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TOPIC REVIEW

Current status of intratumoral therapy for glioblastoma

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Abstract With emerging drug delivery technologies becoming accessible, more options are expected to become available to patients with glioblastoma (GBM) in the near future. It is important for clinicians to be familiar with the underlying mechanisms and limitations of intratumoral drug delivery, and direction of recent research efforts. Tumor-adjacent brain is an extremely complex living matrix that creates challenges with normal tissue intertwining with tumor cells. For convection-enhanced delivery (CED), the role of tissue anisotropy for better predicting the biodistribution of the infusate has recently been studied. Computational predictive methods are now available to better plan CED therapy. Catheter design and placement—in addition to the agent being used—are critical components of any protocol. This paper overviews intratumoral therapies for GBM, highlighting key anatomic and physiologic perspectives, selected agents (especially immunotoxins), and some new developments such as the description of the glymphatic system.

Keywords Glioblastoma multiforme · Intratumoral therapy · Gliadel · Convection enhanced delivery

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Introduction

The idea of delivering drugs or larger therapeutic molecules directly into the brain or tumor bed—thereby circumventing the blood–brain barrier (BBB)—continues to be extremely attractive for neurosurgeons. While current therapy for newly-diagnosed glioblastoma (GBM) includes the maximum safe cytoreductive surgery followed by concurrent temozolomide and fractionated external beam radiotherapy, the median overall survival is only 14.6 months with a "progression-free" interval of only 6.9 months [1]. While there are many options for recurrent GBM [2], there currently is no established standard of care [3]. The highly invasive character of GBM cells confounds our ability to effectively eliminate them with surgical resection; subsequent radiation and chemotherapy entail considerable localized tissue damage and systemic toxicity. Successful delivery of therapeutic agents to residual GBM cells remains a very significant challenge, especially beyond areas of contrast enhancement, in relatively normal brain. Since Ehrlich described the BBB in 1885, it has been widely appreciated that drugs and other therapeutic macromolecules have extremely limited penetration into CNS when delivered systemically [4, 5].

Neurosurgeons and their colleagues have therefore explored multiple modes of intratumoral therapy for GBM, including instillation of chemotherapy, induction of an immunologic response, gene therapy, interstitial wafer chemotherapy, convection-enhanced delivery (CED) and (recently) nanoparticle administration, to name but a few (Fig. 1) [8, 13, 14]. Fortunately, as the bioengineering and neurosurgical communities advance the field of drug delivery, intratumoral therapy for GBM continues to evolve and is still promising. The purpose of this focused review is to provide the practicing neuro-oncologist and neurosurgeon with insights into intratumoral drug delivery for GBM,
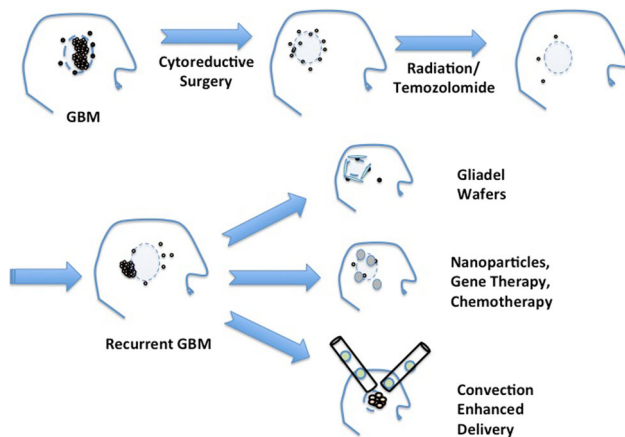
Fig. 1 GBM is treated with cytoreductive surgery when possible followed by chemotherapy and radiation therapy as the standard of care. When there is recurrent GBM, neurosurgeons have multiple modes of intratumoral therapy including: instillation of chemotherapy, nanoparticles, gene therapy, interstitial wafer chemotherapy, and convection-enhanced delivery

including anatomic and physiologic considerations, and recent therapeutic agents, highlighting immunotoxic therapy.

Anatomic and physiologic considerations

Successful therapy for GBM will likely be based on continued improvements in our understanding not only of the therapeutic agent, but also the nature of brain parenchyma adjacent to (and beyond) the resection cavity. Tumor-adjacent brain is not just a sponge or gel; rather, it is an extremely complex living matrix which includes neurons, glia, immune cells, cellular processes, blood vessels, fiber tracts, extracellular matrix, defined extracellular spaces, and the interstitial space. In patients, these components are not normal brain; they have been variably affected by radiation and chemotherapy, and the infiltrating malignant cells themselves. Molecules delivered into brain parenchyma are affected by all of these factors, which may vary from patient to patient. Drug binding, clearance, destruction, and/or uptake by non-neoplastic cells all have potential adverse effects on therapeutic efficacy and can increase toxicity.

Anatomically, brain parenchyma and tumor—adjacent brain are predominantly cellular, and the interstitial fluid "bathing" the cells plays a critical role in their homeostasis, and drug delivery. Therapeutic agents vary in their solubility and movement (such as diffusion) within interstitial fluid. The interstitial space of the brain—being both extracellular and extravascular—is separated from ventricular CSF by ependyma, and from the subarachnoid CSF by the *glia limitans* (a layer of interdigitating astrocytic processes with an overlying basement membrane). The perivascular (or

Virchow-Robin) space is an extension of the subarachnoid space. Use of an Ommaya reservoir effectively delivers drug to the intraventricular CSF, but not necessarily to the brain interstitial fluid [6]. It has been calculated that the concentration of a drug being directly infused into brain parenchyma decreases *logarithmically* with each millimeter of distance from the catheter used for CED [6]. It is because of such considerations in scale, that while in small animal models treatment efficacy is high, such results in do not translate into success when dealing with the large brains and ventricular anatomy of humans. In the mouse brain, the entire parenchyma is within 5 mm of the CSF surface. In the human brain, this distance reaches 50 mm, effectively precluding therapeutic drug distribution into brain parenchyma from the CSF space alone [6].

The lack of a lymphatic system for the brain has long puzzled some neuroscientists, who have wondered exactly how the brain clears extracellular proteins and toxic substances. Recently, it has been shown that CSF enters the parenchyma along subarachnoid "paravascular" spaces, mixes with interstitial fluid, and then is cleared along paravenous drainage pathways [6]. This circulation has been dubbed the "glymphatic system", is dependent on aquaporin-4 water channels, and is reportedly more active during sleep. While interstitial fluid movement undoubtedly affects drug movement, other variables also need to be studied in more detail clinically. The resistance of brain tissue is a major factor which reduces delivery to brain beyond the catheter tip [6]. Such resistance can also unintentionally direct flow along the catheter tract, although this problem has been minimized by modifications in catheter design [7]. If a substance is being infused into a tumor cavity, gliosis at the cavity wall creates an additional barrier to the brain interface. In addition, intratumoral pressure gradients siphon drug towards areas of less resistance such as the cisterns and interstitial spaces. These barriers for drug delivery, create challenges in effective drug distribution.

Gene therapy, interstitial wafers, and chemotherapy

The concept of directly delivering genetic material to modify tumor cell phenotype has been appealing to neuro-oncologists for decades. The transfer of genetic material into a patient's cell for therapeutic processes is the general definition for "gene therapy [7]." A broader definition includes transfer of genetic material to boost the immune system, enzyme prodrug therapy, oncoloytic therapy, transfer of tumor suppressor or anti-angiogenesis genes, or transfer of antisense oligonucleotides [7]. There are challenges with gene therapy which are inherent in the mode of drug delivery, and transduction efficiency. For instance, to

date, intracerebral injection allows localized delivery to a few tumor cells at the site of the injection, but does not penetrate to other tumor cells deep in (otherwise normal) parenchyma.

The genetic material is typically transfected through viral vectors that ideally transduce tumor cells while avoiding normal cells. The major limitation with the viral transfection is the host immune response which limits the viral spread to a few tumor cells. This limitation of viral transfection therapy must be addressed through new drug delivery methods that bypass the host's immune system.

Interstitial BCNU wafers provide an FDA-approved localized drug delivery method that neurosurgeons can employ when treating recurrent GBM. 1,3-*bis* (2-chloroethyl)-1-nitrosourea (BCNU) delivered into the tumor bed by biodegradable polymer wafers is thought to treat a 2 cm margin of brain surrounding the tumor cavity, where 90 % of GBMs recur [8]. Animal studies suggest that penetration of BCNU occurs mostly in the first 4 days with therapeutic concentrations of the drug, at 1 cm beyond the margins [9, 10]. Reported and potential complications of BCNU wafers include infection, impaired wound healing, CSF leak, tumor cyst formation, seizures, and cerebral edema [8]. The limited success of BCNU wafers could be related to the efficacy of BCNU itself on malignant tumor cells, as well as the concentration and depth of penetration into the parenchyma [8].

In addition to wafer implantation, there have been clinical trials of the direct infusion of other chemotherapeutic agents. It is important to appreciate that inadvertent injection of chemotherapy into an Ommaya reservoir (for instance) has been reported to be lethal [11]. Paclitaxel is an antineoplastic agent that promotes the assembly of microtubules into a metastable state which cells cannot disassemble [12]. On infusion of paclitaxel for recurrent grade III or IV gliomas, Lidar et al. demonstrated an overall median survival of 7.5 months. However, there were a significant number of treatment-related adverse events including transient neurological deterioration from cerebral edema (20 %), bacterial infections (15 %), and chemical meningitis (30 %) [13]. The lack of specificity and the chemical meningitis associated with paclitaxel in the CSF space made it an unattractive agent for GBM treatment. With all of these agents, apart from the challenges of drug delivery, there are additional challenges including the heterogeneous nature of GBM, and the ability of GBM cells to develop resistance, and otherwise elude therapy.

Convection-enhanced delivery

CED is a technique that propels therapeutic molecules via continuous infusion directly into the tumor bed or tumor–adjacent brain, thus circumventing the BBB. This is often accomplished through direct stereotactic intracerebral catheter placement, with a pump used as the continuous source of fluid carrying the therapeutic agent. The pump provides a constant microfluidic flow rate that is administered to promote the efficacy of fluid transfer to the brain parenchyma. In previous trials, the flow rate administered in patients is at 0.5 mL/h for 96 h [14]. The key limitation of higher flow rates of fluid is backflow. Backflow or reflux is described as the fluid discharge around the catheter shaft back out of the brain instead of into the parenchyma. Backflow-free catheter designs are being developed that has increased the flow rates to higher values that include: channel-inducing catheters and dual-action backflow-free catheters [15]. Pumps that provide a longer continuous lower flow rate are being utilized to prevent backflow such as the Alaris® pumps and Medtronic Synchromed-II pumps [16, 17]. These pump systems are implantable and provide continuous flow at flow rates at 5μL/min.

To date, immunotoxins have been most extensively tested in clinical trials utilizing CED (Table 1). The initial CED trials had demonstrated, through small phase I and II trials, a good safety profile and some limited efficacy in small cohorts. TF-CRM 107, a diphtheria toxin fused to Tranferrin-C, had some initial promise through a phase I trial demonstrating greater than 50 % decrease in tumor volume on MRI in 9 of 15 patients [18]. These results were not reproduced in the phase II trial with a 39 % response rate in 44 patients, therefore the phase III trial was aborted [19]. Around the same time, the PRECISE trial was initiated that compared the efficacy of citredekin besudotox with Gliadel chemotherapy wafers through a randomized trial. Eventhough the survival benefit was not significant (36.4 vs. 35.3 weeks), 68 % of the catheters were misplaced and the progression free survival was significant (17.7 vs. 11.4 weeks; p < 0.0008) [20]. The PRECISE trial highlighted the need to have improved computational modeling and image guidance in catheter placement, and there is a belief that the trial failed to demonstrate efficacy due to this misplacement of catheters.

The fluid carries, or advects, agents through the interstitial space by means of a small, constant pressure gradient [21, 22]. If CED is applied after resection of a brain tumor, the microinfusion catheters placed under stereotactic guidance target the peritumoral region with bulk flow, supplementing intrinsic diffusivity of either small or large therapeutic compounds to greatly enhance their distribution within the brain [21]. Since CED depends on fluid flow to carry the agent, it is possible to achieve a relatively constant concentration of drug spanning a predictable distance from the infusion site before the drop-off [23]. This provides superior localization to residual tumor cells, given accurate catheter placement [23, 24]. Another theoretical advantage relates to the BBB itself, which would be

Table 1 Comparison of CED clinical trials for immunotoxins

Agents	Description	Phase	Result	Toxicities	Limitations
TP-38 (Kunwar et al. [45])	Genetically modified Pseudomonas exotoxin fused with TGF-α and EGFR	Phase I	Overall survival 28 weeks; 33 weeks survival in subset of 20; 20.1 weeks survival in residual disease; 1 patient 260 week survival	5 patients with seizures (hx previous seizure disorders); Grade 3 or 4 toxicity in 2 patients	Assessed by SPECT for infusate and ineffective delivery in 81 % patients; Majority of catheters had leakage into CSF space and backflow
Cintredekin (IL-13/PE-38) (Kunwar et al. [20]; Vogelbaum et al. [46])	Pseudomonas exotoxin A fused to IL-13	Phase I (3 studies)	51 patients; Overall survival 45.9 weeks; 9 patients progression free survival for 1 year; 7 for 2 years	Grade 3 or 4 toxicities with 6 patients developing hemiparesis	
		Phase III	Randomized against Gliadel wafers; Median survival 36.4 weeks compared to 35.3 weeks for Gliadel		Inadequate drug distribution; Improper catheter placement
IL-4 and Pseudomonas (Rand et al. [47]; Weber et al. [48])	Pseudomonas exotoxin fused with IL-4	Phase I	Overall survival for recurrent GBM was 5.8 months compared to resection alone	No systemic toxicities; Cerebral edema, seizures, headaches	
		Phase II	Randomized open label trial; Intratumoral infusion of toxin then resection after end of infusion		Results of trial not published
TGF-β2 (AP12009) (Schlingensiepen et al. [49])	Antisense oligonucleotide that binds to TGF-β2 mRNA to inhibit translation	3 Phase I and II trials	Median overall survival 44 weeks for GBM; Median overall survival is 146.6 weeks for anaplastic astrocytomas	29 treatment related toxicities minor and limited to grade 2 or 3	Phase 3 was initiated but stopped due to lack of enrollment
Cotara (Patel et al. [50])	Antibody specific for histone H1-DNA complex labeled with ^{131}I	Phase I and Phase II trials	51 patients enrolled; Median survival in GBM is 37.9 weeks	18 patients with grade 3 or 4 neurotoxicity; 4 patients with grade 3 systemic toxicities	
TransMID-107 (TF-CRM 107) (Weaver and Laske [19]; Laske et al. [18])	Diphteria toxin fused to Transferrin-C	Phase I	Greater than 50 % decrease in tumor volume on MRI in 9 of 15 patients	Severe Neurologic or systemic toxicity	
		Phase II	44 patients; 39 % response rate	11 % cerebral edema side effect	Phase 3 trial not completed due to poor results

expected to conversely limit the *egress* of the therapeutic agent from the brain, enhancing effectiveness and limiting systemic exposure [23].

Given that the efficacy of any drug delivered by CED will be dependent on the ability to achieve sufficient concentrations within the targeted region, much attention has been placed on the factors that dictate optimal catheter placement [24, 25]. If catheters are inaccurately placed, leakage of infusate into the intraventricular spaces and subarachnoid space may result in poor drug delivery and distribution [25]. Currently, catheters do generate backflow in the tissue-free region along the outer surface of the catheter [25–28]. In addition, any large (i.e. millimeter sized) bubbles may redirect flow away from the catheter tip

Table 2 Approaches for GBM intratumoral therapy

Approach of therapy	Pros	Cons	Examples
Gene therapy	Viral Transfection that effects tumor cells and avoids normal cells Can boost immune system, enzyme prodrug therapy, oncolytic virus therapy, transfer tumor suppressor or anti-angiogenesis genes, transfer of antisense oligonucleotides Demonstrated safety in patients in clinical trials	Limited transduction efficacy Host immune response limits viral spread	Current phase II trial of Adenovirus-tk vector and valacyclovir with surgery and chemoradiotherapy Phase Ib trial of therapy has demonstrated 25 % survival of patients for 3 years-therapy is thought to produce protective immunity
Interstitial BCNU wafers	FDA approved therapy of placing BCNU wafers into tumor bed during resection of recurrent GBM Only FDA approved therapy for recurrent GBM Localized drug delivery into tumor site Good safety profile	Limited drug delivery of BCNU CSF leaks Wound healing issues Tumor cyst formation Cerebral edema Limited depth of penetration of drug	Gliadel wafers is FDA approved for neurosurgeons to place in recurrent GBM in the tumor cavity
Intratumoral chemotherapy injection	Paclitaxel efficacy with median survival of 7.5 months in recurrent grade III or IV gliomas	Severe treatment related adverse events Transient neurological deterioration from edema, bacterial infections, and chemical meningitis Resistance of GBM cells to certain chemotherapeutic agents If injected to Ommaya can be lethal therapy	Trials have demonstrated a severe toxicity profile for this mode of therapy in patients
Convection enhanced delivery	Demonstrates good penetration of therapeutic agents to areas of tumor Clinical trials have demonstrated efficacy when catheters are well placed in progression free survival Demonstrates a good safety profile in patients Patients can receive repeated therapies without recurrent craniotomies	Backflow of therapeutics from catheter is an engineering challenge Trials have not demonstrated survival benefit, however trials demonstrated misplaced catheters Requires rigorous computational models for catheter placement	PRECISE trial demonstrated a progression free survival of 17.7 versus 11.4 weeks when compared to Gliadel wafers; however overall survival was not significantly different Convection enhanced delivery with immunotoxins has been the most extensively studied mode of therapy for GBM through clinical trials
Nanoparticle delivery	Iron-oxide nanoparticles with stereotactic radiosurgery in trial to induce heat and synergistically induce cytotoxicity for GBM Median survival 13.4 months No systemic side effects	Single arm clinical trials, preliminary data on safety Indefinite exclusion of subsequent MR imaging; need to removal metal within 40 cm of treatment area Worsened hemiparesis in 4 patients after therapy Not specific in therapy	One clinical trial in Germany in 66 patients with recurrent GBM demonstrated overall survival of 13.4 months when used with SRS, but no control in the study Requires more clinical trials and randomized studies to assess efficacy

in unpredictable ways. Thus, optimization of devices and of various protocols constitute an extremely important part of improving the efficacy of CED [29–32].

Future CED efforts will benefit from the expanded use of reliable computer modeling, and real-time monitoring of catheter placement and the infusion process [33, 34]. Failures in early clinical trials involving CED may have been due (at least in part) to an incomplete understanding of tissue physiology (e.g. inhomogeneities in fluid pathways of the brain). It is very encouraging that the role of

tissue anisotropy for better predicting the drug biodistribution by CED has recently been studied, both experimentally and with computer models [35–38]. Advances in experimental techniques are currently aimed at achieving a better understating of the biomechanical interactions between convective drug transport, and the complexities of the brain parenchyma [39, 40]. Vigorous use of interventional MR, with software enabling rapid imaging of catheter placement, will greatly aid future studies of CED.

Intratumoral delivery of nanoparticles

Biocompatible iron-oxide nanoparticles have recently been directly delivered to the tumor bed in GBM patients, then stimulated by an alternating magnetic field to induce heat. The heat produced by the magnetic nanoparticles, in addition to 5 fractions of stereotactic radiotherapy of 5×2 Gy per week, was thought to induce a synergistic cytotoxicity [41]. A single arm clinical trial in 2 centers in Germany investigated this therapy in 66 patients (59 recurrent GBM patients). The median overall survival was 13.4 months, while the median overall survival from diagnosis of primary tumor was 23.2 months. The tumor volume at entry correlated significantly with survival. There were no systemic side effects of therapy, such as iron toxicity. 4 patients exhibited worsening of hemiparesis following nanoparticle instillation but did have a degree of weakness before the procedure [41]. The major limitations of this study in recurrent GBM patients were two-fold: the indefinite exclusion of subsequent MR imaging due to artifact from the iron oxide, and the need for removal of all metal from within 40 cm of treatment area, including all dental work.

Conclusions

Despite progress on multiple fronts, including the identification of favorable prognostic markers such as IDH mutations, the outlook for most patients with GBM remains dismal [2]. This review provides background for neurosurgeons and neuro-oncologists seeking information on intratumoral therapy (such as CED) for their GBM patients (Table 2). BCNU wafers remain an FDA-approved therapeutic option. Gene therapy, and intratumoral chemotherapy have been tried, while CED of immunotoxins has been studied more extensively. CED remains a promising technique for administering anti-cancer agents in the context of experimental trials for GBM patients. Notably, advances have been made in understanding the basic neurophysiology of the brain parenchyma, e.g. clarifying the nature of the circulation of interstitial fluid.

Advances in bioengineering have included using tissue anisotropy for improved prediction of drug biodistribution, understanding the complexities of convective drug transport, and improving techniques for catheter placement.

A critical task that needs to be achieved clinically in order to allow for successful treatment of GBM patients with CED is to be able to distribute the therapeutic agent over large areas of the brain in a predictable, sustainable, and controlled fashion. Recently, preliminary studies of magnetic drug targeting [42, 43] and ultrasound -assisted methods [44] have been reported. Such techniques may soon be able to generate the additional guidance needed to steer agents placed within the tumor bed to desired target locations deep within the brain parenchyma, beyond the reach of even the most deftly-guided intravascular microcatheters, for extended time periods. The possibly of intratumoral therapy for GBM patients, while challenging, continues to offer an intriguing possibility for neurosurgeons.

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