Therapeutic Delivery to Central Nervous System

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KEYWORDS

• Glioblastoma • Clinical trials • Blood-brain barrier • Blood-brain-tumor barrier
• Convection-enhanced delivery

KEY POINTS

- The blood-brain barrier (BBB) and blood-tumor-barrier (BTB) present substantial barriers to delivery of therapeutic agents to the CNS.
- Intrinsic BBB mechanisms to passively or actively transport molecules severely restrict delivery of therapeutic agents.
- This hurdle is addressed by disrupting or bypassing the BBB to allow agents to enter central nervous system (CNS) tissue.
- Direct administration of agents to bypass the BBB include implantable controlled-release polymer systems, intracavitary drug delivery, direct injection of viral vectors, and convection-enhanced delivery (CED).
- CED uses direct pump-mediated continuous infusion into the tumor bed or tumor adjacent brain, circumventing the BBB. This approach has shown promising results with infusion of immunotoxins, chemotherapy, and viral vectors.

INTRODUCTION

In the United States, glioblastoma (GBM) has an incidence of 3.2 per 100,000 population.[1] Median overall survival (OS) for patients with newly diagnosed GBM is 12 months to 18 months,[2] with median progression-free survival (PFS) of only 6.9 months. Following recurrence, salvage treatment provides only 6 months to 8 months of additional survival.[3] The 3 major treatment modalities have not changed for over 3 decades.[2] Maximum safe resection with postoperative adjuvant radiation and chemotherapy via the Stupp protocol remains the standard of care.[4] The only new technology to have significantly changed outcomes is tumor treating fields. The addition of tumor treating fields to maintenance temozolomide in newly diagnosed GBM significantly increased PFS by 2.7 months and OS by 4.9 months.[5] There is no established standard for recurrent GBM.[6] Multiple therapeutic strategies have demonstrated minimal survival benefit but remission has yet to be achieved.[7]

CHALLENGES IN TREATING GLIOBLASTOMA

The effectiveness of therapeutics for GBM is limited due to the presence of blood-brain barrier (BBB) and blood-brain-tumor barrier (BTB) and cellular/genetic heterogeneity as well as an immunosuppressive tumor microenvironment.[8] Cellular pleomorphism associated with GBM provides a therapeutic challenge, even when drug delivery is achieved in target tissue. Four transcriptional profiles—classical (epidermal growth factor receptor [EGFR] drive), proneural (platelet-derived growth factor–driven), mesenchymal (neurofibromatosis type 1 driven), and neural—have been identified.

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Once administered, therapeutic agents can select for proliferation of resistant cell types.[8] This phenomenon has been shown with temozolomide treatment of GBM.[9]

Although complete resection of the enhancing component of GBM is associated with increased survival, microinvasive infiltrating tumor cells throughout the normal parenchyma prevent surgical treatment from being curative.[6,7,10] Deeply infiltrative cells around the tumor periphery already may represent a more resilient cell population that initiates and drive tumor recurrence.[9,11] GBMs also contain discrete populations of cancer stem cells that are highly resistant to therapy and can redevelop into a large mass after the primary tumor is resected.[8,9] Furthermore, the cellular, genetic, and epigenetic biology of GBM is complex, and a single genetic or epigenetic target has not yet been discovered that would make targeted therapeutics more likely to be effective.[7] This heterogeneity likely increases over time and is revealed in biopsies of recurrent disease.[9]

Treatment of the residual, nonenhancing disease also is made difficult due to the presence of the BBB, which limits the ability of systemically delivered to achieve therapeutic concentrations within the tumor infiltrated brain. This issue extends to treatment of unresectable enhancing tumor, because the BTB may be partially open (to administered contrast agents) but not necessarily to therapeutic drugs. The full physiology and significance of the BBB and BTB on the growth and treatment resistance of GBM are not completely understood but present a substantial barrier to be overcome in the development of CNS directed therapeutics.[9]

THE BLOOD-BRAIN BARRIER

The restrictive function of the BBB remains one of the most significant challenges in treatment of GBM.[12] The BBB is formed by endothelial tight junctions, the basement membrane, and astrocyte foot processes, otherwise referred to as the neurovascular unit. Because the BBB relegates relatively unrestricted entry into the parenchyma to small (<400 Da) and lipophilic molecules, approximately 98% potential neurotherapeutics are unable to access the CNS.[8,10,13,14] To cross the BBB, lipid-mediated diffusion allows small molecules (with molecular weight <400 Da and <8 hydrogen bonds) to pass. Other endogenous transport systemics include carrier-mediated transport and receptor-mediated transport.[14] Membrane proteins act as transporters for small molecules, including ions, nutrients, and molecules for metabolism.[13] The BBB is not homogenous and there is variable permeability throughout the vasculature; there is more permeability in large vessels and less permeability due to tighter junctions in smaller ones. Permeability also changes over time, increasing with angiogenesis and with insults, such as ischemic injury.[15]

THE BLOOD-BRAIN-TUMOR BARRIER

The BTB forms after seeding of the parenchyma with tumor cells. The rapid expansion of colonizing cells quickly outgrows the existing blood supply, leading to tissue hypoxia. Up-regulated hypoxia-inducible factor 1 stimulates vascular endothelial growth factor (VEGF). VEGF causes breakdown of existing BBB cytoarchitecture as well as angiogenesis of structurally abnormal capillaries with increased permeability.[16–18] The combination of abnormal vasculature and tumor cells becomes the BTB.[18] Alteration in vascularization caused by growth of high-grade gliomas results in leakiness of the BTB, represented clinically by areas of contrast enhancement as well as surrounding vasogenic edema on magnetic resonance imaging (MRI).[16,17] These areas also lack typical structures of the BBB, including tight junctions.[18] Despite the disruption of the typical BBB architecture, the BTB continues to limit ingress of therapeutic molecules.[18] The BTB is heterogeneous, however, even within the same tumor, further complicating the therapeutic possibilities.[17]

STRATEGIES TO OVERCOME THE BLOOD-BRAIN BARRIER/BLOOD-BRAIN-TUMOR BARRIER

Strategies used to obtain adequate intratumoral drug concentrations may either take advantage of intrinsic BBB characteristics or disrupt or bypass the BBB to allow agents to pass through (**Table 1**). Passive targeting at sites of BBB disruption, active targeting via receptor-mediated transport, and immunotherapy take advantage of intrinsic properties of the BBB to deliver therapeutics. BBB disruption strategies include chemical—via osmotic agents or cytokines—and mechanical—via focused ultrasound (FUS) or laser interstitial thermal therapy (LITT). BBB bypass strategies include surgically implanted wafers, injections, and convection-enhanced delivery (CED).

Passive Targeting via Disrupted Blood-Brain Barrier at Glioblastoma Sites

GBM is associated with pathologic microvascular proliferation resulting in abnormal leaky tumor vessels, which disrupt the BBB at the tumor core and allow penetration of molecules up to 20 nm to

Table 1
Major categories of therapeutic strategies to overcome the blood-brain barrier and blood-brain-tumor barrier, along with specific examples

Passive BBB penetrating therapies	Traditional Chemotherapeutics (e.g. temozolomide)		[19–23]
Actively targeted BBB penetrating therapies	Receptor mediated transport	Transferrin	[24–27]
		Lipoprotein receptor related protein (LRP)	[29]
		Integrins	[30]
		D-glucose transporter (GLUT)	[31]
		Glial Fibrillary Acidic Protein (GFAP)	[32]
		Connexin 43	[32]
		Epidermal Growth Factor Receptor (EGFR)	[33–35]
		Interleukin 13 (IL-13)	[36]
		Fibroblast Growth Factor Inducible 14 (Fn14)	[37]
	Liposomes	Transferrin	[39–43,85]
		GFAP	[32,39]
		GLUT	[39,44]
Immunotherapy	Vaccines	DCVax-L	[2,46]
		EGFRvIII	[47–50]
	Chimeric Antigen Receptor (CAR) T-Cells	EGFR v III	[46]
		IL-23R alpha 2	[51,52]
Blood Brain Barrier Disruption	Osmotic - Mannitol		[9,12,52,54]
	Intra-Arterial		[54,55]
	Chemical, Bradykinin		[12]
	Ultrasound		[12,52,56,57]
	LITT		[58–60]
Directly Administered Therapeutics (implant or single injection)	Implantable Polymer Systems	Carmustine wafers (Gliadel)	[6,9,10,12,52,61]
	Direct Injection - Vectors	Toca511	[2,64]
		Parvovirus – ParvOnyx	[6,64]
		Adenovirus-HSVtk	[65]
		Adenovirus – DNX – 2401	[66]
		HSV – Mo32	[67]
		HSV – G207	[68]
Directly Administered Therapeutics (Convection Enhanced Delivery)	Immunotoxins	Transferrin – Diptheria	[6,12,69]
		Cintredekin Besudotox	[12,45,70–72]
		IL-4 conjugated to Pseudomonas exotoxin (PE38KDEL)	[12,69]
		TGF-alpha conjugated to Pseudomonas exotoxin (TP-38)	[12,69]
	Oligonucleotides	AP 12009	[12]
	Viral Vectors	Poliovirus (PVSRIPO)	[2,46,62–64,73–75]
	Chemotherapy	Paclitaxel	[12,69]
		Topotecan	[3,12,77]
		Temozolomide	[69,78]
	Nanoparticles	Magnetic Beads	[6]
		Liposomes	[79]

100 nm.[8] Passive targeting of molecules takes advantage of the at least partially disrupted BBB within the solid and enhancing portion of GBM; however, the infiltrating tumor cells in the periphery remain sequestered behind an intact BBB, largely impenetrable to systemic delivery of therapeutic agents.[7] This remains a challenge to traditional systemic chemotherapy regimens.[19–22]

A review of phase 0/window of opportunity clinical trials performing tissue-based assessments after systemic delivery of a drug showed that levels of drug accumulating in enhancing versus nonenhancing tumor tissue varied substantially with slower drug distribution in nonenhancing areas. Other studies, however, have shown similar drug levels within the tumor and the normal brain. Even when drug levels were found to accumulate in tissue, clinical activity of the drug often was lacking.[23]

Active Targeting via Receptor-Mediated Transport

Active nanotherapeutic targeting involves taking advantage of cell surface receptors preferentially expressed on GBM tumor cells. A specific targeting molecule and delivery system then must be designed. Several targets have been attempted in preclinical studies, including transferrin receptors,[24–28] lipoprotein receptor–related protein,[29] integrins,[30] D-glucose transporter (GLUT),[31] glial fibrillary acidic protein (GFAP),[32] connexin 43, EGFR,[33–35] interleukin (IL)-13,[36] and fibroblast growth factor–inducible 14 (Fn14),[37] with promising results.[8] Transferrin-conjugated nano-based drug delivery systems have been in human clinical trials without definitive results to this point.[8]

Macromolecule drug delivery systems, such as liposomes and polymers, increase efficacy, stability, and half-life of anticancer drugs while reducing toxicity to healthy tissues.[38] Liposomes can deliver small molecules with specificity to the nervous system by coupling to aptamers or monoclonal antibodies against transferrin receptors,[39–43] GFAP,[32,39] or GLUT4.[39,44] Liposomes have shown increased transport of both daunorubicin and doxorubicin to the brain.[39]

Biological Targeting of the Brain via Immunotherapy

One of the functions of the BBB is to help maintain the restricted immune environment of the CNS, and it has been well recognized that gliomas produce an immunosuppressive tumor microenvironment.[28] The immunosuppressive nature of the CNS and lack of a foundational mutations to target limit the efficacy of vaccines in GBM. Other considerations include the need for frequent steroid administration in this population, which can inactivate induced immune responses.[45] Nonetheless, a variety of types of systemic immunotherapeutics have been developed for GBM and rely on the ability of cellular and humoral elements of the immune system to effectively bypass or overcome restrictions imposed by the BBB.

Vaccines

Cancer vaccines aim to elicit T-cell responses with tumor cell killing properties. Vaccines investigated in GBM have either been peptide or dendritic cell vaccines. Peptide-targeted vaccines include the IMA950 peptide cocktail, a personalized peptide vaccination for recurrent GBM, and a peptide covering the IDH1R132H mutation in newly diagnosed grade III/IV tumors.[45] Dendritic cell therapy targets include the DCVax-L trial[2,46] and several ongoing clinical trials (NCT00323115 and NCT01280552).[46] Of particular note are the studies involving a dendritic vaccine targeting EGFRvIII, which progressed through phase I[47] and phase 2 in both newly diagnosed GBM[48] and recurrent[49] GBM with promising results but ultimately failed to increase survival in a phase 3 trial.[50]

Chimeric antigen receptor T cells

Chimeric antigen receptor (CAR) T cells are engineered to recognize tumor-associated antigens and bind to both antigens and activate T cells in a manner not dependent on MHC complexes.[10] CAR T-cell–based therapies have shown efficacy in murine glioma models. The patient's tumor sample is examined for tumor-specific antigens and a CAR is selected that is specific for that individual tumor. The lack of well-described and consistent tumor antigens in GBM has limited this technology. Three antigens have been targeted with clinical results—EGFRvIII, IL13Rα2, and HER2. EGFRvIII CARs showed improved survival in a preclinical mouse model. These are undergoing further investigation in a phase 2 trial (NCT01454596).[46] IL13Rα2 CAR can kill GBM and stem cells. It has shown promising clinical activity in clinical studies.[46] HER2 is a tyrosine kinase whose up-regulation portends a poor prognosis in GBM. Early clinical data show some clinical activity of CAR in recurrent HER2-positive GBM. Other targets are under investigation.[46] A case report of CAR–T cells targeting IL13Rα2 in recurrent GBM showed complete regression of all intracranial and spinal tumors lasting 7.5 months.[51] A phase I clinical trial is currently under way (NCT02208362).[51]

Blood-Brain Barrier Disruption Strategies

Several substances and states open tight junctions, including neurotransmitters, hormones, and inflammatory mediators; physiologic states, such as hypertension, hypoxia, or ischemia; or hypertonic substances, including mannitol,

bradykinin, and angiotensin peptides.[12] This disruption increases spaces in between the tight junctions, thereby increasing drug permeability.[52] In GBM, the mostly commonly used of these are mannitol and FUS.

Osmotic

Mannitol Disrupting the BBB first was attempted more than 30 years ago via using hyperosmotic therapy to improve delivery of chemotherapy to brain tumors.[53] Osmotic BBB disruption can be achieved by intra-arterial (IA) infusion of a hyperosmotic agent, usually mannitol. Rapid diffusion of water out of cells causes shrinking of endothelial cells with opening of tight junctions for several hours. Subsequent administration of IA chemotherapy can increase concentrations of chemotherapeutic agents in the parenchyma up to 90-fold in animal models. Methotrexate delivery is increased 4-7-fold by addition of IA osmotic BBB disruption.[12] Retrospective studies demonstrated survival benefits with intraarterial mannitol infusion.[52] IA delivery of bevacizumab after BBB disruption with IA mannitol for recurrent GBM showed encouraging results in PFS (10 months), and all patients had radiographic response within 1 month with 8 showing decrease in tumor and 6 showing stable tumor.[54] This method remains limited, however, by toxicity and complexity of IA administration[52] and has not shown definitive efficacy in clinical trials.[9,55]

Bradykinin Mediators of the inflammatory response also disrupt tight junctions in vasculature. A bradykinin agonist RMP-7 selectively disrupts the BBB in regions of the BTB compared with nontumor BBB. Unfortunately, this agent has been associated with high levels of toxicity and further clinical development has been abandoned.[12]

Ultrasound

MRI-guided FUS (MRgFUS) disrupts BBB through targeted ultrasound beams that use thermal and mechanical stress to disrupt endothelial cells. The addition of microbubbles that expand and contract with ultrasound beams can transiently open the BBB.[52] MRgFUS causes focal openings that reverse within 23 hours.[12]

FUS has the potential to generate cytotoxicity within tumor tissue, enhance delivery of therapeutic agents, and improve extracellular distribution as well as stimulate an immune response in the tumor microenvironment, minimizing toxicity to normal tissue.[56] Multiple phase I clinical trials for GBM are under way.[9] In rat models, a combination of microbubbles and FUS-enhanced brain penetration of carmustine (BCNU).[52]

Currently, this technology requires a bone window in the skull, but recent advances in MRgFUS systems allow precise, temporally and spatially controllable, and safe externally delivered transcranial ultrasound energy, which is effective at disrupting the BBB as demonstrated by enhancement in white matter after gadolinium administration.[57] Technological advances like phased-array transducers and real-time temperature monitoring thus have made FUS more practical in treatment of glioma.[56] The actual impact of MRgFUS-induced BBB disruption on the ability of therapeutics to achieve adequate concentrations in brain or brain tumor tissue remains an area of active investigation.

Laser interstitial thermal therapy

Data from mouse models and patients who underwent laser ablation for GBM indicate that thermal therapy transiently increases BBB/BTB permeability from with a peak estimated at 1 week to 2 weeks post-treatment and lasting 4 weeks to 6 weeks.[58–60] In mouse modules, molecules up to 150 kDa are able to enter the CNS after LITT and infiltrate into a surround penumbra around the treated area and LITT in combination with doxorubicin was associated with increased survival.[58,60] A clinical trial investigating the combination of LITT and doxorubicin in adult populations recently has been completed (NCT01851733).[58]

Directly Administered Therapeutics

Another solution for this therapeutic delivery problem posed by the BBB is direct delivery of therapeutics into the tumor or post–resection cavity via bypassing the normal barrier. Multiple attempts at administration have been focused on implantable controlled-release polymer systems, various catheter devices for intracavitary drug delivery, direct injection of viral vectors, and CED.[6,12]

Implantable polymer systems

Implanted polymers aim to provide continuous drug delivery using a wafer with a controlled, sustained release rate.[12] Biodegradable polyanhydride wafers loaded with carmustine (Gliadel, Arbor Pharmaceuticals, Atlanta, Georgia) increase survival by 8 weeks when placed at recurrence and 2.3 months during primary resection.[10,61] The FDA approved carmustine wafers for use in recurrent high-grade glioma in 1996 and primary high-grade glioma in 2004.[8]

Phase 3 clinical trials have shown significant survival benefits with carmustine wafer placement intraoperatively but widespread use continues to be limited by toxicity concerns, wafer dislodgement, obstructive hydrocephalus, cyst formation,

high infection rates, wound healing concerns, costs, and practical implications that carmustine wafer placement restricts patients from recruitment into clinical trials.[6,9,12,52]

Intraventricular/intracavitary catheters

Intraventricular or intracavitary approaches have been used to deliver bolus or infusion of chemotherapy directly into the ventricles or a tumor cyst or cavity. Agents, such as nitrosourea and methotrexate, have been tried. Concerns remain about infection, catheter obstruction, and inadequate drug distribution.[12] Intraventricular injection has limited use for parenchymal brain tumors because there is limited flow between the cerebrospinal fluid space and the intracellular space of the brain.[2] This strategy remains useful in some situations for treatment of leptomeningeal disease.

Direct injection

Viral therapy can be divided into 2 groups—replication-competent oncolytic viruses and replication-deficient viral vectors used as a delivery mechanism for therapeutic genes.[62] Oncolytic viruses transduce neoplastic cells and selectively replicates and induces systemic antitumor immunity.[63]

Toca 511 Toca 511 is a retroviral replication competent vector encoding the cytosine deaminase that converts the antifungal drug 5-fluorocytosine into the antineoplastic drug 5-fluorouracil. Phase I and preclinical studies indicated that this agent produced both antineoplastic activity and immune activation.[2] In a phase I trial (NCT01470794) of Toca 511 injected into the resection cavity of patients with recurrent high-grade gliomas followed by cycles of oral 5-fluorocytosine, median OS was 14.4 months. Five patients demonstrated complete response and were alive 33.9 months to 52.2 months after Toca 511 administration.[64] A randomized phase 2/3 trial versus standard of care (NCT02414165) used direct injection of retrovirus into the surgical resection cavity after bulk tumor removal to transduce the gene cytosine deaminase into infiltrating tumor cells.[2] This trial failed to meet its efficacy endpoint and further development was halted by the sponsor.

Oncolytic H-1 parvovirus (ParvOryx) In a phase I/IIa trial for recurrent GBM, an oncolytic parvovirus was administered via intratumoral or intravenous injection prior to resection and then again around the resection cavity after resection. Median OS was 15.5 months after oncolytic H-1 parvovirus whether it was administered IV or intratumoral.[64]

This technique also remains limited because intracerebral injection localizes delivery to cells at the site of the injection but does not penetrate tumor cells deep in parenchyma. The host immune response also limits viral transfection therapy beyond a few local cells.[6]

Adenovirus Adenovirus with herpes simplex virus (HSV) tyrosine kinase (sitimagene ceradenovec) followed by intravenous ganciclovir in patients with newly diagnosed resectable GBM underwent a phase 3 trial (EudraCT number 2004–000464–28) increased median time to death or reintervention but did not change OS.[65]

A phase I study of DNX-2401 (NCT00805376), a tumor-selective, replication-competent oncolytic adenovirus, was performed in patients with recurrent malignant glioma. This was administered via intratumoral injection or implanted catheter. Some patients (20%) had survival greater than 3 years from treatment and 12% showed a 95% or greater reduction in enhancing tumor.[66]

Herpes simplex virus M032 is an oncolytic HSV that selectively replicates in tumor cells. It also can act as a viral vector for molecules, such as IL-12.[67] This is now in a phase I clinical trial (NCT02062827).

Another HSV derivative (G207) was used with intratumoral inoculation into recurrent malignant glioma and was found to have no significant safety concerns.[68]

Convection-enhanced delivery

Overview First proposed in 1994,[3] CED uses direct pump-mediated continuous infusion into the tumor bed or tumor adjacent brain, circumventing the BBB. This strategy uses pressure-driven bulk flow via a small pressure gradient from a pump that pushes solute through a catheter targeted within the CNS. Stereotactically placed catheters are implanted through a burr hole near the therapeutic target—that is, enhancing tumor tissue—and attached to an infusion pump that directs the therapeutic agent at a predetermined concentration, rate, and duration.[12]

By creating a pressure gradient, CED can produce superior drug distribution compared with diffusion-based methods and allows adjustments to pressure and flow parameters to optimize distribution to the tumor area.[2,15] CED limits the potential for neurotoxicity because drug concentrations at the location of the delivery device do not need to be as high as if delivered via diffusion, which produces a steep concentration gradient.[3] CED can infuse agents regardless of their molecular size over clinically relevant distances, bypass the BBB, provide targeted delivery via catheter

placement, and limit toxicity because distribution of drug drops off sharply in normal tissue.[15] This strategy avoids large boluses producing cerebral edema or intracranial pressure elevations.[12]

Multiple therapeutic agents have been investigated as potential CED infusates for glioma therapy, including immunotoxins, oligonucleotides, chemotherapy, and viral vectors.[3]

Immunotoxins Immunotoxins frequently have been investigated in conjunction with CED. Targeted immunotoxins are protein toxins produced by bacteria that are cytotoxic, which, coupled to carrier ligands used for cellular targeting, can become tumor selective complexes. They are more potent than traditional chemotherapeutic agents.

Transferrin–diphtheria conjugates Conjugated toxins include transferrin–diphtheria conjugates (TF-CRM107). Phase I and phase 2 studies show promising tumor response in patients with malignant brain tumors and no significant neurotoxicity.[12] A phase I trial showed 50% decrease in tumor volume on MRI in 9/15 patients. Phase 2 trials, however, showed only a 39% response.[6] A phase 3 clinical trial of CED delivery into unresectable tumors compared with best medical therapy for GBM was halted due to an intermediate futility analysis.[12,69]

Cintredekin besudotox IL-13, which targets IL-13R α2 receptors overexpressed on malignant glioma cells, has been conjugated to truncated Pseudomonas exotoxin (PE38QQR)—a cytotoxin, to create cintredekin besudotox (CB). Phase I and phase 2 studies in the recurrent GBM setting showed that optimal CED infusion was via multiple catheters placed peritumorally status post–gross total resection.[12] A subsequent phase I study in the newly diagnosed setting was performed in which following gross total resection, CB was infused via 2 to 4 intraparenchymal catheters for 96 hours, with subsequent radiation with or without temozolomide in 22 patients. This was well tolerated without significant toxicity.[12,70]

The first completed phase 3 trial that used CED as the delivery approach was the NeoPharm PRECISE trial. It randomized 296 patients with recurrent GBM treated with gross total resection of recurrent enhancement to treatment with CB via CED or carmustine chemotherapy wafers implanted at the time of surgery.[71] There was no significant difference between the 2 groups in median survival—36.4 weeks for CED and 35.3 weeks for wafers.[72] PFS, however, favored the CED group at 17.7 weeks versus 11.4 weeks. A high rate of catheter misplacement was noted in this study.[36]

Interleukin 4 conjugated to Pseudomonas exotoxin IL-4 conjugated to Pseudomonas exotoxin (PE38KDEL) has been infused intratumorally into recurrent high-grade gliomas over 4 days to 8 days via 1 to 3 catheters and resulted in tumor necrosis in 6 of 9 patients. Phase I/2 trails of this agent have suggested an increase in overall median survival compared with historical controls.[12] Another study with 25 GBM patients showed tumor necrosis in a majority of patients. A case study of recurrent GBM treated with NBI-3001 showed survival of 36 months.[69]

TP-38 Malignant brain tumors overexpress EGFR via amplification of EGFR gene on chromosome 7p. Two ligands of EGFR are epidermal growth factor and Transforming growth factor (TGF)-α and can be used to target cytotoxic agents to EGFR expressing glioma cells. TP-38 is a recombinant toxin of TGF-α and an engineered Pseudomonas exotoxin—PE-38. This combination demonstrated therapeutic efficacy in murine models of intracranial epidermoid carcinoma, increasing survival. A phase I/2 trial using CED of TP-38 showed an acceptable safety profile.[12] In a case study of recurring GBM, PFS lasted 43 months. In 20 patients with recurrent or progressive malignant brain tumors, however, a high rate of failed intraparenchymal distribution with leaks into the subarachnoid space or ventricles was seen.[69]

Oligonucleotides

AP 12009 Overexpression of TGF-β2 in malignant tumors facilitates tumor development and metastasis. It has been targeted with AP 12009—an antisense oligonucleotide that targets the mRNA encoding TGF-β2. An open-label dose-escalation study showed median survival data greater than historical standards.[12] No further development has ensued, to date.

Viral vectors

Poliovirus An oncolytic polio-rhinovirus chimera (PVSRIPO) was developed for intratumoral injection into recurrent GBM.[2] PVSRIPO was derived from the live attenuated Sabin poliovirus vaccine.[62] It is a replication-competent attenuated poliovirus with its internal ribosome entry site substituted for that of rhinovirus type 2, preventing propagation in neurons.[64] The insertion of regulatory sequences derived from human rhinovirus allows the virus to selectively replicate within and destroy cancer cells.[73]

Poliovirus targets the poliovirus receptor CD155.[2] Analysis of high-grade malignant tissue found CD155 expressed in all cells and is upregulated, making this tissue very susceptible to

the treatment.[73] In preclinical studies, PVSRIPO was shown to have cytotoxic effects on GBM cells in vitro.[46] Administration of PVSRIPO in mouse glioma models causes a rapid immune cell infiltrate at the site.[74]

A phase I clinical trial of intratumoral delivery of PVSRIPO in recurrent GBM via a surgically implanted catheter reported better survival rates at 24 months and 36 months compared with a historical control.[46,75] A phase I (NCT01491893) dose escalation trial used CED to infuse PVSRIPO into 61 recurrent supratentorial grade IV gliomas with median OS of 12.5 months.[64] Three patients had a sustained disease-free state 5 months to 12 months post-treatment.[63] Several limitations in the size and location of recurrent tumor were noted as well as development of significant cerebral edema.[2]

Combination therapy with PVSRIPO and lomustine showed a benefit in a subset of patients, leading to an ongoing randomized phase 2 trial of PVSRIPO alone or in combination with single-cycle lomustine in patients with recurrent GBM (NCT02986178).[2,64,76]

Chemotherapy A variety of conventional chemotherapies have been evaluated preclinically and in early-stage clinical trials; to date, none has gone on to full therapeutic development. Paclitaxel has been delivered by intratumoral CED in recurrent GBM with effective convection and a high antitumor radiographic response rate of 73% across 15 patients, although there were significant treatment-associated complications.[12,69] Topotecan in both free and liposomal-coated forms has been infused into rat models of GBM with improvement in survival and without significant neurotoxicity.[12] A phase Ib study of CED delivery of topotecan in patients with recurrent malignant gliomas found significant antitumor activity demonstrated by radiographic changes and prolonged OS with minimal associated toxicity.[77] Topotecan had favorable PFS and OS rates of 23 weeks and 60 weeks, respectively.[3] CED administration of temozolomide combined with whole-cell tumor immunizations in a mouse model of glioma significantly reduced tumor volume and increased T-cell intratumoral influx.[78] Translation to the clinical setting has been limited by the poor solubility of temozolomide in aqueous solution. A single 2015 study showed the bevacizumab administered via CED showed favorable survival compared intravenous bevacizumab in a highly selected patient population.[69]

Nanoparticles/liposomes Nanoparticles, such as magnetic beads measuring 15 nm to 80 nm, can be delivered with CED and loaded with bioactive molecules with high tissue clearance or reactivity rates.[3] Iron oxide nanoparticles delivered directly to the tumor bed in GBM patients have been stimulated by an alternating magnetic field, which causes production of heat. This was combined with fractionated stereotactic radiosurgery for synergistic cytotoxicity. This strategy demonstrated good outcomes but limited future care of the patient by making MRI unreliable due to artifact.[6]

Liposomes have been used to deliver nonreplicating adenoviruses containing the HSV–thymidine kinase (tk) gene into GBM with tumor reduction greater than 50% in 2/8 patients.[69] CED of HSV–tk failed to demonstrate survival benefits. A liposome encapsulated CED injection also did not show good benefit, because liposomes were retained at the site of injection, likely because they were large and positively charged.[79]

Practical considerations of convection-enhanced delivery The concept of CED was first introduced in 1994, but as of yet the limited number of agents to make it to phase 3 trials have not shown significant benefit. Areas for optimization of this strategy include technical considerations of catheter placement, catheter design, adequate distribution of agents, imaging of distribution, and timing of treatment.[9,52]

Catheter placement In the phase 3 PRECISE trial, position of nondedicated CED catheters (these were catheters that were designed to drain cerebrospinal fluid) was optimal in only 51% of patients, and drug distribution likely was adequate in less than 20% of patients. Optimal placement, defined somewhat arbitrarily based on limited clinical data, without imaging confirmation of distribution, was catheters placed 2.5 cm into the brain, at least 0.5 cm from the ependymal surface, and without pial or ventricular penetration.[61] Stereotactic implantation of catheters theoretically allows for precise targeting, but this also is affected by multiple clinical factors, including targeting accuracy, suitability of targets, locations of sulci, and other fluid spaces and (at the time of that study) inability to actively track catheter placement with image guidance. Clinically determined variables for catheter placement included intratumoral versus peritumoral locations, which can have an impact on the volume of drug distribution.[71,80]

Catheter design Catheter design considerations include materials, impact of design on placement procedure, and device dimensions. One issue with CED catheters is reflux—or the infusate moving back along the shaft of the cannula. Risk of reflux depends on fluid viscosity, flow rate, hydraulic resistance of tissue, the outer radius of the catheter,

and the tissue deformation by catheter and infusion.[71] For nondedicated CED catheters, studies have shown that rates greater than 0.5 μL/min to 1 μL/min resulted in reflux.[3,61] There was a need for specialized catheters that could provide higher rates of infusion (up to 50 μL/min) with low risk of reflux in order to cover targets tissues that are on the order of tens to hundreds of cubic centimeters. Catheter materials must achieve a balance between rigidity for targeting and flexibility for prolonged administration outside the operating room (OR). Cannula size is one of the most easily modifiable factors determining effectiveness of CED. In general, smaller-bore cannulas perform better than larger ones and provide reflux-resistant fluid flow at a greater rate.[71] Past work suggests that a 27-gauge catheter provides an outer diameter needed to prevent reflux of infusate along the cannula, but cannulas this small are hard to position and manipulate. One solution for achieving this goal was with the development of rigid step-down catheters.[15] A step design cannula, in which the outer diameter of the cannula is progressively reduced, in steps, prevents reflux in vivo and maximizes distribution of agents delivered in the brain.[81] This design feature, which has been used by 2 commercialized devices (SmartFlow [MRI Interventions, Irvine, CA] and Alcyone MEMS Cannula [Alcyone Lifesciences, Lowell, MA]), demonstrates reflux-resistant flow but is limited to use in the OR only (and for the SmartFlow device, in an intraoperative MRI only) due to the rigid design of the cannulas, which are not amenable to use outside of the OR environment. A third commercialized device (SmartFlow [Brainlab]) makes use of the step-down tip design coupled to a flexible proximal catheter and a bone anchor. Another catheter design approach, which has yet to be commercialized, demonstrated a greater volume of distribution with use of a porous membrane along the distal part of the catheter as opposed to a step-down approach.[82] The fourth device to be commercialized, the Cleveland Multiport Catheter (Infuseon Therapeutics, Cleveland, OH), is a flexible device that can be secured for use outside of the OR and deploys 4 independent delivery microcatheters to provide a reliable, high-volume delivery of therapeutic agents to the brain. A pilot trial, published in 2019, in 3 patients demonstrated adequate delivery from all catheters and no significant complications.[80]

Volume of distribution The efficacy of a drug delivered by CED depends on ability to achieve sufficient concentrations within the targeted region.[6] Successful infusion relies on the cannula being inserted in a location where the infused agents achieve a predetermined volume and shape within a given amount of time.[71] Key factors have been identified that affect the distribution of solutes delivered using CED, including infusion rate and volume, cannula size, the interstitial fluid pressure and tumor cytoarchitecture, and integrity of the BBB—a partially or fully opened BBB allows the infusate to diffuse out into the microcirculation, which acts as an infinite concentration sink.[12]

In CED, the bulk flow of interstitial fluid mediates drug distribution. Infusion rate and volume have an impact on this distribution. Because CED distributes infusate within interstitial space, the volume of distribution necessary varies depending on local conditions within the CNS, including edema, location, and white versus gray matter.[15] Because interstitial fluid pressure is higher in brain tumors (up to 50 mm Hg) compared with normal brain (1–2 mm Hg), this creates a pressure gradient, which moves infusate out of the tumor toward lower pressure in surrounding normal brain.[15] Affected tissue also tends to be heterogenous, limiting the homogenous distribution of infusate to all tumor tissue.[12] Additionally, in white matter regions, diffusion may follow existing white matter tracts, especially those already affected by edema.[3]

The concentration of a drug directly infused into brain parenchyma decreases logarithmically with each millimeter of distance from the CED catheter.[6] Also, because the drug undergoes positive pressure delivery to the area, drug residence time is short, decreasing the opportunity for water-soluble drugs to penetrate cell membranes or to interact with receptors.[15]

Monitoring Monitoring the distribution of an infusate delivered via CED remains an important consideration for determining whether an agent is likely to have reached its therapeutic target in the brain. Initial clinical work focused on indirect measures of distribution. Diffusion-weighted imaging on MRI showed early visualization of changes from CED infusions than traditional sequences.[79] Real-time visualization of the CED process in patients has been achieved with use of tracers that can be visualized with CT or MRI (eg, iodinated contrast agents or chelated gadolinium agents). This approach allows for real-time modification of the plan for reflux or otherwise suboptimal delivery.[12] These remain indirect methods, however, because they do not image the therapeutic agent itself. Direct imaging of the therapeutic agent has been achieved in limited situations, for example, in the development of a theragnostic drug for treating diffuse intrinsic pontine glioma.[83]

Long-term treatment A limitation of CED is that the currently commercialized catheters can be

implanted only temporarily. Versions with accessible ports for long-term infusion are being explored in animal models and to some extent with customized systems in clinical patients.[3,84] CED infusions have been studied for up to 32 days in pig models using a single proximal ventricular catheter and topotecan. Although inflammation adjacent to the catheter tract at the time of placement is limited to a 50-μm radius,[3] long-term infusion via catheter is limited by gliosis around the catheter tip.[6] Drug stability and pump design also remain challenges for long-term infusion.[84]

SUMMARY

Therapeutic strategies for GBM face several hurdles, and development of novel therapeutics and delivery strategies must occur simultaneously to overcome physiologic barriers, such as the BBB and BTB. Use of strategies to disrupt or bypass the native BBB are necessary to deliver adequate concentrations of therapeutic agents. The ideal methods and agents to accomplish this goal, however, are yet to be determined. Therapeutic delivery via drug-embedded biodegradable wafers should be viewed as a proof of principle that establishes that direct delivery to the brain can provide clinical benefit. Further development of methods to break down or bypass the BBB and BTB is necessary in order to have reliable platforms on which to determine whether new therapeutic agents are likely to have meaningful activity in patients with GBM.

CLINICS CARE POINTS

- The BBB presents a substantial barrier to be overcome in the development of therapeutic delivery to the CNS.
- Strategies to obtain adequate intratumor drug concentrations may either take advantage of intrinsic BBB mechanisms to allow molecules to pass through or be transported or disrupt or bypass the BBB to allow agents to enter CNS tissue.
- Multiple attempts at direct administration of agents to bypass the BBB include implantable controlled-release polymer systems, various approaches for intracavitary drug delivery, direct injection of viral vectors, and CED.
- CED uses direct pump-mediated continuous infusion into the tumor bed or tumor adjacent brain, circumventing the BBB. This approach has shown promising results with infusion of immunotoxins, chemotherapy, and viral vectors.

DISCLOSURE

Dr M.A. Vogelbaum: indirect equity and royalty interests in Infuseon Therapeutics, Inc. Honoraria from Celgene, Blue Earth Diagnostics, and Tocagen.

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