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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

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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.[25] 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 drug 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.[23] 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.[4] 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 fenstrations 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 molecular weights and are largely excluded from the CNS. Carrier- or receptor-mediated transport, nanoparticles, vasomodulators, and osmotic BBB disruption techniques 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 (V_d). 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.[11,24] Infusion rate and volume of infusion (V_i), however, are key components that impact on infusate distribution, and are also important variables to be considered in terms of risk of backflow. The V_d of an infusate will initially correlate in a linear fashion with V_i, even large (80 kDA) molecules.[4] However, in animal models, rates greater than 0.5–1 μl/min have resulted in significant backflow, rendering the V_d independent of V_i.[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 V_d.[61] As improvements are made to delivery methods that result in a reduction in propensity for backflow, a more linear relationship between V_d and V_i likely may be achieved, thereby facilitating higher rates of infusion.[4,32]

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.[16,40,50] Gray and white matter differ tremendously from one another. White matter exhibits less resistance to extracellular bulk flow,[16,52,65] while gray matter exhibits more regional homogeneity, yielding more isotropic drug delivery.[30] 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.[33] 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.[33] White matter also differs greatly based upon white matter tract direction, yielding regionally dependent anisotropy.[30,33] 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.[50] Despite these variables, experiments involving CED to normal brain tissue have shown relatively predictable drug distribution patterns.[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.[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 cytoarchitecture, rich in vascularity, with a complex interstitial composition.[20] Mathematical models and tracer studies in clinical trials illustrate the preferential movement of infusate along the path of preexistent white matter edema,[65] increased V_d/V_i in regions of hypercellularity,[33] and faster drug clearance through pathologic, "leaky", tumor vasculature.[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.[20] This outward pressure gradient conducts fluid rapidly out of diseased tissue.[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.[20,63] 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.[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.[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.[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.[65] Technically, catheter placement can be more difficult with the presence of artificial dura and greater CSF space, potentially altering catheter trajectory and placement.[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.[58,66] 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 μl/min).[38] This V_d is of course contingent upon the molecule not binding to the extracellular matrix and undergoing only slow degradation.[38] Molecules that undergo more rapid degradation (such as growth factors) may exhibit substantially lower V_d.[38] Furthermore, slowly degraded molecules may undergo additional postinfusion diffusion-driven distribution over ensuing days.[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,[9] nanoparticles,[12] or incorporated them into liposomes.[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.[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.[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.[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 *et al.* evaluated the impact of cannula diameter on propensity

to backflow and found that increasing cannula diameter from 32–28 gauge resulted in statistically significant backflow without increasing volume of distribution in Sprague Dawley rats.[11] Mathematical modeling supports these principles[38] and catheter design advancements have focused on flexible,[17] fine-tipped catheters,[60,72] in order to enhance V_d via reduction of backflow. Newer designs include step-down cannulas, which have a smaller diameter at the tip than along the majority of the shaft, to assist in their surgical placement while allowing the actual infusion catheter tip to be exceedingly small, limiting backflow.[15,21,32] Using an infusion cannula with inner diameter of 152 microns (outer diameter 356 microns), V_d was shown to be linearly associated with V_i at rates up to 1 μl/min with a 72-kDa infusate (gadolinium–albumin conjugate) in the primate brainstem.[32] Even smaller infusion catheters (inner diameter 102 microns) have been show to reach 5 μl/min of infusion or greater without backflow, however, the authors of this study recognize higher rates may result in local tissue injury.[21] With low flow rates, multiple catheters may more optimally deliver necessary volumes over short periods of time while allowing a more conformal V_d to the target tissue.[60,72]

Finally, the catheter terminus has been the focus of recent investigations that attempt to optimize forward flow while minimizing backflow.[41,44] The coaxial multiport catheter design, which has multiple outflow ports along the distal catheter wall, was shown to allow infusate egress from the proximal port only; once sufficient pressure was reached to overcome tissue plugging of a single port, it would continue to flow from that port, never reaching pressure needed to overcome tissue plugging of the other ports.[44] A hollow fiber catheter design with a sealed end and a 3 mm long, circumferentially porous tip (0.45 microns average pore diameter) was compared with infusions with a 28g needle in a murine model. The hollow fiber catheter resulted in an V_d of Evans blue dye infusion 2.7 times greater than with the 28g needle and achieved 4- to 10-fold greater adenoviral mediated gene transfer.[41] New catheter designs such as this will improve V_d and perhaps greatly affect the efficacy and outcome in future clinical trials.

Catheter placement and impact on CED

As previously discussed, the complex tissue properties of the normal brain relating to its heterogeneous and anisotropic architecture are amplified by the distortions in structure caused by neoplasia and the impact of surgical resection.[20] The heterogeneity in brain architecture is reflected in the spatial variability of the V_d/V_i ratio. This variability is felt to have an impact on the optimization of catheter placement as it impacts the expected pattern of infusate distribution. Experience relating to the use of open-ended single port catheters in various parts of the brain led to the development of a set of guidelines governing their use.[53] 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."[33,50] 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."[50] 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.[26,51]

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,[25,39] and that drug distribution was likely to be adequate in less than 20%.[52] 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.[25,35,49,50,68,69]

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-diethyenetriamine-pentaacetic acid (Gd-DTPA) or I-123-Albumin in animal models[12,36] and human studies.[50,65] Furthermore, real time imaging has been described in animal studies[3,14,22] with use of Gd-enhanced liposomal delivery methods[22] and iron oxide-loaded nanoparticles,[3,18] and in humans with use of Gd-DTPA[33] or Gd-DOTA[48] co-infusion. These methods potentially can allow the neurosurgeon to adjust flow rates, in real time, based on visualization of reflux.[62] In the canine model, liposomal delivery methods were found to accurately reflect drug V_d.[14] 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.[33,65] However, in human trials, the correlation between Gd-DTPA V_d and target tissue response to therapy were surprisingly similar.[51,65] These correlations were also observed in animal studies[36] and computational models.[33] 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.[30] Factoring catheter and infusate characteristics as well as magnetic resonance imaging (MRI)-determined anatomy and tissue properties, Linninger *et al.* demonstrated the possibility of mathematical, patient-specific prediction models incorporating diffusion tensor imaging (DTI) data.[30]

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[32] and spinal cord.[31] 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.[1,10] Reports in a pediatric patients receiving CED with intrinsic brainstem glioma describe transient neurological symptoms, reversible with cessation of therapy and steroid treatment,[33] or potentially preventable with lower rates and volumes of infusion.[1] Many reports exhibit neurologic changes with infusion that are transient and reversible over several days.[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.[56] 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.[56] In a randomized clinical trial, complications rates were no different as compared with implantable polymers,[25] however, other reports raise concerns associated with targets in eloquent areas already compromised by neoplastic infiltration.[56]

CLINICAL TRIALS

CED clinical trials have been carried out with various agents including conventional chemotherapies,[8] cytotoxin-ligand conjugates targeting cell surface receptors,[27,67-69] and monoclonal antibodies with[42] or without[70] radioactive isotope conjugates, antisense oligonucleotides,[5] and liposomal vectors engineered to deliver gene therapy.[65] 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 "1st 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 Tf-CRM107, was aborted with the latest data published regarding

Table 1: CED clinical trials: Targeted fusion toxins

Drug name	Active agent	Ligand/ target	Study population	Recent status	Catheter description	Concentration, rate, dose	References
TransMID (Tf-CRM107)	Mutant diphtheria toxin	Transferrin/ transferrin receptor	Refractory or recurrent MG	Low efficacy in phase III, aborted	Sialstic infusion catheters (2.5 mm OD)	0.67 mcg/mL @ 0.2 mL/h total: 40 mL	Phase I[27] PhaseII[67] PhaseIII: Aborted
NBI-3001[1],* (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	-	6 mcg/mL total: 40 mL	Phase I/II[68,69]
Cintredekin besudotox[2] (IL-13-PE38QQR)	Mutant pseudomonas exotoxin	Recombinant human IL-13/IL-13 receptor	First GBM recurrence	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[26] Phase III PRECISE Trial[25]
Cintredekin besudotox[2] (IL-13-PE38QQR)	Mutant pseudomonas exotoxin	Recombinant human IL-13/IL-13 receptor	Newly diagnosed MG	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[64]
TP-38	Mutant pseudomonas exotoxin	TGF-α domain/EGFR	Recurrent or progressive MG or metastases	Survival benefit in phase II	Ventricular catheter (OD 2.1 mm) (Medtronic Inc, USA)	100 nanog/mL @ 0.4 mL/h Total: 40 mL	Phase I/II[49]

All reported CED clinical trials treating gliomas utilizing targeted fusion toxins. [1]: Inland Labs Inc., Desoto, Texas, * Now called PRX-321 (Protox Therapeutics, BC, Canada), [2]: Neopharm, IL, USA. MG: Malignant glioma, OD: Outer diameter, ID: Inner diameter, IL: Interleukin, GBM: Glioblastoma multiforme, EBRT: External beam radiation therapy, TMZ: Temozolamide, TGF: Transforming growth factor, EGFR: Epidermal growth factor receptor

Tf-CRM107 being the phase II trial from 2003.[67] The other phase III trial, the PRECISE trial, did not reveal statistically significant improvement in survival.[25] The study compared citredekin besudotox (CB), a chimeric pseudomonas exotoxin with recombinant human interleukin (IL)-13, to Gliadel intracavitary chemotherapy wafers.[25] Although no survival benefit was found, the study was impaired by its statistical design, which required a >50% survival benefit over the active control arm. Furthermore, the authors of the study noted that only 68% of catheter placements were performed per protocol specifications. Despite these limitations, there was a statistically significant improvement in progression-free survival (17.7 vs. 11.4 weeks; $P = 0.0008$), although this was not a prespecified analysis.[25]

A phase I clinical trial studied the use of CB in newly diagnosed malignant glioma patients who were also being treated with standard of care external beam radiation therapy and temozolomide concurrently.[64] This study seemed to indicate that the dose of CB that was being used in the recurrent GBM setting was also safe when used in combination with chemoradiation.

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.[42] 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,[7] and low-flow delivery techniques.[6,37,43] Although low flow diffusion methods work best for molecules with high diffusion coefficients,[20] most often these are low molecular weight substances, which are also cleared from tissue rapidly.[12,66] 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.[57]

Novel strategies for delivery of conventional chemotherapies to the brain include CED [Table 3], as well as conjugation with macromolecules or nanoparticles.[12,14,47] Recent clinical trials utilizing CED have investigated carboplatin[72] and topotecan.[8] Topotecan showed promising results with

Table 2: CED clinical trials: Chimeric monoclonal antibodies

Drug	Active agent/ mechanism	Ligand/target	Study population	Status	Catheter	MTD	References
Murine mAB 425[1]	mAb via EGFR antagonism	EGFR mAB/EGFR receptor	Recurrent or inoperable MG	Phase I toxicity	Ventricular-type catheter	Total planned dose not achieved	Phase I[70]
Cotara[2] (^{131}I-chTNT -1/B MAb)	I^{131}/Radiation delivery	DNA histone (H1) complex mAb/necrotic neoplastic antigents	Recurrent or inoperable MG	Phase I/II well tolerated	Peritoneal catheter	0.18 mL/h 18 mL	PhaseI/II[42]

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., meningitis, 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/h Total 40 mL	Phase Ib[8]
Topotecan	Topoisomerase I inhibition	Pediatric DIPG	Tolerable safety profile with lower rate infusion	Silastic infusion catheter, single hole 2.5 mm OD	0.034-0.067 mg/mL @ 0.02 ml/h Total 5.3-6.04 mL	Phase Ib[1,8]
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[71]

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

Table 4: CED clinical trials: Other novel therapeutics

Drug	Active agent/ mechanism	Carrier	Study population	Status	Catheter	MTD	References
Trabedersen[1] (AP 12009)	TGF-B2 antisenseRNA/ TGF-B2 inhibition	-	Recurrent or refractory MG	Completed, well tolerated SAPPHIRE trial recruiting	-	2.48 mg @ 4 μL/min Multiple cycles	Phase IIb[5]
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 Total 2 ml	Phase II[9]
LIPO-HSV-1-*tk*+GCV	HSV-1-*tk*/GCV sensitization	Cationic liposome	GBM	Well tolerated	Silicon catheter[2]	<6 mL/h	Phase I/II[65]

All reported CED clinical trials treating gliomas utilizing other therapeutics 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

favorable progression-free and overall survival rates of 23 and 60 weeks, respectively.[8] 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 inrinsic pontine gliomas.[1] 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.[1]

There are multiple other classes of therapeutic agents that are being investigated as potential CED infusates for glioma therapy. These include gene therapies,[2,65,71] oligonucleotides,[5,9] nanoparticle conjugates,[3,12,18,54] liposomes,[14,34,65] and viral particles.[2,71] 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.[11] In the CNS, liposomal encapsulation can potentially reduce unwanted, early drug–tissue interaction, allowing for greater volumes of distribution, reduce tissue clearance rates,[14] and provide a vector for gene therapy delivery.[65] Liposomes can carry MRI contrast agents themselves, as has been shown in animal models.[14]

While liposomes are promising as carrier agent for therapeutic CED, nanoparticles are emerging as smaller, potentially more efficient vehicles.[3,12,18,47,54] 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.[12] 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).[3] 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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