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NOVEL TREATMENTS

New Methods for Direct Delivery of Chemotherapy for Treating Brain Tumors

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Despite advances in diagnostic imaging and drug discovery, primary malignant brain tumors remain fatal. Median survival for patients with the most severe forms is rarely past eight months. The severity of the disease and the lack of substantial improvement in patient survival demand that new approaches be explored in drug delivery to brain tumors. Recently, local delivery of chemotherapy to brain tumors has provided a way to circumvent the blood-brain barrier, allowing delivery of chemotherapy drugs directly to malignant cells in the brain. Two methods of local delivery have been developed: polymeric-controlled release and convection-enhanced delivery. Controlled release utilizes degradable or non-degradable polymers as carriers of chemotherapy; polymer implants or microparticles are implanted locally to introduce a sustained source of drug for periods of days or months. Convection-enhanced delivery employs the bulk flow of drugs dissolved in fluid, which is introduced intracranially using a catheter and pump. The convective fluid flow is capable of delivering drugs great distances within the brain, potentially treating invasive cells at a distance from the catheter infusion site. These two new delivery strategies are capable of delivering both standard chemotherapeutic drugs and new methods of anti-cancer therapy. Taken individually, or used in tandem, they represent a potential revolution in brain cancer treatment.

INTRODUCTION

Each year, approximately 14,000 people are stricken with brain cancer. The disease occurs across both social and economic lines, with incidence rates peaking both in childhood and later in old age. Despite advances in imaging technology — which has led to earlier diagnosis of many tumors — the ability to treat the most aggressive form of brain cancer, glioblastoma multiforme (GBM)†, has not improved since 1980. The one-year survival rate for invasive central nervous system (CNS) cancer was 57.9 percent in 2002, and survival for GBM in particular is even lower [1].

Gliomas are primary CNS tumors arising from the glial cells. Malignant gliomas have a characteristic ability to infiltrate healthy brain tissue and form satellite tumors. This capacity for migration makes them exceedingly difficult to treat and invariably fatal. Even after resection, invasive cells can give rise to tumors within centimeters of the resection site [2]. Untreated malignant tumors can eventually spread to the contralat-

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†Abbreviations: GBM, glioblastoma multiforme; CNS, central nervous system; EVAc, polyethylene-co-vinyl acetate; BBB, blood-brain barrier; p(CPP-SA), polybis(p-carboxyphenoxy)propane-sebacic acid; BCNU, carmustine; 4-HC, 4-hydroperoxycyclophosph amide; PLA, polylactic acid; PGA, polyglycolic acid; PLGA, polylactic-co-glycolic acid; TM, temozolomide; PVA, polyvinyl alcohol; CED, convection-enhanced delivery; PEG, polyethylene glycol; AAVs, adeno-associated vectors.

eral hemisphere [3]. Many forms of systemic chemotherapy are excluded from the CNS by the blood-brain barrier (BBB) [4]. A few compounds — such as the class of antiproliferative drugs called nitrosoureas (including carmustine and lomustine) or other alkylating agents (temozolomide) — have some ability to cross the BBB and have been used clinically [5]. Unfortunately, systemic delivery of these agents appears to offer modest benefit as a supplement to radiotherapy [6,7].

Over the past two decades, a variety of approaches to enhance the activity of systemically delivered chemotherapy drugs have been tested. Hyperosmolar BBB disruption has been used to enhance BBB transfer of chemotherapy agents, with mixed results. One study, using PET imaging to evaluate a combination of methotrexate and hyperosmolar BBB disruption, indicated a negligible effect in brain tumors, which is echoed by the marginal findings in clinical trials [8,9]. A variety of approaches have been tested for enhancing BBB permeability of systemically administered drugs — by modification with hydrophobic side groups, conjugation to ligands with known BBB carriers, such as transferrin, or encapsulation in liposomes or nanoparticles — but none of these approaches have impacted clinical treatment of glioma [10].

The failure of conventional systemic drug delivery for glioma has motivated more direct approaches to drug delivery. Direct intracranial drug delivery would eliminate the need for a chemotherapeutic agent to cross the BBB. The ability to bypass the BBB would enable a wider range of agents — such as paclitaxel, doxorubicin, immunotoxins, and even gene therapy vectors — to be evaluated for brain cancer treatment. This review describes two of the most promising approaches for direct delivery of agents to intracranial tumors: polymeric-controlled release and convection-enhanced delivery.

POLYMERIC-CONTROLLED RELEASE

Polymeric-controlled release has long been used for drug delivery. Some early systems — the five-year subcutaneous Norplant® contraceptive and the conjuctival Ocusert® system for glaucoma — have proven the effectiveness of this approach for both systemic and local therapy [11]. The controlled release of drug also protects it from elimination [12].

Controlled release systems can be designed from both degradable and nondegradable polymers. When constructed from nondegradable polymers, drug release is usually governed by diffusion of the drug through the matrix. In contrast, release from degradable polymers is governed by a combination of drug diffusion through the polymer and erosion of the polymer matrix. Polymers can be combined into copolymers to tune degradation and release characteristics. Correctly designed, polymer and drug systems can provide reliable sustained release for periods of days or many years (see review in [12]).

Non-degradable Polymer Systems

Delivery systems constructed from nondegradable polymers can be employed when a removable system is required. The most common nondegradable polymer system is a copolymer of ethylene and vinyl acetate. Polyethylene-co-vinyl acetate (EVAc) materials exhibit excellent biocompatibility and are typically implanted chronically. EVAc have been developed for the controlled release of DNA, antibodies, as well as chemotherapeutics [13,14]. Two studies that examined the delivery of amsacrine and mitoxantrone in rat glioma models observed potent anti-tumor effects [15,16]. While the engineering of these systems is highly developed — so that delivery systems of virtually any size, shape, rate, and duration of release can be produced — the persistence of the polymer after delivery limits their clinical use.

Degradable Polymer Systems

Controlled release systems using biodegradable polymers are more common than non-degradable systems. The biodegradable systems offer the same advantages as the persistent wafers, but they completely erode during delivery and are cleared

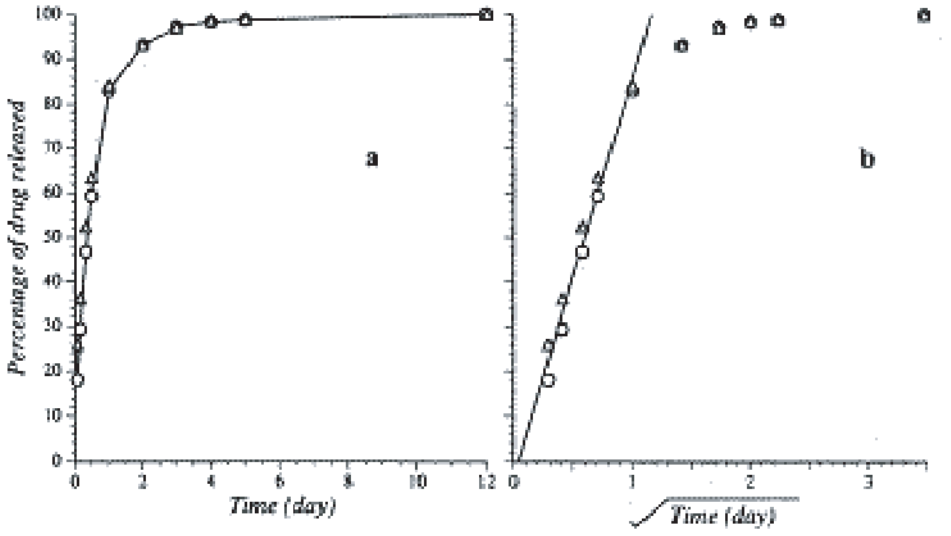

Figure 1: **The cumulative release of BCNU into a well-stirred reservoir as a function of time (a) and the square root of time (b).** The linear portion indicated in b is indicative of diffusion controlled release from a planar geometry. Reprinted with permission from Springer Science and Business Media: Fung, L. K. et al. Chemotherapeutic drugs released from polymers: distribution of 1,3-bis(2-chloroethyl)-1-nitrosourea in the rat brain. Figure 2. Pharmaceutical Research. 1996;13:671-82.

from the body. This disappearance attenuates the response to the implant and makes it clinically attractive. Most systems are diffusion regulated and the kinetics are well-characterized [17]. Many degradable systems are designed to erode via hydrolysis, taking advantage of the prevalence of water in the human body. For example, a variety of controlled release systems have been designed around the hydrolysable anhydride bond. Copolymers are typically coupled with anhydride bonds to control the rate of hydrolysis [12]. The addition of a copolymer affects the degradation of the polymer device. The correct copolymer system can achieve ordered erosion, which provides a consistent release of drug. The most common copolymer systems used intracranially is polybis(p-carboxyphenoxy)propane-sebacic acid (p(CPP-SA).

p(CPP-SA)-based delivery systems have been characterized for a variety of drugs and already are used clinically. Many controlled release systems are based on an implantable wafer, which has been studied with the drugs mitoxantrone, carmustine (BCNU), 4-hydroperoxycyclophosphamide (4-HC), paclitaxel, carboplatin, and adriamycin [18-21]. The characteristics of drug release from wafers depend on the polymer and drug used. A typical controlled release curve for BCNU is shown in Figure 1 [22]. The linear region in Figure 1b indicates that the drug release is diffusion controlled [12]. In drug-polymer systems with a high degree of surface associated drug, a burst release phase is observed. p(CPP-SA) wafers of BCNU and 4-HC have demonstrated release for 50 days. The release of paclitaxel proceeded at a much lower rate, less than 0.01 mg/day, and for a much longer period of time (160 days). The slower release rate can be attributed to the hydrophobicity of the drug that causes a strong affinity for the polymer. The controlled release of drugs from these wafers has demonstrated performance in many *in vitro* and *in vivo* glioma models. Studies have demonstrated improved performance of these wafers when compared to free drug administration in a rat model challenged with an intracranial 9L tumor [23]. Small cylindrical wafers have been studied in the same way [18].

The p(CPP-SA) wafer loaded with BCNU has undergone further characterization and is available clinically as Gliadel®

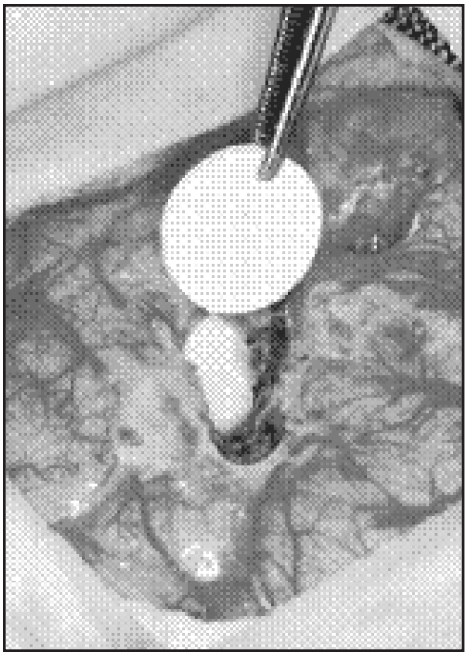

Figure 2: **Intracranial placement of Gliadel® wafer.** The wafer is implanted in the cavity left after surgical resection of the tumor. Wafers are dime-sized and impregnated with carmustine. Reprinted with permission from Fleming. Pharmacokinetics of the carmustine implant. Clinical Pharmacokinetics. 2002;4(6):403-419 (Figure 1, page 405).

[24]. The Gliadel® wafer is 14 mm in diameter and 1 mm thick. It is loaded with 7.7 mg of the drug carmustine and is implanted intracranially after surgical debulking of the tumor (Figure 2). Gliadel® has been studied for clinical use in initial treatment, treatment of recurrences, and in conjunction with radiotherapy for malignant gliomas [25-27]. In all cases, therapy with Gliadel® was well tolerated with no significant increase in toxicity, infection, or inflammation. The majority of studies indicated a modest improvement in survival for patients with malignant gliomas that received Gliadel® [28,29]. Further research is directed at improving the Gliadel® wafer by examining dosing and combination therapy [30].

Fatty acid dimer copolymers use the same polyanhydride linkages, but they offer a distinct advantage over carboxyphenoxy propane polymer systems. FAD-SA is typically formed into a disk shape and then implanted intracranially. The primary use of FAD-SA is the controlled delivery of the drug 4-hydroperoxycyclophosphamide (4HC) [31]. FAD-SA is used for delivery of this drug because 4-HC is hydrolytically unstable in the p(CPP-SA) wafer [32]. The ability to tailor the chemical and physical properties of the vehicle to the drug is one of the advantages of polymeric delivery.

Other degradable polymers are also useful for drug delivery. Biodegradable polymer matrices based on polymers of lactide and glycolide are perhaps the most popular platform for local drug delivery. Polylactic acid (PLA), polyglycolic acid (PGA), and their copolymer polylactic-co-glycolic acid (PLGA) have a long history of use as biomaterials, beginning in the 1970s with biodegradable sutures. Matrices made from these polymers are biocompatible, hydrophobic, and degrade to the naturally occurring monomers via ester hydrolysis. Polymer nanospheres, microspheres, and wafers of varying sizes are made via emulsion/solvent evaporation, salt leaching, and other methods [33]. When making spherical particles using the emulsion process, the solvent, surfactant, and polymer properties can be modified to tune size and release characteristics [34,35].

Implantable PLGA matrices loaded with chemotherapeutics are currently under development. The implants can be in the form of electrospun scaffolds, thin films, or even wafers. The process of electrospinning uses a voltage differential to produce a nonwoven mesh. Paclitaxel has been mixed with the polymer solution before electrospinning to create a mesh with drug-delivery capability [36]. The drug-loaded mesh has controlled release properties and was effective *in vitro* against C6 glioma cells. A mesh delivery system might have advantages over a wafer, because the mesh can potentially conform to the shape of the resection cavity. The C6 glioma line was also used to evaluate the controlled release of radioiododeoxyuridine from a thin film of PLGA [37]. Biodegradable PLGA wafers containing BCNU can be used in an analogous method to Gliadel®. The release profile of BCNU

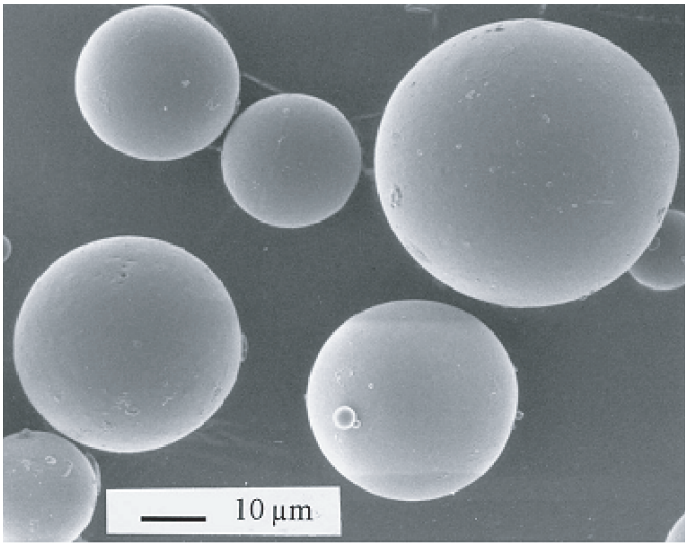

Figure 3: **SEM image of PLGA microparticles loaded with BCNU.** The particles were formed using the solvent extraction/evaporation method. Average sphere diameter is 30 µm. Reprinted with permission from Elsevier. Painbeni T, et al., Internal morphology of poly(D,L-lactide-co-glycolide) BCNU-loaded microspheres. Influence on drug stability. European Journal of Pharmaceutics and Biopharmaceutics. 1998;45:31-9.

from the PLGA wafer shows a similar profile and duration when compared to the p(CPP-SA) wafer [38]. A reformulated wafer made of compressed BCNU containing microparticles yielded a longer *in vitro* release profile, 70 days compared to seven [39].

PLGA nanoparticles and microparticles can be fabricated using the single emulsion method to encapsulate hydrophobic compounds and the double emulsion method to encapsulate hydrophilic compounds (Figure 3) [40,41]. The advantages of polymer particles lie in the route of administration. Polymer nanoparticles may be administered using a burr hold and catheter, which is significantly less invasive than the implantation of polymer wafers.

Polymeric-controlled release is able to administer drugs intracranially, which would be excluded for systemic use or as a new route of administration. This is the case with doxorubicin (adriamycin), which exhibits dose-limiting cardiotoxicity [42]. The drug temozolomide (TM) has demonstrated clinical efficacy when given systemically [5]. A controlled release form of TM using PLGA microparticles gave the characteristic biphasic release profile, burst release followed by a linear period, with a 35-day release period [43]. The TM microparticles demonstrated cytotoxicity in culture with C6 cells and could be administered intracranially as part of the same regimens currently evaluating systemic TM.

Polymeric-controlled release systems can be engineered for drugs, such as paclitaxel, that are difficult to administer with conventional methods. Two drug properties that can limit traditional use are hydrophobicity and toxicity. Paclitaxel is hydrophobic and sparingly soluble in water; this restricts its use in injection buffers. Intravenous chemotherapy with paclitaxel utilizes an adjuvant called Cremophor EL to disperse the drug, which can cause serious side effects. PLGA is naturally hydrophobic and encapsulates hydrophobic drugs efficiently. The hydrophobicity of a drug also affects its release profile. Paclitaxel preferentially partitions inside PLGA and exhibits a lengthy release curve. A study with PLGA microparticles showed a sustained release of paclitaxel for more than 60 days without a burst release period [44]. The controlled release of paclitaxel also limits the systemic toxicity. The release is so slow that a variety of coencapsulants have been evaluated to quicken the release of paclitaxel from PLGA matrices. Two examples are isopropyl myristate and vitamin E TPGS [45,46]. Both emulsifiers produced a burst release period. The formulation using vitamin E TPGS decreased the release time compared to particles made with the surfactant poly(vinyl alcohol) (PVA) [47].

Controlled release systems may be particularly useful for agents produced by biotechnology, such as the proteins and nucleic acids that are needed for immunotherapy or gene therapy. The rare instances of complete recovery from malignant gliomas typically have been attributed to an immune response. This observation triggered the search for compounds that could cause immune cell-mediated cytotoxicity. Type 1 interferons show antitiumor activity but have a short half-life and high dose toxicity [48]. The short half-life necessitates a continuous delivery for the molecule to be active, but the continuous delivery will pose the risk of side effects. Encapsulating these agents protects them from elimination and provides a means to control the amount released. Interleukin-18, which can be used in this manner, can be encapsulated in PLGA microspheres and is active upon release [49]. PLGA can also encapsulate and release viable adenovirus [50]. The controlled release approach improved *in vivo* efficacy.

Polymeric-controlled release provides a biocompatible, tunable platform in which drug loading, release rate, longevity, and form can be altered via polymer combination and processing. The method of delivery, as witnessed by Gliadel®, adds minimal complexity, requires no additional surgical procedures, and minimizes solubility limitations. Furthermore, the controlled release of the drug slows elimination and increases duration of exposure. This increases the amount of drug administered without exposing the tissue to high concentrations that could cause tissue damage. Most importantly, polymeric-controlled release has a clinical history of beneficial use.

While controlled release systems can deliver drugs for long periods of time locally in the brain, local penetration of the drug is frequently limited by diffusion [21]. When low diffusion coefficients are coupled with a high rate of elimination, drug distance from the delivery locus can be limited to millimeters [51]. The extracellular matrix (ECM) of the brain also imposes its own limits on diffusive transport. The ECM of the brain is a hydrated environment with a low volume fraction, a high degree of tortuosity, and small pore size [52-55]. The local environment of a tumor limits diffusion even further [56]. These factors conspire to confine a high drug concentration to within 3 mm of the delivery site [24]. This distance is exceeded by invasive glioma. Controlled release also is limited by size. The polymer delivery system must be large enough or be used in enough amount to deliver clinically relevant drug dosage.

CONVECTION-ENHANCED DELIVERY

Convection-enhanced delivery (CED) was developed to deliver compounds throughout the brain to overcome the diffusion barrier seen with polymeric-controlled release [57]. CED utilizes an applied external pressure gradient to induce fluid convection in the brain. Fluid is typically administered via a small catheter using a pump [58]. Because moderately high pressures (up to 70 mmHg) must be used to drive convective flows, such procedures are plagued by backflow along the catheter and often subject the tissue to high pressures. The increase in pressure is due to occlusions that may block the catheter from delivering an adequate flow rate. The use of microfabricated silicon probes reduces those concerns and improves on the general delivery method [59]. The outlet of the silicon probes is along an axis perpendicular to the insertion direction; this geometry prevents tissue from plugging the orifice. A controlled pressure source in stream with a fluid reservoir ensures operation at constant pressure. This prevents the pressure spikes that accompany constant volume delivery. An added advantage to constant pressure delivery is the ease with which fluid properties can be determined using simple mathematical models.

CED and Drug Delivery

The main benefit to administering drug via CED is the greater distribution volume. Studies that have compared a bolus injection to CED have noted a larger distribution and a greater efficacy [60, 61]. The benefits are derived from the greater distribution and a con-

Table 1: Therapeutic agents evaluated in clinical trials for glioma treatment.

TF-CRM107
cpIL-4-PE
IL13-PE38QQR
TGFα-PE38 (TP-38)
LIPO-HSV-1-tk
Paclitaxel
Cotara®

Adapted from [62].

tinued exposure due to the long infusion time. The technique is inherently flexible and can be used in chemotherapy, gene therapy, and immune therapy. Methods of drug delivery using free drug have been studied in animals and clinically. The drugs administered run the gamut from nontraditional compounds to typical chemotheraputic drugs. Typical clinical use of CED is for salvage therapy after a recurrence of glioma and follows one of two protocols. Patients are either given local infusions after surgical resection or given infusions directly into the tumor. Drugs used clinically include both targeted toxins and traditional chemotherapeutics (Table 1). Studies using the drug paclitaxel have observed the highest response rates, which are around 75 percent. Typical response rates for targeted toxin treatment were lower [62]. Response rate and the occurrence of adverse events have been observed to be dose dependent [63]. Ongoing clinical trials include the CED of IL13-PE38QQ, and the CED of topotecan.

The drugs listed in Table 1 reflect only a small sample of the therapeutic agents that have been evaluated in animal models — which include the traditional chemotherapy drugs BCNU and topotecan [64,65]. However, the drugs available for delivery via CED are still limited by solubility. A way to avoid solubility issues and protect antineoplastic agents from elimination is to encapsulate them. Recent research studied nanoliposomal encapsulated CPT-11 in a rat glioma model [66]. The study showed that CPT-11 benefited from the increased distribution via CED and a longer residence time.

Large particles, with severely restricted diffusion, stand to benefit most from CED.

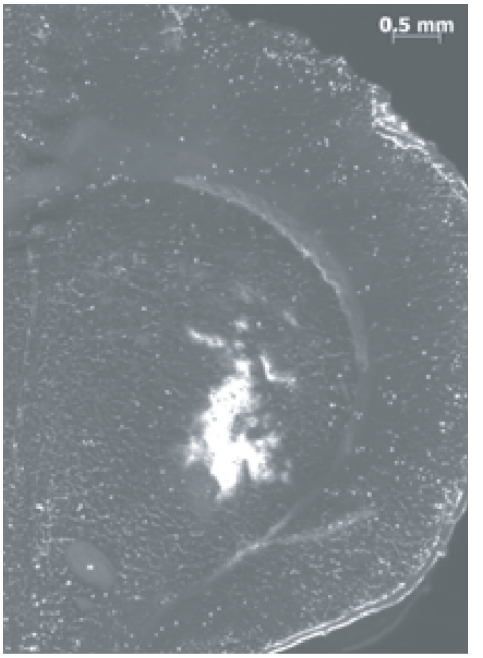

Figure 4: 20 nm Polystyrene beads delivered via CED into the caudate of a rat. Image shows local nanoparticle penetration after a 5 µL infusion (Sawyer AJ, Neeves KB, Foley CP, Olbricht WL, and Saltzman WM, unpublished data).

Accordingly, several research groups are determining and improving the penetration of particles within the brain delivered via CED (Figure 4). Studies looking at the size of particle infusate concluded that smaller particles, around 20 nm, distributed further than larger particles [67]. The same behavior was observed using liposomes [68]. Interestingly, particles 40nm and larger had similarly restricted distributions. The surface properties of the small particles play a significant role in their volume distribution. Surfaces that were neutral, negatively charged, or coated with poly(ethylene glycol) (PEG) or bovine serum albumin (BSA) maximized distribution volume [69]. Coatings that were positively charged severely restricted particle distribution. Adjuvants have been used to improve distribution regardless of particle properties. A hyperosmolar infusion of mannitol significantly increased volume distribution [68]. When the infusate experiences specific cell binding, an infusion of excess unencapsulated ligands can increase the distribution [70].

Table 2: Advantages and disadvantages of polymeric-controlled release and convection-enhanced drug delivery.

	Advantages	Disadvantages
Polymeric-controlled release	• Sustained drug release • Define release kinetics • Tunable release properties • Low invasiveness • Low peak drug release limits tissue damage • Biocompatible • Localized delivery	• Poor drug penetration • Drug dosage limited by implant size
Convection-enhanced delivery	• Large drug distribution volume • Flexible therapy protocol • Consistent drug concentration	• Invasive • Long infusion times • Potential high intracranial pressures • Unpredictable drug distribution

One objective of the previous particle infusion studies was to model the delivery of either viral vectors that could be used for gene therapy or drug loaded particles. CED has the potential to improve gene therapy by increasing the available concentration of vectors. Two studies looked at the distribution of adeno-associated vectors (AAVs) administered via CED [71,72]. Each realized a greater and more homogeneous distribution of transduction by combining AAVs with CED, which was further improved with adjuvant heparin.

CED and Imaging

CED has the ability to improve both the imaging and treatment of brain tumors. This allows for a combination approach that can monitor the distribution of drugs as they are being delivered [73]. To observe the distribution via CED, liposomes were labeled with the MRI contrast agent gadolinium. The gadolinium liposomes can then be infused with particles of similar size and monitored using MRI. This approach was validated in a primate model [74]. The distributions observed via MRI completely coincided with distributions determined using fluorescence. Administering contrast agent along with chemotherapeutic drugs allows for the initial volume distribution to be observed and for tissue necrosis to be monitored within that distribution area [75].

CED is limited by its invasiveness and by the anatomical influences on drug distribution. CED requires the insertion of a catheter several centimeters deep into the brain, which can cause tissue damage and may induce air bubbles [76]. The anatomy of the brain affects the distribution of drugs. White matter tracks provide areas of comparatively high fluid conductivity. If the catheter is inserted through white matter, for example the corpus callosum, the high conductivity combined with reflux up the catheter siphons drug away from parenchyma. The perivascular spaces have also been observed to collect infusate during CED [77]. The unpredictable flow can lead to collection of drug either in the perivascular spaces, wound track, or under the scalp. This has caused incidences of edema and wound dehiscence. The localized high dose area caused the same symptoms during the delivery of viral vectors [78].

Clinical Trials

A Phase III randomized clinical trial (PRECISE TRIAL) comparing the outcome between Gliadel and CED of IL13-PE38QQR has been completed (unpublished data). This study randomized patients with GBM for treatment after they had failed conventional therapy (surgery, radiotherapy, +/- chemotherapy). This study revealed no sig-

nificant difference in outcome. Median survival following tumor recurrence was 35.3 weeks for the Gliadel and 36.4 weeks for IL13-PE38QQR. It is anticipated that inaccurate catheter placement and unresolved problems with adequate drug distribution may have contributed to the absence of benefit for the CED arm. These data support the need for continued research in improving drug distribution and better delivery methods.

CONCLUSIONS

Local delivery to brain tumors can be accomplished using the two strategies of polymeric-controlled release and convection-enhanced delivery. Each technique strives to address the need for controllable intracranial drug delivery. The two technologies offer unique benefits and suffer distinctive limitations, which are listed in Table 2. The principle disadvantage to controlled release is the restricted drug distribution. The limitations imposed by diffusion within the brain limit drug penetration to a region smaller than the typical invasive area of malignant gliomas.

CED's strength lies in the potential for large distribution volume of infused drugs. The long infusion times and unpredictable distribution have also caused an abundance of side effects in recent clinical trials. Trials using paclitaxel have noticed a high rate of drug related adverse events that include wound dehiscence, inflammation, and edema [79,80]. These side effects are attributed to drug backflow along the catheter, and drug localization in the perivascular and subarachnoid spaces. Infusing an encapsulated drug may decrease the incidence of these adverse events.

OUTLOOK

CED was developed as a method to address the shortcomings of polymeric-controlled release. Coincidentally, many of the flaws in CED are the strengths of a polymeric-controlled release approach. Encapsulation of drug would limit the reflux and promote better wound healing after delivery. Delivering encapsulated drug could shorten the infusion time. A shorter infusion time would deliver a lower maximum drug concentration which could address the instances of edema and inflammation. Moreover, a combined treatment strategy could truly localize the delivery by restricting it to a prescribed area. Nanoparticle technology has advanced such that high levels of targeting ligand can be expressed on the surface of the degradable particles [81]. These particles could then be targeted to a subpopulation of cells.

A combined approach is not without its potential pitfalls. The polymer particles would have to be large enough to deliver a clinically relevant dose. The increase in size could restrict the distribution of particles in the parenchyma. While the adjuvants could improve the distribution, a multi-focal delivery strategy may be necessary to circumvent the transport limitations.

Local delivery to brain tumors has already provided a modest increase in survival when used in addition to surgery and radiotherapy. Despite the advances, GBM remains fatal regardless of the mode of treatment. There is untapped potential in both of the local delivery strategies discussed here. Polymeric-controlled release and CED can be used as techniques to administer the standard agents, combinations of drugs, as well as new methods of anti-tumor therapy.

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