|--------------------|-------------------------|---------------|------------------|-------------------------------|-----------------------|----------------------|------------|
| Murine mAb 425     | mAb via EGFR            | EGFR         | Recurrent or inoperable MG | Phase I                      | Ventricular-type catheter | Total planned dose not achieved | Phase I[19] |
| Cotara             | I131/Radiation delivery | DNA histone (H1) complex mAb/necrotic neoplastic antigens | Recurrent or inoperable MG | Phase I/II well tolerated | Peritoneal catheter | 0.18 mL/h 18 mL | PhaseI/II[42] |
| (I131-chTNT -1/B MAb) |                        |               |                  |                               |                       |                      |            |

All reported CED clinical trials treating gliomas utilizing monoclonal antibodies. 1: Merk (KGaA), 2: Perigrine Pharmaceuticals Inc, CA, USA. MAb: monoclonal antibody, MG: Malignant glioma, EGFR: Epidermal growth factor receptor, MTD: Maximum tolerated dose

Table 3: CED clinical trials: Conventional chemotherapeutic agents

| Drug               | Mechanism                  | Study population | Status                        | Catheter              | MTD                  | References |
|--------------------|----------------------------|------------------|-------------------------------|-----------------------|----------------------|------------|
| Paclitaxel         | Microtubule stabilization/mitosis inhibition | Recurrent MG     | High complication rate (i.e., meningeitis, HCP, and/or neurologic deterioration) | Modified ventricular catheter with single end port (Medtronic Inc, USA) | 0.3 mL/h Total 18 mg | Phase I/II[28] |
| Nimustine hydrochloride/ Gd-DOTA | DNA alkylation          | Pediatric pontine GBM | Initial tumor regression Ongoing pilot study | 18 gauge single-port central venous catheter (~1.27 mm OD) | 0.25 mg/mL+ 1 mM Gd-DOTA @ 5 mcl/min Total 7.02 mL | Ongoing pilot[48] |
| Topotecan          | Topoisomerase I inhibition | Recurrent or progressive MG | Tumor regression and tolerability in Phase Ib | Silastic infusion catheter, single hole 2.5 mm OD | 0.1 mg/mL @ 200 mcl/l Total 40 mL | Phase Ib[10] |
| Topotecan          | Topoisomerase I inhibition | Pediatric DIPG    | Tolerable safety profile with lower rate infusion | Silastic infusion catheter, single hole 2.5 mm OD | 0.02 mL @ Total 5.3-6.04 mL | Phase Ib[10] |
| Carboplatin        | DNA synthesis and repair  | Recurrent or progressive GBM | Ongoing                        | Step-down catheter design 0.6 mm OD | <0.18 mg/mL @ <0.01 mL/min Total 60 mL | Study design[11] |

All reported CED clinical trials treating gliomas utilizing conventional chemotherapies. MG: Malignant glioma, HCP: Hydrocephalus, Gd: Gadolinium, DOTA: Gadolinium chelator, OD: Outer diameter, GBM: Glioblastoma multiforme, DIPG: Diffuse intrinsic pontine glioma
favorable progression-free and overall survival rates of 23 and 60 weeks, respectively.[6] In a feasibility report of two patients also enrolled in the aforementioned study, Anderson et al. demonstrate the infusion of topotecan in the brainstem of two pediatric patients with diffuse intrinsic pontine gliomas.[7] Although infusion rates/drug concentrations required reduction due to local neurological declines, the tolerability with lower infusion rates exemplifies the possibility of treating brainstem lesions, albeit cautiously especially in those with mass effect.[8]

There are multiple other classes of therapeutic agents that are being investigated as potential CED infusates for glioma therapy. These include gene therapies,[9,10,11] oligonucleotides,[12,13] liposomes,[14,15,16] and viral particles.[17] One approach that has generated substantial interest regards the use of liposomal encapsulation. Liposomes have been used to encapsulate a multitude of therapeutics and prolong their half-life systemically, and they may have particularly advantageous properties when used to deliver therapeutics via CED.[18] In the CNS, liposomal encapsulation can potentially reduce unwanted, early drug–tissue interaction, allowing for greater volumes of distribution, reduce tissue clearance rates,[19] and provide a vector for gene therapy delivery.[20] Liposomes can carry MRI contrast agents themselves, as has been shown in animal models.[21]

While liposomes are promising as carrier agent for therapeutic CED, nanoparticles are emerging as smaller, potentially more efficient vehicles.[22,23,24] For example, magnetic nanoparticles such as maghemite (15–80 nm), can be delivered via CED and loaded with bioactive molecules, which would normally have high tissue clearance or reactivity rates, and be utilized as MRI contrast agents.[25] Polymeric nanoparticles offer similar advantages, where they can be conjugated to numerous chemotherapies in addition to a contrast agent, and fabricated for optimal convection characteristics (<100 nm).[26] While there are many permutations being investigated in animal models, no particular vehicle has been proven to be reliably better, and few have been tested in clinical trials [Table 4].

**CONCLUSION**

CED facilitates the implementation of novel, targeted chemotherapies that would previously have been excluded from the CNS via systemic delivery. In addition, CED provides clinicians with enhanced delivery of historically proven, conventional chemotherapeutics. To be considered successful as a delivery method, CED will require optimization of infusate/vector characteristics, catheter properties and placement techniques, as well as real-time infusate distribution tracking and potentially accurate, patient specific distribution prediction models. Once optimized, CED conveys the opportunity of more effectively delivering antineoplastic agent to these infiltrative neoplasms than has been achieved with conventional (oral and parenteral) routes of delivery.

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**Table 4: CED clinical trials: Other novel therapeutics**

| Drug | Active agent/mechanism | Carrier | Study population | Status | Catheter | MTD | References |
|------|------------------------|--------|-----------------|--------|----------|-----|-----------|
| Trabedersen<sup>1</sup> (AP 12009) | TGF-B2 antisenseRNA/TGF-B2 inhibition | - | Recurrent or refractory MG | Completed, well tolerated SAPPHIRE trial recruiting | Silicon catheter<sup>2</sup> | 2.48 mg @ 4 µL/min | Phase IIb<sup>51</sup> |
| CpG-28 (ODNs) | CPG-ODN/TLR-9-mediated tumor rejection | Phosphorothioate backbone | Progressive GBM | Well tolerated PFS at 6 months, 19% | Seldiflex and plastimed | 10 mg/mL @ 4 mg/h | Phase II<sup>53</sup> |
| LIPO-HSV-1-dk+GCV | HSV-1-dk/GCV sensitization | Cationic liposome | GBM | Well tolerated | Silicon catheter<sup>2</sup> | <6 mL/h | Phase I<sup>55</sup> |

All reported CED clinical trials treating gliomas utilizing other therapies or newer delivery methods. 1: Antisense Pharma, Regensburg Germany. 2: Phoenix Biomedical, Valley Forge, PA. MG: Malignant glioma, ODN: Oligodeoxynucleotides, PFS: Progression-free survival, GBM: Glioblastoma multiforme, TGF: Transforming growth factor β2.
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