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Convection-enhanced delivery for high-grade glioma

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Abstract

Glioblastoma (GBM) is the most common adult primary malignant brain tumor and is associated with a dire prognosis. Despite multi-modality therapies of surgery, radiation, and chemotherapy, its 5-year survival rate is 6.8%. The presence of the blood-brain barrier (BBB) is one factor that has made GBM difficult to treat. Convection-enhanced delivery (CED) is a modality that bypasses the BBB, which allows the intracranial delivery of therapies that would not otherwise cross the BBB and avoids systemic toxicities. This review will summarize prior and ongoing studies and highlights practical considerations related to clinical care to aid providers caring for a high-grade glioma patient being treated with CED. Although not the main scope of this paper, this review also touches upon relevant technical considerations of using CED, an area still under much development.

Keywords

BBB | CED | glioblastoma | immune therapy | treatment

Overview

Glioblastoma (GBM) is the most common adult primary malignant brain tumor and is associated with a dire prognosis despite multi-modality therapies of surgery, radiation, and chemotherapy.[1] The presence of the blood-brain barrier (BBB) is one factor that has made GBM difficult to treat. The treatment modality of convection-enhanced delivery (CED) has the goal of providing local infusions of drugs directly into the tumor bed, thereby surpassing the BBB. While the technique of CED is validated, no therapeutic agent as yet gained approval for this type of delivery and thus, remain an area of active investigation. The benefits of administering an effective therapy via CED would be multifold, including direct delivery of a drug that would not otherwise cross the BBB; limit the incidence of systemic toxicity, a significant limiting factor in current cancer therapy; and improve survival in GBM patients.

CED was first introduced by Bobo et al in 1994.[2] The concept involves inserting a catheter into the tumor bed and using an infusion pump to generate positive pressure to distribute the drug.[2] The benefit of positive pressure, CED, is that the distribution of drug depends on the infusion rate and not the drug's molecular size, which limited previously tried local therapies that relied solely on diffusion.[3,4]

Since its introduction, much research has been done using CED to deliver various drugs directly into brain tumors, with many lessons learned along the way.[5–9] While this review will briefly describe the technical considerations, its focus is not geared toward the neurosurgical or imaging considerations around CED, a field in active development. This review will summarize the strengths and limitations of previous studies, introduce ongoing studies, and share practical considerations to assist clinicians caring for GBM patients treated via CED.

Technical Considerations

CED requires a neurosurgical procedure to insert one or more catheters that will administer the drug into the patient's tumor bed. Tumor size and location, choice of catheter, optimal catheter placement, and infusion rates, as well as confirmation of optimal drug delivery, are key components of successful CED therapy.

Tumor Size and Location

As the infusate will direct toward areas of least resistance, it has been demonstrated that the drug will preferentially flow along white matter tracts, areas of already present peri-tumoral edema or even into CSF spaces, all of which would affect the efficacy of the infused agent.[10–12] Furthermore, the surgical procedure itself and the inserted CED catheter can all increase intracerebral edema.[10] The mass effect of larger tumors often itself triggers neurological decline, making it unsafe to add additional volume with CED infusate. Edema in an area without much room for the brain to compensate such as in the brainstem or cerebellum can compromise consciousness. Edema that involves or is within proximity to eloquent cortex can cause serious neurological deficits such as weakness or aphasia. Given the risk of symptomatic edema from the treatment, decreased efficient distribution of the infusate near cerebrospinal fluid spaces, and risk of infection,[13,14] human studies have tailored inclusion and exclusion criteria based on these potential issues. Most clinical trials have limited the tumor size to less than 4 × 4 cm in bidimensional measurements and excluded patients with tumors in the posterior fossa. Investigators also use guidelines to place catheters at least 1-2 cm from the subarachnoid spaces and resection cavities and at least 0.5 cm from the ependymal space.[5,13]

Catheter Type

Initially, catheters used were ventricular-cardiac/peritoneal catheters.[4] More recently, catheters have been developed for this specific use and are being evaluated as part of clinical trials, but as no drug has yet obtained FDA approval for CED administration, no CED-specific catheter has also received FDA approval.[4] There are multiple catheter designs available, although the most ideal form has yet to be established.[3,15] The materials of the catheter should be rigid enough to avoid straying from the intended trajectory, but allow some flexibility to reach the targeted area.[4] The materials and size should also be designed to optimize flow and reduce infusate reflux. Reflux occurs when the pressure gradient between the tumor and catheter equalize, and the infusate backflows up the catheter or away from the targeted tissue.[3] Softer cannulas and catheters may mitigate backflow up the catheter by reducing the amount of trauma and cavity formation that occurs during catheter placement.[2,3,16] Improved flow with large cannula diameters with higher rates from the smaller catheter tips theoretically maximize drug infusion.[17] However, this must be balanced with the fact that high infusion rates promote reflux because pressure by the infusion process can overwhelm interstitial pressure.[18] Different types of catheters include rounded tip catheters, step-down cannulas with a smaller tip than the rest of the catheter to reduce reflux, and recessed-step cannulas which have a step-down cannula with outer reinforcement, all designed to decrease tissue pressure and reduce reflux.[3,15,17] Hollow-tipped cannulas with multiple nano-sized openings have been tested in rat models to allow for higher distribution of infusate than a single opening.[19] Catheters with a succession of openings along the catheter length have been found to be ineffective, as most of the infusate ends up delivered via the proximal tip.[20] Flexible catheters are an option to consider for longer infusions in mobile patients, and potentially for repeat treatments.[3]

Additional catheters in development and early investigation include porous membrane catheters, valve tip catheters, and the Cleveland Multiport Catheter (CMC), consisting of a central catheter shaft that houses four independent infusion microcatheters released after insertion.[21–24]

Catheter Placement

As mentioned above, the infusate will travel more efficiently along white matter tracts, could be shunted away from the desired area of infusion due to close contact with CSF spaces, or be limited due to gray matter, areas of scarring from prior surgery, or severely increased intracranial pressure.[13] Thus, optimal cannula placement is a key component to effective therapy, as inaccurate catheter placement will result in suboptimal drug delivery to the most at-risk areas of tissue for recurrence. A follow-up analysis of the only phase III trial of CED performed to date (PRECISE trial) revealed that less than 50% of patients had optimal cannula placement, which had a significant impact on progression-free survival (PFS).[6,25] This fact limited the evaluation of the effectiveness of the drug studied. Notable variables that affect catheter placement are training and experience of the neurosurgeons and software to guide placement. While all sites participated in the same amount of training in the PRECISE trial, neurosurgeons who had performed at least two catheter placements had greater accuracy.[25] Experience correlated with overall survival (OS), although the authors argued that the experience of the neurosurgeon might be less relevant than demonstrated and the difference observed might be due to a selection bias, with healthier patients being referred for clinical trials to busier academic brain tumor centers.[25] While intraoperative navigation systems are used routinely by neurosurgeons, software navigation tools are being actively developed to better predict optimal drug delivery.[25,26]

Optimal Drug Delivery

During drug development, a consideration includes ensuring the stability of the infused agent while it circulates through the tubing and catheter. A loss of potency from the entrance of the tubing and to the catheter tip must be eliminated or accounted for, to ensure the dosage administered at the tumor level is known. Another consideration is tracking delivery of the infusate into the tumor bed. Initial studies did not track the drug distribution, and the results of these studies were limited by possibly poor drug distribution[6] or delivery of drug to undesirable places such as the ventricles.[27] Initially, it was shown that the co-infusion of gadolinium-diethylene triamine pentaacetic acid (Gd-DTPA) with a large molecular tracer during CED of an immunotoxin as part of treatment for recurrent GBM, was able to accurately demonstrate the anatomic and volumetric distribution of large molecules used for antitumor therapy and provide additional imaging about leaks into

cerebrospinal fluid spaces and resection cavities.[28] This assumed that the diffusion of contrast correlated with the diffusion of the infusate and did not quantify the drug distribution.[28] Later, due to its small size and rapid reuptake by the extensive vascularization of the enhancing portion of the infused GBM, Gd-tracer was shown less effective in predicting percentage of tumor coverage when compared head to head with a larger PET tracer (^{124}I-albumin) in another immunotoxin trial from the same group.[26] Similar to catheter development, extensive work is being done in developing better technology to predict, image, and confirm the distribution of the agent infused by CED, with the goal of predicting treatment response.[26]

Prior Experience

Of parallel importance to the technique of CED is an effective therapeutic agent, and below is a summary of pivotal trials to date.

As previously mentioned, in 1994, Bobo et al introduced the idea of CED, which tested the theory in cats and reported its feasibility. They reported that fluid convection directly into the brain parenchyma, via a pressure gradient during interstitial infusion, can improve the distribution of molecules. This was proposed as a more ideal way of direct therapy to the tumor than diffusion, which was the method being tested at that time, and was limited by the need for large enough drug to create a concentration gradient, at the risk of toxicity, slower diffusion by larger molecules, and risk of losing smaller molecules via capillary leak.[2]

In 1997, a phase I study of a transferrin receptor-based diphtheria toxin (Tf-CRM-107) was tested in 15 patients with GBM and was deemed safe to pursue in a phase II multicenter trial for recurrent or progressive anaplastic astrocytoma (AA) or GBM.[29,30] The treatment was in essence a genetic mutant of diphtheria toxin. There were 21 with disease control (9 SD, 7 PR, and 5 CR) out of the 44 patients enrolled, and the most common side effects were malignant cerebral edema (8 patients) and new seizures (3 patients).[30]

In 2003, Kawakami introduced an interleukin-4-*Pseudomonas* exotoxin chimeric fusion protein (IL4-PE, NBI-3001, PRX321) for malignant glioma therapy. IL-4 receptors are overexpressed in glioma cell lines, and though the significance of this is unknown, Kawakami et al designed a receptor-targeted cytotoxic agent comprised of IL-4 and *Pseudomonas* exotoxin. In preclinical models, the toxin was found to be highly cytotoxic to IL-4 receptor-positive cancer cells.[31] Based on the preclinical study results, a phase I clinical trial was performed of delivery of the drug via CED in patients with recurrent malignant gliomas.[32] Nine patients were enrolled. There were no systemic toxicities. Seven patients developed cerebral edema and increased intracranial pressure, requiring craniotomy. Six of the nine patients had glioma necrosis on biopsy, of whom one remained disease-free for >18-month post-procedure. Based on this phase I study, the IL-4 cytotoxin was deemed relatively safe and without systemic toxicity and warranted further study.[32] A subsequent dose-escalation trial affirmed the drug's safety profile.[33] A phase II study for recurrent GBM was approved (CLARITY-1) but withdrawn due to lack of funding (NCT00797940). There are no currently active trials of this particular compound, however, there is a different fusion protein of IL-4 linked to a modified *Pseudomonas* exotoxin A (PE) and targets the IL-4 receptor (MDNA55) currently being studied and is described below.[8,34]

In 2005, Patel et al reported the results of Cotara, a chimeric monoclonal antibody specific for a universal intracellular antigen exposed in the necrotic core of malignant glioma.[7] Using barium-impregnated cardiac/peritoneal catheter and via stereotactic catheter placements, the drug was infused via CED over 1-2 days.[7] Fifty-one patients received the drug (37 recurrent GBM, 8 newly diagnosed GBM, and 6 with recurrent AA).[7] Adverse events in order of more to less frequent included cerebral edema, headache, convulsions, worsening of known seizure disorder, focal neurological deficits (hemiparesis, aphasia), generalized weakness and nausea.[7] Neurological symptoms improved within days to a week. When symptoms failed to improve, it was usually due to tumor progression.[7] Procedural-related adverse effects included headache, erythema/bleeding, extravasation, and phlebitis.[7] One patient died due to radiation-induced necrotic changes from the infused drug.[7] Systemic adverse events were mild.[7] They concluded that better distribution of the drug was associated with better outcomes, but longer infusions were not more beneficial (48 h vs 24 h).[7] They also concluded that infusion of the drug was feasible and tolerable.[7]

In 2007, Sampson et al reported phase I results of using TP-38, a recombinant chimeric protein that targets the epidermal growth factor receptor (EGFR) via CED.[35] EGFR is overexpressed in malignant gliomas, but is expressed in only low levels in normal brain tissue.[36,37] TP-38 contains a mutated form of the *Pseudomonas* exotoxin, where its native binding domain is replaced with transforming growth factor alpha in order to target the EGFR receptor.[35] Twenty patients were enrolled (17 GBM). All toxicities were neurologic and none systemic. Two patients had significant responses and were progression-free at 198 weeks and >211 weeks, respectively, after therapy, at the time of the manuscript.[35] The investigators did drug distribution imaging (via SPECT imaging of coinfused radiolabeled albumin), and ultimately the trial was stopped prematurely based on imaging studies that failed to show adequate delivery of the drug in a majority of cases due to catheter issues, in which some catheters leaked infusate into the subarachnoid or intraventricular spaces. Thus, no maximum tolerated dose was determined, and the efficacy and toxicity endpoints were likely limited by the low number of patients (3/16 imaged) with successful parenchymal infusions of the drug. Toxicity was thus attributed to infusion volume, recurrent tumor, or stereotactic catheter placement, not to the toxin itself. One theory for the inadequate drug delivery was the catheters used, ventricular catheters with perforations extending proximally from the catheter tip for 17 mm. It was hypothesized that the infusate left from the more proximal ports and into unintended areas of the brain with lower resistance.

In 2010, the results of the phase III study of IL13-PE38QQR (cintredekin besudotox [CB]) in recurrent GBM were reported; this was the first randomized phase III trial of a

drug administered via CED for recurrent GBM (PRECISE study).[6] Husain et al first presented the discovery of IL-13 receptor (IL-13R) as a potential target for therapy and the development of an IL-13R-directed cytotoxin in 2003.[38] The IL-13R is overexpressed in malignant glioma cell lines, but present in low levels in normal brain cells.[39] IL13-PE38QQR is a recombinant fusion protein composed of IL-13 and a mutated form of *Pseudomonas* exotoxin. In vitro study demonstrated the IL-13 cytotoxin to be selective for GBM cells and not normal brain cells.[38,40] When tested in vivo for efficacy, the drug was deemed effective to causing tumor necrosis with minimal inflammatory reaction or systemic toxicity.[38] It was most effective when administered intra-tumorally, as opposed to intravenously or subcutaneously.[38] Subsequent phase I/II studies in recurrent and newly diagnosed malignant gliomas deemed it safe with promising efficacy prompting a phase III trial.[9,38,40,41] Common toxicities were headache, sensory deficits, seizures, and focal neurological deficits, and the majority (77%) resolved.[41] Notably, optimal catheter positioning confirmed radiographically was a survival determinant.[41] The phase III PRECISE study compared a CED infusion of the study drug to Gliadel wafers (GW) in patients with recurrent GBM.[6] Two hundred and ninety-six adult patients with first recurrence of GBM across 52 neurosurgery sites in the United States, Canada, Europe, and Israel were randomized in a 2:1 ratio between March 2004 and December 2005 to receive either postoperative intraparenchymal CB or intraoperative GW placement. GW are a local treatment of biodegradable polymers impregnated with chemotherapy (carmustine) surgically implanted in the tumor bed which demonstrated improvements in survival and are currently FDA-approved for use in recurrent GBM.[42] This was the first phase III randomized controlled trial of an agent administered via CED with an active comparator in GBM patients.[6] This trial showed that CED of the studied toxin was equivalent to the FDA-approved treatment, GW.[6] Limitations included that tumors of the original specimens of enrolled patients were not evaluated for the presence of IL-13 receptors.[6] Variability of IL13 expression may have contributed to the negative results, as well as inaccurate catheter positioning in almost half of the patients and the fact that the delivery of drug was not measured, with later analysis revealing that inaccurate catheter placement likely ultimately affected the delivery of the drug to the tumor bed.[6] There were standard training sessions and mock cases of catheter planning, reviewed and approved by a central review committee. Moreover, a stereotactic frame or stereotactic frameless navigation system was used for catheter placement. Despite these attempts to optimize catheter placement, almost 50% of patients had suboptimal catheter positioning.[6] Adverse effects were similar between CB and GW, most commonly focal neurological deficits, cerebral edema, depressed mental state, and deep venous thrombosis. There was a higher incidence of pulmonary embolism in the CB group, thought attributed to a longer length of hospital stay.[6] There are a couple of notable points from the study. While the median survival times were similar between the two groups (45 weeks for CB patients, 40 weeks for GW patients), both groups had much greater survival times compared to prior historical controls (28 weeks for GW), an almost 40% improved survival compared with prior experience.[6] This emphasized the importance of comparing new therapies to an active control group, as the influence of other factors besides the studied therapy (surgical techniques, supportive management) would potentially influence the survival of the control group. Despite its limitations, this study provided lessons learned regarding technical considerations and encouraged further study of CED treatments if a more effective targeted therapy and technical advancements in the delivery were developed.

In 2011, Bruce et al evaluated CED of topotecan in a phase Ib study to determine the maximum tolerated dose.[43] Topoisomerase I levels are higher in glioma cells than in the normal brain. Topotecan is a topoisomerase I inhibitor that is cytotoxic to glioma cells, but nontoxic to normal brain. Sixteen patients were treated (10 GBM) with topotecan via CED without significant toxicities. There was minimal drug-associated toxicity, most common were seizures, headaches, fatigue, and worsening hemiparesis. The authors describe two patterns of responses, early responders and patients demonstrating radiographic regression following an original progression, which they described as pseudo-progression. Median PFS (mPFS) was 23 weeks and median OS (mOS) was 60 weeks. This study established a maximum tolerated dose for subsequent studies.

In 2018, Vogelbaum et al[24] published results of a pilot trial of the CED infusion of topotecan using the Cleveland Multiport Catheter (CMC), a central catheter shaft that housed 4 independent infusion microcatheters released after insertion. In the first pilot trial published, the investigators aimed to evaluate the delivery characteristics of the CMC in patients with high-grade glioma. Two catheters were placed, one into enhancing tumor and one into non-enhancing tumor, followed by deployment of the microcatheters. Topotecan and gadolinium-DTPA (Gd-DTPA) were infused intraoperatively and postoperatively for a total of 96 h with the same rate for all microcatheters and delivery was assessed by intermittent MRI. A total of three patients were enrolled. The authors reported that the volume of distribution was about 10-fold greater in non-enhancing infiltrative disease than in enhancing disease. Furthermore, no hemorrhages related to catheter placement or removal were observed and all three patients completed treatment per protocol. While the first patient survived an additional 93 weeks after infusion, the other patients died from continued tumor progression within 4 months. Trials examining higher flow rates are ongoing.

Most recently, Wang et al reported the feasibility and safety of CED of carboplatin in a phase I study.[44] Ten patients with recurrent WHO grade III or IV glioma were treated with escalating doses of CED carboplatin via catheters placed at the time of recurrent tumor resection. Carboplatin is a platinum drug with antitumor activity against gliomas; however, its systemic use in brain tumor patients has been limited by inability to penetrate an intact BBB in effective concentrations and systemic toxicities.[45] Animal studies demonstrating efficacy when carboplatin is administered via CED motivated this phase I trial.[46,47] After intraoperative confirmation of recurrence, 1-4 catheters were inserted stereotactically into the area surrounding the resection cavity, and infusion of carboplatin followed for

72 h.[44] Ten patients (9 GBM, 1 grade III oligodendroglioma) were enrolled. There was a single adverse event possibly related to study treatment (generalized tonic-clonic seizure), but it was in a patient with a partially controlled seizure history. Two patients experienced partial seizures within 4 weeks following surgery and infusion, but given their pre-surgical history of seizures, it was not clear the events were attributed directly to the treatment. Moreover, patients reported that the overall seizure frequency seemed reduced post-surgery and treatment. There were no systemic toxicities associated with carboplatin administration observed. mPFS was 2.1 months and mOS was 9.7 months, which compared favorably to trials using systemically administered carboplatin, where mOS was around 6 months.[48–50] Of note, there was a phase III study of AP 12009 (trabedersen), a phosphorothioate antisense oligodeoxynucleotide specific for the mRNA of human transforming growth factor beta 2 (TGF-β2), which is overexpressed in high-grade glioma. This was terminated earlier due to low enrollment and no conclusive endpoint analysis was performed (NCT00761280).

Ongoing Studies

There are multiple active and recruiting phase I and II CED studies available for adult patients with gliomas (Table 1). Some notable studies are highlighted below.

Chronic CED of Topotecan (NCT03154996)

In an earlier phase Ib study of CED with topotecan by Bruce et al, two patients became long-term survivors, one of whom received 4 days of treatment.[43,51] Based on preclinical trials demonstrating rats treated with longer infusions had an increase in median survival,[52] the authors are now investigating the safety of chronic CED infusions of topotecan via an implantable subcutaneous pump in humans via a phase Ib study. They have already demonstrated chronic infusions of topotecan up to 32 days via a subcutaneous implantable pump to be safe in animal models.[53] The explanation for why prolonged infusions may be more efficacious is that as a topoisomerase I inhibitor, topotecan acts during the S-phase of the cell cycle; thus, a greater duration of treatment ensures more cells will enter the S-phase and experience the cytotoxic effects of the drug.[51,54] The phase Ib study of chronic CED of topotecan via an implantable subcutaneous pump has recently concluded enrollment and results are currently being analyzed as of December 2020.[51] The study will evaluate the safety of this method of drug delivery in five patients with GBM. The study also used gadolinium as a co-infusate with the study drug, with hopes of validating gadolinium as a surrogate marker of drug infusion, and also will report their use of MRI-localized biopsies to evaluate treatment samples.[51]

D2C7 (NCT02303678)

D2C7-IT is a scFv Mab fragment immunotoxin with high binding affinity for both EGFRwt- and EGFRvIII-expressing GBM cells and coupled with a *Pseudomonas* exotoxin. Investigators at Duke University Medical Center have demonstrated that 100% (50/50) of EGFR-amplified GBM cases and 76% (39/51) of non-EGFR-amplified cases reacted with the D2C7 mAB.[55] The EGFR pathway is a major oncogenetic pathway of malignancy in GBM, and EGFRwt and EGFRvIII are two amplified and/or overexpressed molecules present in the majority of GBMs. In this study, patients will have their tumor pathology analyzed for expression of EGFRwt and EGFRvIII and reactivity to the D2C7-Mab. The investigators also address limitations of the PRECISE study by using Brainlab software to guide catheter placement, and co-infusing gadolinium with the drug to monitor delivery of the drug via MRI. The primary objective is determining

Table 1. Active CED Trials for Adult Patients With Glioma

Study	Trial Number	Phase	Status
D2C7 for recurrent malignant glioma	NCT02303678	1/2	Recruiting
D2C7-IT with atezolizumab for recurrent gliomas	NCT04160494	1	Recruiting
PVSRIPO for recurrent GBM	NCT01491893	2	Active
PVSRIPO and pembrolizumab in patients with recurrent glioblastoma (LUMINOS-101)	NCT04479241	2	Recruiting
MDNA55 in recurrent or progressive GBM	NCT02858895	2	Completed, awaiting results
EGFRvIII CART cells for recurrent GBM (INTERCEPT)	NCT03283631	1	Suspended, awaiting protocol amendment
^{186}Rhenium nanoliposomes (^{186}RNL) in recurrent glioma	NCT01906385	1/2	Recruiting
Topotecan via CED for recurrent grade III/IV glioma	NCT03927274	1	Recruiting
Recombinant bone morphogenetic protein 4 administered via CED in progressive or multiple recurrent GBM	NCT02869243	1	Active
Nanoliposomal irinotecan for recurrent high-grade glioma	NCT02022644	1	Active
Convection-enhanced delivery of OS2966 for patients with high-grade glioma undergoing a surgical resection	NCT04608812	1	Recruiting

Abbreviations: CAR T, chimeric antigen receptor T; CED, convection-enhanced delivery; GBM, glioblastoma.

the maximum tolerated dose, with secondary objectives of evaluating OS, and the association of EGFRwt and EGFRvIII expression and OS. The study will also explore quality of life and cognitive function, describe infusate distribution and estimate tumor coverage, assess association of tumor coverage and OS, and describe MRI changes visualized on imaging due to intratumoral inoculation of the drug, genetic predictors of response or failure of response to treatment with the drug. Preliminary results were presented and worsening neurological deficits were related to inflammation of the eloquent cortex near infused tumor.[56] The maximum tolerated dose was determined by phase I study, and enrollment is ongoing on a phase II dose expansion phase (NCT02303678). The team recently initiated enrollment on a phase I safety study of D2C7 administered via CED concomitantly with atezolizumab for patients with recurrent GBM. Atezolizumab is a programmed cell death ligand 1 (PD-L1) blocking antibody (NCT04160494). Checkpoint inhibitors such as atezolizumab block ligands expressed by tumor cells that activate pathways that suppress T cells.[57] Ligands include PD-1, PD-L1, and PD-L2, and therapies that involve blocking antibodies to these ligands have been efficacious and tolerable in other cancers such as melanoma.[58] The team also recently initiated enrollment on a phase I safety study of D2C7 and an anti-CD40, 2141-V11, both administered via CED in patients with recurrent high-grade glioma (NCT04547777). CD40 ligation activates antigen-presenting cells (APCs) and enables antigen processing and presentation to T cells.[59–61] Combining checkpoint inhibitors with immune therapy may allow for more effective immune response.

PVSRIPO (NCT01491893)

PVSRIPO is a live attenuated poliovirus 1 (Sabin) vaccine with its cognate internal ribosome entry site replaced with human rhinovirus type 2. The replaced ribosome entry site causes neuroincompetence[6–9] and ablated neurovirulence.[5] A phase I study of adult patients with recurrent WHO grade IV malignant glioma compared to a historical control group from the same institution who would have qualified had the PVSRIPO been available at that time.[5] From May 2012 to May 2017, 61 patients were treated. Most common adverse events were: headache, hemiparesis, seizure, dysphagia, and cognitive disturbance. Less common adverse events were: hemianopia, confusion, fatigue, nausea, and gait disturbance. Focal neurological deficits were attributed to inflammation of the infused tumor. There were no cases of encephalomyelitis, poliomyelitis, meningitis, or systemic autoimmune reactions. One patient who died of cerebral edema and seizure was later found to have progression on autopsy explaining these events. mOS appeared longer in the treatment group (12.5 months, 95% CI, 9.9-15.2) than historical controls (11.3 months, 95% CI, 9.8-12.5) and another comparison group, NovoTTF-100A treatment group (6.6 months), a device FDA-approved for recurrent GBM.[62] However, the main difference was the OS at 24 and 36 months, which reached a plateau at 21% for patients treated with PVSRIPO, while the OS of historical controls declined to 14% (95% CI, 8-21) and 4% (95% CI, 1-9), respectively. Notable points include that assessment of tumor progression vs pseudo-progression was difficult. Most patients demonstrated an increase in fluid-attenuated inversion recovery (FLAIR) signal abnormalities. On contrast imaging, all patients showed initial increase in lesion size associated with polycystic degradation ("soap bubble" appearance). These changes were attributed to inflammatory tissue responses (pseudo-progression) and were evident for several months before contraction of the tumor indicating treatment response. Peri-tumoral inflammation was managed initially with dexamethasone, but to not interfere with the potential mechanism of the immune therapy and avoid long-term side effects of steroids, a maximum of 4 mg/day was decided, and patients in need of symptomatic control beyond this dose of dexamethasone were prescribed bevacizumab 7.5 mg/kg administered intravenously every 3 weeks as long as necessary to control symptoms. Lastly, one patient suffered an intracranial hemorrhage due to removal of the catheter. Seven months after the infusion, the patient had recurrent tumor and lomustine chemotherapy was prescribed, to which the lesion regressed after one cycle of therapy, demonstrated as cystic degeneration on imaging. After 12 months of therapy, the patient had a complete response and remained disease-free for an additional 20 months and alive for more than 57.5 months after the PVSRIPO infusion. Subsequent to this patient, 11 patients out of 37 who were treated with chemotherapy after progression following PVSRIPO showed rapid decline in tumor volume, typically after the first cycle of chemotherapy. At the time of publication, 8 patients had a durable radiographic control, with 2 having had a complete response at more than 70.4 months and more than 15.1 months after the infusion.[5] There is currently an ongoing phase II study of PVSRIPO (NCT01491893) based on the safety results of the phase I study and a trial evaluating PVSRIPO in combination with pembrolizumab in patients with recurrent GBM (LUMINOS-101) recently started accruing patients (NCT04479241).

MDNA55 (NCT02858895)

MDNA55 is a fusion protein of IL-4 linked to modified PE and targets the IL-4 receptor.[34] The IL-4 receptor is overexpressed in GBM,[39] but not in the normal brain. It is also expressed by myeloid-derived suppressor cells and tumor-associated macrophages, which are key components of the tumor microenvironment.[63] Medicenna is a multicenter phase IIb study of MDNA55 administered via CED in patients with recurrent or progressive GBM. Patients who had de novo IDH-wildtype GBM at initial diagnosis and suffered a first or second relapse that were not treated with surgical resection were enrolled.[34,64,65] Their initial tumors were analyzed for IL-4 receptors. The drug was administered via CED over 24-48 h. Analysis of drug delivery was performed by co-infusion of Magnevist. Interim analysis after 40 patients revealed a mOS of 11.6 months. Patients with high IL-4R had improved survival (n = 21, mOS = 15 months) compared to those with low IL-4R expression (n = 15, mOS = 8.4 months).[8] Adverse events were similar to the phase I and II trials, the most common being cerebral edema and seizures.[64,65] The trial has since completed enrollment of 52 patients with recurrent GBM,

and final results are eagerly anticipated. A Late Breaking Abstract poster presentation of updated clinical data from the company's phase IIb recurrent GBM trial was presented at the 36th Annual EORTC-NCI-AACR ("ENA") Symposium on Molecular Targets and Cancer Therapeutics and reported a mOS of 11.9 months, which was comparable to earlier reported mOS of 11.6 months, and an OS at 24 months of 20%. Patients with high IL-4R expression and participants with low IL-4R expression that received a high dose of MDNA55 treatment had a mOS of 14.0 months (comparable to mOS of 15 months reported earlier) and an OS at 24 months of 20%. On October 15, 2020, the company announced having obtained support from the FDA for a landmark registration trial of MDNA55 allowing use of an external control in two-thirds of the control arm.

CAR T Cells Targeting EGFRvIII (NCT03283631)

Chimeric antigen receptor T (CAR T) cells are T cells with synthesized immune receptors that target tumor cells with specific surface antigens.[66] Patients undergo leukapheresis to collect their peripheral blood mononuclear cells, which are then modified to express the desired receptor.[66] Their effectiveness in melanoma,[67] leukemia,[68] and lymphoma,[68,69] and the ability to be modified to target different antigens has now grown interest in applying CAR T cell therapy to primary brain tumors. The therapy can be administered intravenously or via CED. Initial results of using CAR T cells targeting the IL-13 receptor via intracavitary administration have been promising.[70–72] IL-13 receptors are overexpressed in >50% of GBM and are a prognostic indicator of poor survival.[73–75] A patient with recurrent GBM and multifocal leptomeningeal disease and very poor prognosis survived 7.5 months after recurrence after intratumoral and intraventricular injections of the drug via Rickham reservoirs,[70] and the phase I study regarding this therapy continues (NCT02208362). A phase I study of CAR T cells targeting EGFRvIII administered via CED in patients with recurrent GBM (INTERCEPT) is currently undergoing protocol amendments and suspended for the time being (NCT03283631).

OS2966 (NCT04608812)

OS2966 is a humanized and de-immunized monoclonal antibody that targets CD29/β1 integrin, an adhesion receptor subunit, which is upregulated in GBM and plays a role in tumor progression, invasion, and drug resistance.[76] This phase 1 study will use the Cleveland Multiport Catheter, which has been in clinical use since December 2014.[24] The catheter is comprised of a central catheter shaft containing four independent lumen microcatheters.[77] All catheters are retracted within the central shaft until the stylet is removed, which causes the microcatheters to deploy radially.[77] Such a catheter is designed to mitigate issues with catheter blockage as the patency of each microcatheter is independent of each other, and to maximize coverage of the infusate.[77] As the catheter is MRI compatible, the study will also use a co-infusate tracer with the study drug and MRI to visualize the distribution of infusion and correct in real-time any leakage outside the target area or infusate reflux. The study will enroll patients with recurrent, supratentorial WHO grade III or IV gliomas with a maximum volume between 2 and 6 cm^3 where surgical resection is clinically indicated and the tumor is stereotactically accessible. The trial will be a single-center, ascending-dose, open-label, 2-part study to determine the safety and tolerability of the study drug and optimal infusion parameters. Part 1 of the study will involve a direct intratumoral infusion of OS2966 directly into the tumor bed by CED up to 4 h. Part 2 of the same will involve a surgical resection of the infused tumor within 1-10 days after part 1, immediately followed by the placement of 2 catheters directly into the surrounding non-enhancing parenchyma. A parenchymal infusion of OS2966 will take place perioperatively over 4 h. Prior to each infusion, a gadolinium contrast agent will be added to OS2966 to enable real-time image guidance during the infusion procedures. The study will employ a concentration-based dosing strategy as opposed to a dose-based strategy. This will result in variable doses is to ensure patients with variable tumor sizes will receive maximal tumor coverage of consistent tissue concentration. The objectives of the study are assessment of safety and tolerability of OS2966, and determination of the optimal biological dose of the study drug. Secondary objectives include efficacy, optimal CED infusion parameter, determination of systemic exposure. Exploratory objectives include characteristics of the pharmacologic effects of OS2966.

Practical Guide to Management

Once patients are selected for a CED trial, providers should be prepared regarding common side effects and approaches to management.

Headaches

Headaches are common. If the patient remains neurologically intact without other neurological complaints, this may be related to the volume of the drug being infused and can be treated with pain medications as needed or even holding the infusion to allow for the brain parenchyma to adjust to the new volume added. Headaches should subside with the cessation of the infusion. If headaches are severe or associated with a neurological deficit or depressed consciousness, this should prompt a noncontrast head CT to rule out cerebral edema, hemorrhage, or hydrocephalus.

Cerebral Edema

If patients have a focal neurological deficit or depressed consciousness, a noncontrast head CT scan should be obtained to rule out cerebral edema. While corticosteroids are a common treatment for intracranial edema and have been shown preclinically to improve CED efficiency when administered pre-infusion,[78,79] it is important for the clinician to have a good understanding of the drug administered via CED. For example, high doses of steroids should be avoided when an intratumoral immunotherapy is

administered, as it would suppress the immune response to a point where the treatment loses efficacy. The maximum dexamethasone dose recommended is 4 mg/day for direct intratumoral immunotherapy trials.[80] For refractory, life-threatening cases of cerebral edema unresponsive to steroids, osmotic agents can be considered. Again, in most cases, the cerebral edema will rapidly resolve with the cessation of the infusion. In the post-CED infusion setting, bevacizumab has been used safely at least 2 weeks after the completion of CED infusion of immunotherapeutic agents.[5] Bevacizumab is a humanized anti-vascular endothelial growth factor (VEGF) monoclonal antibody FDA-approved for the treatment of recurrent GBM that can decrease edema by normalization of the vasculature and decreased vascular permeability.[81,82]

Fever

An appropriate workup should occur should a patient have a fever, and antibiotics judiciously started only if clinical suspicion or support for an active infection is apparent. Fever can also be associated with a chemical meningitis, in which case supportive care is recommended. Given the hypercoagulable state of malignant glioma patients and the limited mobility during the infusion, venous thromboembolic workup should be completed in the event of unexplained fever.

Intracerebral Hemorrhage

The risk is low for intracerebral hemorrhage after catheter removal and placement and is often asymptomatic and can be managed conservatively with just observation. To limit the risks of intracerebral hemorrhage, some clinical trials of CED are now requiring for a platelet count of at least 125 000 prior to the insertion of the CED catheter.[5]

Seizures

Seizures are a common side effect of the treatment. They can be new-onset seizures or worsening of prior seizure history. One should evaluate for cerebral edema or intracerebral hemorrhage and treat accordingly, with the addition of standard anti-epileptic treatment. If patients have poor mental status out of proportion to imaging findings, prolonged electroencephalogram to rule out subclinical seizures would be appropriate.

Suboptimal catheter placement, reflux of the infusate, and poor distribution of drug can also heighten the risk of complications, and these are variables that are currently being addressed in the clinical trials.

Pseudo-progression

Lastly, an area of active discussion is how to evaluate for radiographic tumor response following the intracerebral administration of a therapy agent via CED. First, the infusion itself into the tumor has been shown to create areas of drug pooling, mostly into areas of extensive necrosis or cysts.[13] This is further complicated when immunotherapeutics are administered, as some patients have delayed responses and until the effect is shown, interval imaging may appear worse, but not be clinically significant (pseudo-progression). CED therapy has introduced a new challenge of how to evaluate imaging criteria as response vs pseudo-progression. Most often, repeat imaging in the near future helps clarify whether there is true progression or immune response and is recommended, at least within 3 months and as early as 4 weeks.[83] In the meanwhile, the neuro-oncology community is developing a response assessment in neuro-oncology tool for immunotherapeutics administered via CED. At the moment, if there are new lesions or a growth in lesion size on repeat imaging after immunotherapy and the patients are asymptomatic, progressive disease is not confirmed unless further progressive changes are identified on follow-up imaging.[83] On the other hand, if a patient has significant neurological decline not attributed to a medication change or event unrelated to CED treatment, then s/he is considered to have progression. Although 6 months is currently suggested, the common timeframe of pseudo-progressive imaging findings remains to be determined based on the peculiarities of each intratumoral therapeutic agent.[83] If it is still unclear whether the patient has progression, then biopsy would be the gold standard.[83]

Future Directions

CED is a modality that bypasses the BBB to administer targeted therapies directly into malignant glioma tissue and surrounding areas. Prior studies have demonstrated safety and promising efficacy, although there is much yet to learn and improve. Current technical challenges that are key components to CED success are determining the optimal type of catheter used to reduce infusate reflux, improving methods to achieve accurate catheter placement, and creating a means to confirm optimum drug delivery to the desired areas. Clinical challenges include the selection of the optimal patients who will most benefit and tolerate the treatment and management of symptomatic cerebral/peri-tumoral edema and other neurological complications during and after the process of the infusion. Until best management practices are elucidated, close communication between the clinical team managing the patient with acute symptoms and the team of investigators evaluating a new drug is essential to ensure that any updated knowledge of the investigational treatments is assimilated into the care of the patient in real-time. For instance, while steroids were suggested preclinically to help the distribution of chemotherapeutic agents infused by CED, they will abrogate the desired immune response generated by infused immunotherapeutics. Furthermore, the process of CED infusion itself, as well as the mechanism of action of the different agents infused, for example immunotherapeutics, further complicate the determination of whether clinical symptoms or radiographic changes are related to the desired immune response, pseudo-progression, or true progression. Scientific challenges include the optimal target, especially in light of the heterogeneity of the tumors.

Despite many unanswered details, much progress and lessons learned have certainly been made in the last two and half decades. Given the lack of survival improvement

in GBM patients with conventional therapies, one should be aware of the active ongoing work around the optimization of drug delivery via CED and understand how to best select, manage and assess patients treated via CED. The work described above mostly focused on the treatment of GBM patients via CED in the intraoperative and inpatient setting, via catheters connected to external pump. However, the expectation is that, as the technology improves, it may be possible to allow routine reinfusion via CED infusion catheter connected to an internalized pump. Such work is already ongoing (NCT03154996, NCT04264143). Furthermore, coupling CED therapy with systemic therapies to suppress the tumor microenvironment via checkpoint inhibitors (ie, anti-PD-L1 antibodies or others) may be a key to optimizing efficacy and is currently being studied.

Overall, CED therapy seems a safe and promising therapy for patients with glioma. Perfecting technique and discovery of the optimal therapeutic drug with current research may unlock the potential for more long-term survivors of this devastating disease.

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