Crossing Borders
Surgically Mediated Drug Delivery Techniques

Ashok R. Asthagiri, M.D., Martin Baggenstos, M.D., and Russell R. Lonser, M.D.

Despite recent insights into the pathobiology underlying central nervous system (CNS) malignant gliomas (MGs) and the development of new putative therapeutic compounds to treat these neoplasms, there remains no curative surgical or medical treatment for these tumors. Extensive surgical resection has been shown to prolong survival but is not a total cure because of widespread infiltrative microscopic disease that extends well beyond the macroscopic or imaging-defined tumor boundaries and outside of what can be feasibly removed.[17,36] The effectiveness of radiation therapy is limited by the intolerance of normal brain parenchyma and results in variable failure patterns. Because of the limitations associated with surgery and radiotherapy, investigation into adjuvant chemobiological agents to treat these tumors has been undertaken. Although a rapidly expanding number of promising therapeutic agents have been developed, antineoplastic regimens have remained unsuccessful in treating MG primarily because of ineffective drug delivery to neoplastic cells.

Currently available delivery paradigms for distribution of antineoplastic agents to the CNS include nonsurgical and surgically mediated techniques. Nonsurgical methods of CNS drug delivery include systemic and intrathecal or intraventricular administration. Systemic delivery is restricted by systemic toxicity, nontargeted distribution, and the inability of most substances to traverse the blood–brain barrier. Diffusion-dependent methods, including intrathecal or intraventricular administration, are limited by nontargeted delivery, inhomogeneous dispersion, and ineffective distribution. To overcome these limitations, investigation of surgically mediated drug delivery methods, including implantation of drug-impregnated polymers and direct convection-enhanced delivery (CED) of therapeutic compounds, has been performed.[1,18]

Drug-impregnated Polymer Implantation

Technique, Pharmacokinetics, and Properties

Technique

Polyanhydride polymers impregnated with drugs that are released when exposed to an aqueous environment can be used to distribute drugs in the CNS. Treatment of MGs in the CNS using antineoplastic agents impregnated into biodegradable polymers has been explored. Specifically, a controlled-release copolymer (polycarboxyphenoxypropane and sebacic acid) loaded with the nitrosourea-alkylating agent carmustine (1,3-bis[2-chloroethyl]-1-nitrosourea [BCNU]) and fashioned into the shape of a wafer or disc (diameter, 1.45 cm; thickness, 1 mm) (Gliadel; MGI PHARMA, Inc., Baltimore, MD) has been used to treat MGs. These copolymer wafers were designed to directly deliver BCNU to the walls of the tumor resection cavity after tumor removal (*Fig. 4.1*).

Pharmacokinetics and Properties

When in continuous contact with interstitial and cerebrospinal fluid, Gliadel wafers release the majority of BCNU into the walls of the tumor resection cavity over a 7-day period but display sustained release of much smaller quantities of drug in vivo up to 30 days after implantation.[8,9,13] Based on preclinical studies, computed tomography imaging, and autopsy findings, the polymer component of the wafer is believed to degrade over 6 to 8 weeks.[3,46] Animal studies reveal that the metabolic products from the degrading polymer are excreted as urine and/or metabolized by the liver and expired as carbon dioxide.[7] Because the drug-impregnated polymers are placed directly into the surgical resection site, they bypass the blood–brain barrier. Previous studies have shown BCNU concentrations approximately 100-fold of those obtained with intravenous BCNU administration while avoiding the toxicity associated with its systemic delivery.[47]

The overall tissue distribution of drug with sustained-release polymer delivery is dependent on diffusion. Therefore, tissue distribution is dependent on drug concentration, molecular weight, and diffusivity. Consistent with this, previous animal data have shown that drug concentrations are highest at the polymer–tissue interface and decrease sharply (250- to 1000-fold decrease in concentration) over a 2- to 4-mm distance from the polymer–tissue interface (*Fig. 4.2*).[8–10,38] Maximal distribution of therapeutic concentrations of BCNU is achieved during the first day after implantation, when inherent bulk flow pathways of the brain parenchyma may carry drug up to several millimeters away from the source.[9,10] Thereafter, the sustained radial penetration and effective

0148-703/08/5501-0027

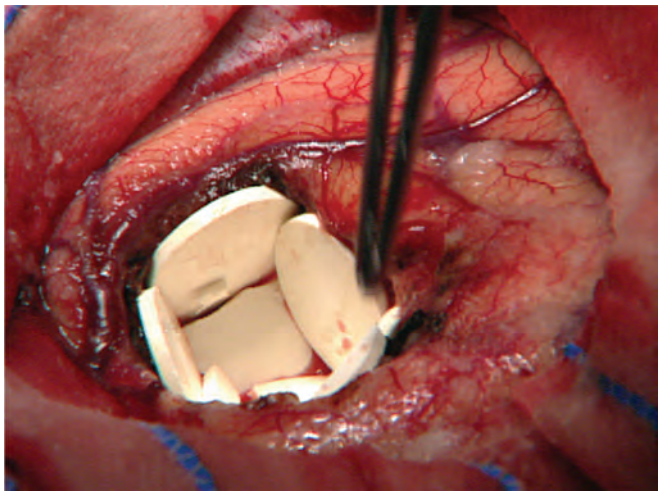

FIGURE 4.1. Intraoperative photograph of the controlled-release copolymer (polycarboxyphenoxypropane and sebacic acid) loaded with the nitrosourea-alkylating agent carmustine (BCNU). The copolymer is fashioned into the shape of a wafer or disc (diameter, 1.45 cm; thickness, 1 mm) (Gliadel) and placed into the surgical resection site after malignant glioma removal. Photograph courtesy of MGI PHARMA, Inc.

volume of distribution (Vd) of BCNU is markedly lower because it is dependent on the steady-state balance that is achieved between diffusion away from the polymer source and its loss resulting from permeation and reaction.[9,34]

Studies for Recurrent Malignant Gliomas

A multi-institutional Phase I–II trial was conducted to establish the safety of BCNU polymer surgical implants in patients with recurrent MG.[3] Twenty-one patients were divided into three groups and treated with increasing concentrations of BCNU-impregnated (1.93, 3.85, and 6.35%) wafers. After BCNU wafer implantation, no evidence of systemic toxicity was observed. Survival appeared to be longer in patients implanted with the wafers impregnated with lower concentrations of BCNU (1.93 and 3.85%) compared with those receiving the highest dose (6.35%).

Based on these Phase I–II trial findings, a Phase III randomized double-blind, placebo-control multicenter trial was performed.[4] Two hundred twenty-two patients with recurrent MG were randomized to receive either BCNU-impregnated (3.85%) or placebo polymer wafers at the time of tumor resection. Overall, median survival was improved in patients with MG receiving BCNU wafers (31 weeks) compared with placebo control subjects (23 weeks; $P = 0.006$). In the subset of patients with glioblastoma multiforme (GBM), the 6-month survival rate was higher in the treatment arm (56%) compared with the control group (36%; $P = 0.02$). Patients with MG who did not have the pathologic diagnosis of GBM at the time of resection did not have prolongation of survival.

Studies with Newly Diagnosed Malignant Gliomas

Confirmation of the safety of sustained-release BCNU–polymer interstitial chemotherapy in recurrent MG and previous reports of additive neurotoxicity resulting from the radiosensitizing properties of BCNU led to a Phase I study using BCNU–polymer implants in patients with newly diagnosed MG.[2] Twenty-two patients with newly diagnosed MG (21 with GBM) were treated with BCNU–polymer implants (3.85%) at initial tumor resection followed by standard external beam radiation therapy (55 to 60 Gy). Findings from this study revealed that the use of BCNU interstitial chemotherapy at the time of initial MG resection was not associated with any systemic toxicity or increased CNS toxicity.

Based on these findings, a Phase III trial to assess the efficacy of BCNU–polymer implants as part of the initial treatment of newly diagnosed MG was performed that included 32 patients undergoing surgical resection and treatment with 3.85% BCNU–polymer wafer (n = 16) or placebo wafer (n = 16) (followed by external beam radiation therapy for both groups).[41] Median survival in the placebo group (39.9 weeks) was shorter compared with the treatment group (58.1 weeks; $P = 0.012$). The 1-, 2-, and 3-year survival rates were improved in the treatment arm (56, 31, and 25%, respectively) compared with the placebo group (19, 16, and 6%, respectively). In the subset of patients with GBM (11 in the treatment group, 16 in the control group), the median survival was 53.3 weeks in the treatment group compared with 39.9 weeks for the control group ($P = 0.008$).

To confirm these findings, a second Phase III double-blind, multicenter prospective randomized study of 240 newly diagnosed patients with MG was performed.[44] Patients were randomized to treatment with BCNU–polymer (3.85%) or placebo wafer after initial MG surgical resection (followed by external beam radiation therapy for both groups; 55 to 60 Gy). Median survival in the BCNU–polymer wafer group (13.9 mo) was increased compared with the placebo group (11.6 mo; $P = 0.03$). Subgroup analysis of patients with GBM revealed a significant survival benefit for patients treated with BCNU–polymer wafers (13.5 mo) compared with the placebo group (11.4 mo; $P = 0.04$). An increase in raised intracranial pressure (9 versus 2%) and cerebrospinal fluid leak (5 versus 0.8%) occurred in patients receiving BCNU–polymer wafer therapy.

Future Applications

The BCNU–polymer combination (Gliadel) is the only sustained-release polymer interstitial chemotherapy licensed for treatment of de novo and recurrent GBM by the U.S. Food and Drug Administration. Although the initial Phase I study suggested the use of a 3.85% BCNU–polymer implant was associated with improved survival compared with higher-dosed wafers (6.35%), preclinical studies in a rat intracranial 9-L glioma model found that increasing the concentration of

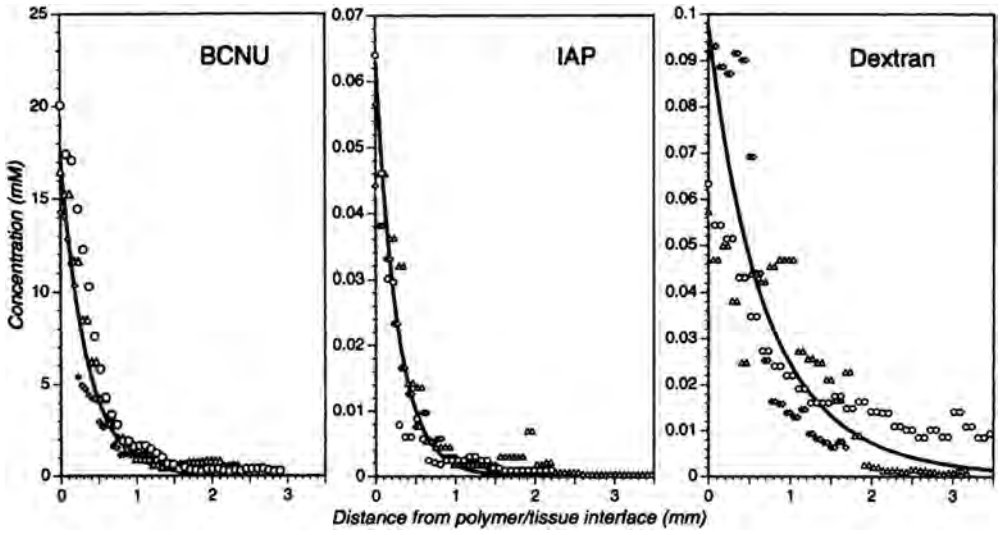

FIGURE 4.2. Tissue concentration profiles in the immediate vicinity of a polymer implant impregnated with radiolabeled compounds, including ^{3}H-carmustine (BCNU), ^{14}C-iodoantripyrene (IAP), and ^{3}H-dextran. Tissue concentration profiles were determined as a function of distance from the edge of the polymer. The solid lines represent the steady-state diffusion model. The ordinate represents the polymer/tissue interface. Reprinted with permission from Strasser JF, Fung LK, Eller S, Grossman SA, Saltzman WM: Distribution of 1,3-bis[2-chloroethyl]-1-nitrosourea and tracers in the rabbit brain after interstitial delivery by biodegradable polymer implants. **J Pharmacol Exp Ther** 275:1647–1655, 1995.[38]

BCNU (up to 20%) improved survival without increasing toxicity.[37] A Phase I–II trial has confirmed the safety of the more concentrated implants in humans and a Phase III trial evaluating the efficacy of the 20% BCNU–polymer implant as compared with the 3.85% Gliadel implant is planned.[28] In addition to dose escalation trials, further investigations examining the potentiation of interstitial BCNU therapy with concurrent systemic O^6-benzylguanine (chemotherapy resistance inhibitor) as well as enhancing drug delivery and efficiency through variable polymer preparations are being performed.[20,33]

Convection-enhanced Delivery

Technique, Pharmacokinetics, and Properties

Technique

Convective distribution of molecules within the interstitial spaces of the CNS relies on a small pressure gradient that drives the movement of solute through the extracellular spaces over volumes and speeds that far exceed that of simple diffusion. During CED, the convective (bulk flow) force used to distribute solute through the extracellular spaces is derived from a small hydrostatic pressure gradient generated by a syringe pump that is in turn transmitted to the point of delivery through a cannula (or catheter) inserted directly into the region to be perfused. Because of the bulk flow properties that underlie convective delivery, there are a number of unique features associated with this drug delivery technique.[1,25]

Pharmacokinetics and Properties

CED bypasses the blood–brain barrier and targets specific CNS structures/regions through the stereotactic placement of an infusion cannula directly into the nervous system parenchyma. Infusate is then delivered directly into the interstitial spaces of the CNS from the cannula (catheter) tip. Because CED relies on bulk flow (not diffusion), distribution is homogeneous. Autoradiographical studies have shown that the concentration of infusate is similar over the perfused region with a precipitous dropoff at the margins of the infusion.[22] This "square-shaped" distribution pattern underscores homogeneous perfusion of tissue possible with convective delivery and the potential to infuse targeted regions of the CNS with high concentrations of drug (*Fig. 4.3*).

Because the distribution of infusate occurs within the interstitial spaces of the CNS, the Vd of infusate is directly proportional to the volume of infusion (Vi) and inversely proportional to the volume of interstitial space within the perfused region. Previous studies have shown that convective perfusion of the normal brain and spinal cord is associated with Vd:Vi ratios of approximately 4:1 to 5:1. Similarly, CED of infusate in the brainstem, where the interstitial space is smaller (as a result of the tightly compacted nature of fibers), is associated with increased Vd:Vi ratios (6:1 to 10:1).[1,22,24]

CED can be used to perfuse small or large regions of the CNS. The previously described Vd:Vi ratio allows for

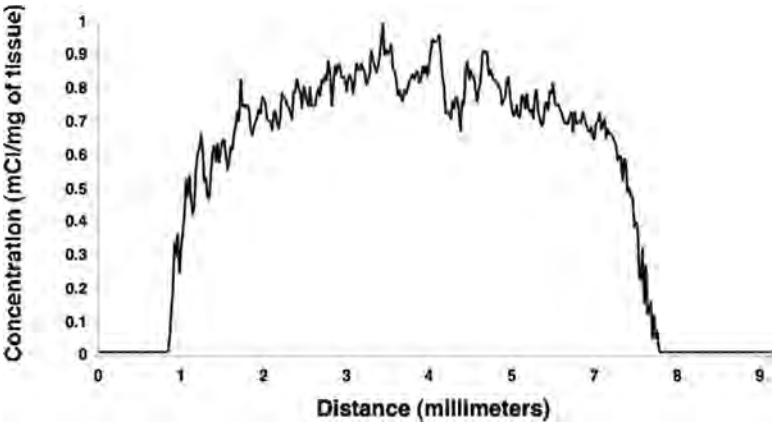

FIGURE 4.3. Graph of a concentration profile from autoradiography demonstrating the "square-shaped" pattern of distribution indicative of relatively uniform concentration of ^{35}S-adeno-associated viral capsid over the infused area. The variance of concentration across the plateau was 12%. Reprinted with permission from Szerlip NJ, Walbridge S, Yang L, Morrison PF, Degen JW, Jarrell ST, Kouri J, Kerr PB, Kotin R, Oldfield EH, Lonser RR: Real-time imaging of convection-enhanced delivery of viruses and virus-sized particles. **J Neurosurg** 107:560–567, 2007.[39]

clinically relevant Vds to be obtained by infusing relatively small volumes. One of the major advantages of CED is the significantly larger Vd (several magnitudes of order larger) that can be achieved compared with that obtained by techniques using a diffusion process alone. Because neural tissue is a porous medium characterized by either isotropic (gray matter) or anisotropic (white matter) transport, the pattern of convective distribution is governed by the immediately surrounding tissue type (gray or white). Perfusion of gray matter, where the cells are embedded homogeneously in an extracellular matrix, will result in a roughly spherical (isotropic) distribution pattern. Conversely, perfusion of white matter tracts will result in preferential flow (anisotropic) of infusate parallel to the surrounding fibers.[23] This is a result of the low hydraulic conductivity along these fiber pathways. This biological circumstance can permit the perfusion of large regions of cerebral cortex and deep brain structures from a single point source in white matter tracts that emanate to these anatomical locations.

Recently, the use of surrogate imaging tracers to track convective delivery in real-time using magnetic resonance (MR) and computed tomography imaging has been investigated.[5,12,24,27] Specifically, a number of low- and high-molecular-weight tracers have been examined as potential surrogate imaging markers to be co-infused with therapeutic compounds. CED and real-time imaging of these tracers have been characterized in the brain, brainstem, spinal cord, and peripheral nerves.[5,26] Because molecules over a wide range of molecular weights move out from the infusion source (cannula or catheter) at a similar rate using convective or bulk flow, a specific surrogate tracer can be used to track a wide variety of different sized therapeutic compounds (*Fig. 4.4*). When the surrogate co-infused tracer is matched to the intrinsic properties of the therapeutic compound infusate, the margin of error in assessing convection-enhanced distribution of the drug itself is in the range of 5 to 15%.[5,26]

Clinical Trials

CED is currently under clinical investigation using a variety of therapeutic agents. Various categories of antineoplastic agents that are being infused include conventional chemotherapeutic compounds, recombinant cytotoxic proteins, and radiolabeled chimeric monoclonal antibodies.

Chemotherapeutic Compounds

Paclitaxel causes a pathological and dysfunctional state of extraordinary microtubule stability, thereby leading to cell death through interference of cell division and vital interphase processes. Preclinical studies confirmed that the antitumor effect seen on ovarian, breast, lung, head, and neck cancers is comparable to effects seen in in vitro glioma cell lines.[40] The systemic toxicity and low parenchymal concentration of paclitaxel achieved through intravenous administration led to a CED based Phase I–II trial for patients with recurrent high-grade MGs.[21] In this study, three patients were initially administered a daily dose of 7.2 mg paclitaxel diluted in 6 mL of normal saline for 5 consecutive days. This dose was reduced in half for the remaining 12 patients as a result of chemical meningitis and ensuing complications leading to death in two of three patients receiving the higher dose. Presumed leakage of paclitaxel into the subarachnoid space and the incision, even at the lower dose, led to a high incidence of chemical meningitis, incisional dehiscence, and infection. Despite these complications, local treatment with paclitaxel showed an antitumor response in 11 of 15 patients.

Recombinant Cytotoxic Proteins

Recombinant cytotoxic proteins have targeted cancer cell specificity that is conferred by a growth factor or surface antigen-binding domain. Endocytosis of the coupled cytotoxic moiety (*Pseudomonas* exotoxin, diphtheria toxin) causes enzymatic inactivation of elongation factor 2, an essential component of protein synthesis, thereby leading to cell death.

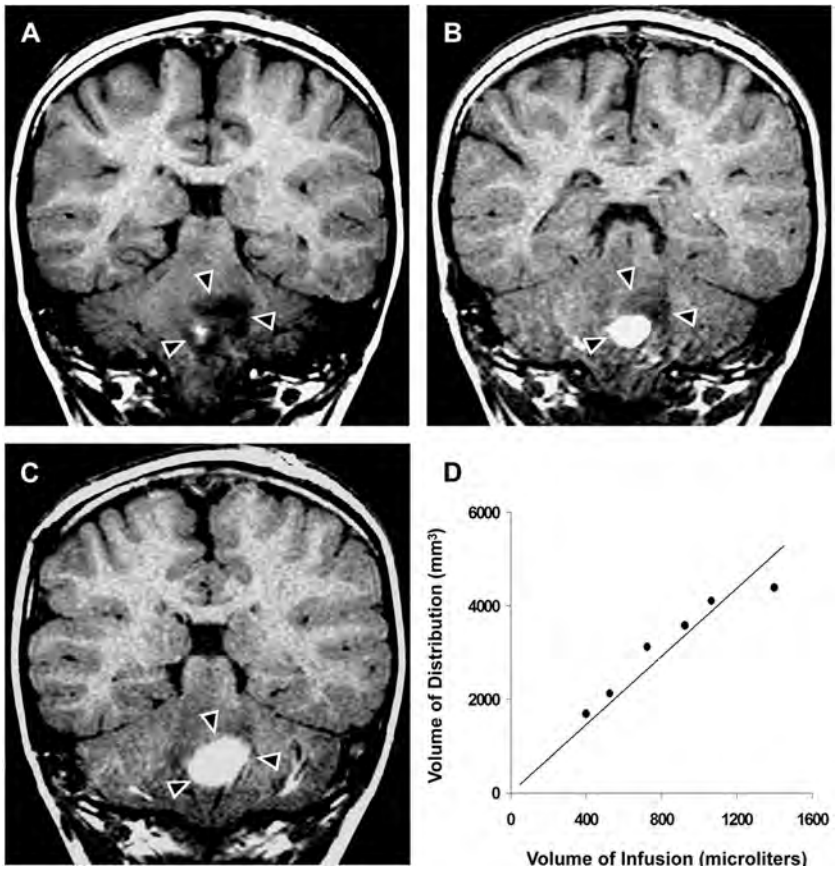

FIGURE 4.4. Real-time MR imaging of convective distribution of interleukin-13 bound to *Pseudomonas* toxin (IL13-PE) and gadolinium-DTPA in a diffuse brainstem glioma. *A–C,* Serial coronal T1-weighted MR imaging during convection-enhanced delivery of IL13-PE co-infused with a surrogate MR imaging tracer, gadolinium-DTPA (total volume infused, 1.4 mL). Sequential imaging during infusion demonstrates perfusion of the hypointense tumor (*arrowheads*) in the pons with drug as shown by the region filled with gadolinium-DTPA (white area). *D,* Volume of distribution increases linearly with volume of infusion ($R^2 = 0.92$). The overall volume of distribution to volume of infusion ratio was 3.7 ± 0.4.

Tf-CRM107 is the prototype recombinant cytotoxic protein and is derived from conjugation of the human transferrin protein to a modified diphtheria toxin. Transferrin receptors mediate the cellular uptake of iron and are notably overexpressed on rapidly dividing cells, including those of GBM.[32] The single point mutation in the diphtheria toxin reduces its cell-binding affinity but retains the toxin's native cytosolic translocation mechanism and ability to inhibit elongation factor 2, thereby allowing Tf-CRM107 to have selective and potent cytotoxicity.[11] A Phase I trial evaluating the toxicity and maximum tolerated dose of Tf-CRM107 therapy delivered through CED in the treatment of refractory and recurrent malignant brain tumors was performed with 18 participants.[19] No systemic clinical toxicity or postmortem extra-CNS findings were attributable to CED of Tf-CRM107. Among 15 evaluable patients, nine had greater than 50% reduction in tumor volume and two had a complete radiographical response. Tumor response appeared to be both concentration- and total dose-dependent. Peritumoral focal brain injury was seen in patients who received a concentration of drug greater than 1.0 μg/mL. Subsequently, 0.67 μg/mL intermediate concentration of Tf-CRM107 was selected for Phase II testing. A Phase II multicenter, open-label, single-arm study was then performed to investigate the safety and efficacy of intratumoral Tf-CRM107 in the treatment of recurrent or progressive malignant glioma.[42] In 34 (44 patients enrolled) evaluable patients, five displayed a complete response and seven had a partial response. Thirteen patients were alive 1 year after infusion, and one patient survived for 3.1 years. No high-grade systemic toxicity was associated with this trial.

Many malignant gliomas and other tumors that metastasize to the brain express high levels of epidermal growth factor receptor as a result of gene amplification or mutation during neoplastic transformation.[45] This receptor has two natural ligands, epidermal growth factor and transforming growth factor alpha, the latter of which was coupled with a genetically engineered *Pseudomonas* exotoxin (PE 38) to produce the TP-38 ligand–exotoxin construct. Nineteen patients with recurrent malignant gliomas (16 GBM, one gliosarcoma, one anaplastic astrocytoma, and one anaplastic oligodendroglioma) and one with metastatic spindle cell sarcoma were enrolled in a Phase I trial that used delivery of TP-38 by CED.[35] Tumors in two of the 15 patients with residual disease at the time of therapy demonstrated radiographical responses. At the time of publication, four patients had no radiographical recurrence of tumor and were 55, 56, 69, and 116 weeks from the time of TP-38 therapy. Currently,

TP-38 therapy is being investigated in a multicenter Phase II study in patients with recurrent or progressive GBM scheduled to undergo gross total resection.

Gliomas are found to express high levels of the IL-13 receptor, whereas normal glia and neurons express very low levels or none at all.[6] Cintredekin besudotox (CB), a recombinant protein consisting of interleukin-13 and a truncated form of the *Pseudomonas* exotoxin (PE38QQR), has undergone extensive clinical testing. Three Phase I studies have been conducted to determine the optimization of catheter placement (IL13PEI-103), intraparenchymal infusate distribution (IL13PEI-105), and the maximum tolerated infusate toxicity (IL13PEI-002) of CB.[15] The studies included a total of 51 patients with malignant gliomas, 46 of which were GBM. There was no systemic toxicity associated with CED of CB. Neurological adverse events possibly attributed to CB occurred at a frequency that can be expected in a population of patients undergoing a surgical procedure for the treatment of a MG. Aside from establishing the maximum tolerated infusate, these studies revealed that infusion durations up to 6 days were well tolerated and deferred stereotactic catheter placement improved catheter positioning and drug distribution. Recently, a Phase III trial including 288 patients randomized to either IL13-PE therapy through CED or Gliadel wafer implantation after surgical resection of GBM (PRECISE trial) was performed. Median survival was similar between the IL13-PE-infused patients (36.4 weeks) compared with patients who underwent Gliadel wafer placement (35.3 weeks; $P = 0.48$).[16]

Analogous to other recombinant cytotoxic proteins, IL4-PE uses the overexpression of interleukin-4 receptors on MG cells to garner cytotoxic specificity.[30] A circular permutation of the interleukin-4 ligand increased receptor binding affinity and this protein was coupled with a modified *Pseudomonas* exotoxin to yield the potent tumoricidal agent, cpIL4-PE.[14,43] An initial pilot study was performed in nine patients to assess the usefulness of intratumoral CED of cpIL4-PE. Dramatic tumor necrosis was observed in six patients, three of whom required surgery within 2 weeks of cpIL4-PE administration. Interestingly, the histopathology reflected the exquisite specificity of the drug, because areas of tumor necrosis were admixed with normal intervening brain tissue. One patient achieved a complete response and remained recurrence-free after 18 months. Although systemic toxicity was avoided, a high incidence of cerebral edema attributed to tumor necrosis was found.[31] A subsequent Phase I dose-escalation study concluded the maximum tolerated dose of cpIL4-PE was a 40-mL infusion of 6 μg/mL. The most frequent neurological adverse events included seizures (84%), headache (45%), weakness (32%), and cerebral edema (32%). No systemic toxicity was directly associated with intratumoral IL4-PE infusion. Although not designed to assess efficacy, 72% of patients showed greater than a 50% reduction in tumor enhancement. Approximately half of these patients had a radiographical response for at least 4 weeks, suggesting a durable effect of cpIL4-PE rather than transient alteration of enhancement patterns resulting from CED. The significant incidence of extensive tumor necrosis and worsening cerebral edema has prompted the incorporation of postinfusion surgical resection into ongoing Phase II trials.[43]

Radiolabeled Chimeric Monoclonal Antibodies

The necrotic core of a malignant solid tumor provides a milieu containing a universal intracellular antigen (i.e., histone H1 complexed to deoxyribonucleic acid), which is targeted specifically by the murine monoclonal antibody constituent of ^{131}I-chTNT-1/B MAb (Cotara, Peregrine Pharmaceuticals, Inc.; Tustin, California). The antigen–antibody complex serves as an insoluble, nondiffusible anchor for the localized delivery of Cotara and its cytotoxic ^{131}I component to surrounding viable tumor cells. A multi-institutional Phase I–II trial was conducted to assess the safety and feasibility of this radiolabeled chimeric monoclonal antibody therapy through CED in patients with recurrent malignant gliomas or newly diagnosed GBM not amenable to surgical resection.[29] A total of 51 patients were enrolled, the first 12 of whom participated in the dose-finding Phase I portion of the study. The delivery of 15,000 cGy to the baseline clinical target volume required a calculated dose of 1.64 mCi/cm^3. During Phase II testing, 26 patients received a 1.0-mCi/cm^3 dose and 13 patients received a 1.5-mCi/cm^3 dose. This was followed by repeat dosing in the 41% of patients who displayed no radiographical progression of tumor within 8 weeks after initial treatment. Single photon emission computed tomography scans were performed 2 weeks postinfusion to assess the activity and localized penetration of Cotara. In a subgroup of six patients who received correlative analysis with preoperative MR imaging, tumor volume coverage varied from 46 to 88%. Overall, the infusions provided adequate localization of radiation therapy coverage with little exposure to surrounding "tumor-free" brain. Although this study was not designed to assess efficacy, analysis of 11 evaluable patients with recurrent GBM receiving a total dose between 1.25 and 2.5 mCi/cm^3 revealed a median survival of 37.9 weeks. One patient had a partial response, six had stable disease, and two patients were alive 104 weeks after treatment. Sixteen percent of patients were found to have brain edema, hemiparesis, and headaches that could be attributed to Cotara administration. One patient receiving a maximal total dose of 3.0 mCi/cm^3 died as a result of radiation-induced necrotic changes.

Future Applications

The real-time determination of drug distribution in future studies will be critical to ensure adequate drug delivery, determine true efficacy of putative therapeutic compounds, gain insight into the properties of CED in the human diseased CNS, and enhance safety. Real-time imaging of

surrogate tracer or labeled drugs will provide investigators the opportunity to determine if drug distribution was sufficient to treat a targeted region of the CNS. This information will be critical to determine if the drug delivered by CED was efficacious. Clinical trials performed to date were not designed to include dependable and precise techniques to determine drug distribution, and thus ambiguity remains as to whether treatment failures are attributable to inadequate delivery or true ineffectiveness of the tested drug. Insights into CED in the human CNS under a variety of pathological conditions can be ascertained through real-time imaging. Factors affecting drug perfusion, including maximal infusion rate, cannula design, and anatomic variables (e.g., ependymal walls, pial surface, and resection walls), will be better understood with real-time imaging feedback. Finally, the ability to image drug distribution should enhance the safety of convective infusion. Imaging will permit cessation of perfusion if infusate is being distributed in unintended regions or once a targeted CNS region is completely treated.

CONCLUSION

The inability of surgical resection and radiation therapy to cure MG necessitates improved adjuvant therapies to enhance survival and ultimately provide a cure. Future developments that exploit the unique properties of surgically mediated drug delivery techniques could lead to improved treatment paradigms for MGs and, ultimately, improved survival.

Disclosure

The authors did not receive financial support in conjunction with the generation of this article. The authors have no personal or institutional financial interest in drugs, materials, or devices described in this article.

REFERENCES

1. Bobo RH, Laske DW, Akbasak A, Morrison PF, Dedrick RL, Oldfield EH: Convection-enhanced delivery of macromolecules in the brain. **Proc Natl Acad Sci U S A** 91:2076–2080, 1994.
2. Brem H, Ewend MG, Piantadosi S, Greenhoot J, Burger PC, Sisti M: The safety of interstitial chemotherapy with BCNU-loaded polymer followed by radiation therapy in the treatment of newly diagnosed malignant gliomas: Phase I trial. **J Neurooncol** 26:111–123, 1995.
3. Brem H, Mahaley MS Jr, Vick NA, Black KL, Schold SC Jr, Burger PC, Friedman AH, Ciric IS, Eller TW, Cozzens JW, Kenealy JN: Interstitial chemotherapy with drug polymer implants for the treatment of recurrent gliomas. **J Neurosurg** 74:441–446, 1991.
4. Brem H, Piantadosi S, Burger PC, Walker M, Selker R, Vick NA, Black K, Sisti M, Brem S, Mohr G, et al.: Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-brain Tumor Treatment Group. **Lancet** 345:1008–1012, 1995.
5. Croteau D, Walbridge S, Morrison PF, Butman JA, Vortmeyer AO, Johnson D, Oldfield EH, Lonser RR: Real-time in vivo imaging of the convective distribution of a low-molecular-weight tracer. **J Neurosurg** 102:90–97, 2005.
6. Debinski W, Obiri NI, Powers SK, Pastan I, Puri RK: Human glioma cells overexpress receptors for interleukin 13 and are extremely sensitive to a novel chimeric protein composed of interleukin 13 and pseudomonas exotoxin. **Clin Cancer Res** 1:1253–1258, 1995.
7. Domb AJ, Rock M, Schwartz J, Perkin G, Yipchuk G, Broxup B, Villemure JG: Metabolic disposition and elimination studies of a radiolabelled biodegradable polymeric implant in the rat brain. **Biomaterials** 15:681–688, 1994.
8. Fleming AB, Saltzman WM: Pharmacokinetics of the carmustine implant. **Clin Pharmacokinet** 41:403–419, 2002.
9. Fung LK, Ewend MG, Sills A, Sipos EP, Thompson R, Watts M, Colvin OM, Brem H, Saltzman WM: Pharmacokinetics of interstitial delivery of carmustine, 4-hydroperoxycyclophosphamide, and paclitaxel from a biodegradable polymer implant in the monkey brain. **Cancer Res** 58:672–684, 1998.
10. Fung LK, Shin M, Tyler B, Brem H, Saltzman WM: Chemotherapeutic drugs released from polymers: Distribution of 1,3-bis(2-chloroethyl)-1-nitrosourea in the rat brain. **Pharm Res** 13:671–682, 1996.
11. Greenfield L, Johnson VG, Youle RJ: Mutations in diphtheria toxin separate binding from entry and amplify immunotoxin selectivity. **Science** 238:536–539, 1987.
12. Groothuis DR: The blood-brain and blood-tumor barriers: A review of strategies for increasing drug delivery. **Neuro Oncol** 2:45–49, 2000.
13. Grossman SA, Reinhard C, Colvin OM, Chasin M, Brundrett R, Tamargo RJ, Brem H: The intracerebral distribution of BCNU delivered by surgically implanted biodegradable polymers. **J Neurosurg** 76:640–647, 1992.
14. Kreitman RJ, Puri RK, Pastan I: A circularly permuted recombinant interleukin 4 toxin with increased activity. **Proc Natl Acad Sci U S A** 91:6889–6893, 1994.
15. Kunwar S, Prados MD, Chang SM, Berger MS, Lang FF, Piepmeier JM, Sampson JH, Ram Z, Gutin PH, Gibbons RD, Aldape KD, Croteau DJ, Sherman JW, Puri RK: Direct intracerebral delivery of cintredekin besudotox (IL13-PE38QQR) in recurrent malignant glioma: A report by the Cintredekin Besudotox Intraparenchymal Study Group. **J Clin Oncol** 25:837–844, 2007.
16. Kunwar S, Westphal M, Medhorn M, Ram Z, Sampson J, Byrne R, Land FF, Tatter S, Piepmeier JM, Barnett G, Guha A, Mooij J, Vogelbaum M, Chang SM, Croteau DJ, Sherman JW, Puri RK: Abstracts for the Twelfth Annual Meeting of the Society for Neuro-Oncology: Results from PRECISE: A randomized phase 3 study in patients with first recurrent glioblastoma multiforme (GBM) comparing Cintredekin Besudotox (CB) administered via convection-enhanced delivery (CED) with Gliadel wafers. **Neuro Oncol** 9:565, 2007.
17. Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, Lang FF, McCutcheon IE, Hassenbusch SJ, Holland E, Hess K, Michael C, Miller D, Sawaya R: A multivariate analysis of 416 patients with glioblastoma multiforme: Prognosis, extent of resection, and survival. **J Neurosurg** 95:190–198, 2001.
18. Langer R, Folkman J: Polymers for the sustained release of proteins and other macromolecules. **Nature** 263:797–800, 1976.
19. Laske DW, Youle RJ, Oldfield EH: Tumor regression with regional distribution of the targeted toxin TF-CRM107 in patients with malignant brain tumors. **Nat Med** 3:1362–1368, 1997.
20. Lawson HC, Sampath P, Bohan E, Park MC, Hussain N, Olivi A, Weingart J, Kleinberg L, Brem H: Interstitial chemotherapy for malignant gliomas: The Johns Hopkins experience. **J Neurooncol** 83:61–70, 2007.
21. Lidar Z, Mardor Y, Jonas T, Pfeffer R, Faibel M, Nass D, Hadani M, Ram Z: Convection-enhanced delivery of paclitaxel for the treatment of recurrent malignant glioma: A Phase I/II clinical study. **J Neurosurg** 100:472–479, 2004.
22. Lieberman DM, Laske DW, Morrison PF, Bankiewicz KS, Oldfield EH: Convection-enhanced distribution of large molecules in gray matter during interstitial drug infusion. **J Neurosurg** 82:1021–1029, 1995.
23. Lonser RR, Gogate N, Morrison PF, Wood JD, Oldfield EH: Direct convective delivery of macromolecules to the spinal cord. **J Neurosurg** 89:616–622, 1998.
24. Lonser RR, Walbridge S, Garmestani K, Butman JA, Walters HA, Vortmeyer AO, Morrison PF, Brechbiel MW, Oldfield EH: Successful and safe perfusion of the primate brainstem: In vivo magnetic resonance

imaging of macromolecular distribution during infusion. **J Neurosurg** 97:905–913, 2002.
25. Morrison PF, Laske DW, Bobo H, Oldfield EH, Dedrick RL: High-flow microinfusion: Tissue penetration and pharmacodynamics. **Am J Physiol** 266:R292–305, 1994.
26. Murad GJA, Walbridge S, Morrison PF, Szerlip N, Butman JA, Oldfield EH, Lonser RR: Image-guided convection-enhanced delivery of gemcitabine to the brainstem. **J Neurosurg** 106:351–356, 2007.
27. Nguyen TT, Pannu YS, Sung C, Dedrick RL, Walbridge S, Brechbiel MW, Garmestani K, Beitzel M, Yordanov AT, Oldfield EH: Convective distribution of macromolecules in the primate brain demonstrated using computerized tomography and magnetic resonance imaging. **J Neurosurg** 98:584–590, 2003.
28. Olivi A, Grossman SA, Tatter S, Barker F, Judy K, Olsen J, Bruce J, Hilt D, Fisher J, Piantadosi S: Dose escalation of carmustine in surgically implanted polymers in patients with recurrent malignant glioma: A New Approaches to Brain Tumor Therapy CNS Consortium trial. **J Clin Oncol** 21:1845–1849, 2003.
29. Patel SJ, Shapiro WR, Laske DW, Jensen RL, Asher AL, Wessels BW, Carpenter SP, Shan JS: Safety and feasibility of convection-enhanced delivery of Cotara for the treatment of malignant glioma: Initial experience in 51 patients. **Neurosurgery** 56:1243–1253, 2005.
30. Puri RK, Leland P, Kreitman RJ, Pastan I: Human neurological cancer cells express interleukin-4 (IL-4) receptors which are targets for the toxic effects of IL4-Pseudomonas exotoxin chimeric protein. **Int J Cancer** 58:574–581, 1994.
31. Rand RW, Kreitman RJ, Patronas N, Varricchio F, Pastan I, Puri RK: Intratumoral administration of recombinant circularly permuted interleukin-4-Pseudomonas exotoxin in patients with high-grade glioma. **Clin Cancer Res** 6:2157–2165, 2000.
32. Recht L, Torres CO, Smith TW, Raso V, Griffin TW: Transferrin receptor in normal and neoplastic brain tissue: Implications for brain-tumor immunotherapy. **J Neurosurg** 72:941–945, 1990.
33. Rhines LD, Sampath P, Dolan ME, Tyler BM, Brem H, Weingart J: O6-benzylguanine potentiates the antitumor effect of locally delivered carmustine against an intracranial rat glioma. **Cancer Res** 60:6307–6310, 2000.
34. Saltzman WM, Radomsky ML: Drugs released from polymers. Diffusion and elimination in brain tissue. **Chemical Engineering Science** 46:2429, 1991.
35. Sampson JH, Akabani G, Archer GE, Bigner DD, Berger MS, Friedman AH, Friedman HS, Herndon JE 2nd, Kunwar S, Marcus S, McLendon RE, Paolino A, Penne K, Provenzale J, Quinn J, Reardon DA, Rich J, Stenzel T, Tourt-Uhlig S, Wikstrand C, Wong T, Williams R, Yuan F, Zalutsky MR, Pastan I: Progress report of a Phase I study of the intracerebral microinfusion of a recombinant chimeric protein composed of transforming growth factor (TGF)-alpha and a mutated form of the Pseudomonas exotoxin termed PE-38 (TP-38) for the treatment of malignant brain tumors. **J Neurooncol** 65:27–35, 2003.
36. Scherer HJ: The forms of growth in gliomas and their practical significance. **Brain** 63:1–35, 1940.
37. Sipos EP, Tyler B, Piantadosi S, Burger PC, Brem H: Optimizing interstitial delivery of BCNU from controlled release polymers for the treatment of brain tumors. **Cancer Chemother Pharmacol** 39:383–389, 1997.
38. Strasser JF, Fung LK, Eller S, Grossman SA, Saltzman WM: Distribution of 1,3-bis(2-chloroethyl)-1-nitrosourea and tracers in the rabbit brain after interstitial delivery by biodegradable polymer implants. **J Pharmacol Exp Ther** 275:1647–1655, 1995.
39. Szerlip NJ, Walbridge S, Yang L, Morrison PF, Degen JW, Jarrell ST, Kouri J, Kerr PB, Kotin R, Oldfield EH, Lonser RR: Real-time imaging of convection-enhanced delivery of viruses and virus-sized particles. **J Neurosurg** 107:560–567, 2007.
40. Terzis AJA, Thorsen F, Heese O, Visted T, Bjerkvig R, Dahl O, Arnold H, Gundersen G: Proliferation, migration and invasion of human glioma cells exposed to paclitaxel (Taxol) in vitro. **Br J Cancer** 75:1744–1752, 1997.
41. Valtonen S, Timonen U, Toivanen P, Kalimo H, Kivipelto L, Heiskanen O, Unsgaard G, Kuurne T: Interstitial chemotherapy with carmustine-loaded polymers for high-grade gliomas: A randomized double-blind study. **Neurosurgery** 41:44–49, 1997.
42. Weaver M, Laske DW: Transferrin receptor ligand-targeted toxin conjugate (Tf-CRM107) for therapy of malignant gliomas. **J Neurooncol** 65:3–13, 2003.
43. Weber F, Asher A, Bucholz R, Berger M, Prados M, Chang S, Bruce J, Hall W, Rainov NG, Westphal M, Warnick RE, Rand RW, Floeth F, Rommel F, Pan H, Hingorani VN, Puri RK: Safety, tolerability, and tumor response of IL4-Pseudomonas exotoxin (NBI-3001) in patients with recurrent malignant glioma. **J Neurooncol** 64:125–137, 2003.
44. Westphal M, Hilt DC, Bortey E, Delavault P, Olivares R, Warnke PC, Whittle IR, Jaaskelainen J, Ram Z: A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. **Neuro Oncol** 5:79–88, 2003.
45. Wong AJ, Bigner SH, Bigner DD, Kinzler KW, Hamilton SR, Vogelstein B: Increased expression of the epidermal growth factor receptor gene in malignant gliomas is invariably associated with gene amplification. **Proc Natl Acad Sci U S A** 84:6899–6903, 1987.
46. Wu MP, Tamada JA, Brem H, Langer R: In vivo versus in vitro degradation of controlled release polymers for intracranial surgical therapy. **J Biomed Mater Res** 28:387–395, 1994.
47. Yang MB, Tamargo RJ, Brem H: Controlled delivery of 1,3-bis(2-chloroethyl)-1-nitrosourea from ethylene-vinyl acetate copolymer. **Cancer Res** 49:5103–5107, 1989.