Investigational New Drugs **22:** 27–37, 2004.

Recent advances in brain tumor therapy: local intracerebral drug delivery by polymers

Christopher Guerin[1], Alessandro Olivi[1], Jon D. Weingart[1], H. Christopher Lawson[1] and Henry Brem[1,2]

[1]*Department of Neurosurgery, Johns Hopkins University School of Medicine, Baltimore, MD 21287, U.S.A.;* [2]*Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD 21287, U.S.A.*

Key words: interstitial therapy, Gliadel®, angiogenesis, chemotherapy, immunotherapy, radiosensitizers

Summary

New approaches to malignant glioma are being actively investigated. Local drug delivery directly to the site of the tumor is one novel approach that has been approved by the US FDA and other regulatory agencies worldwide. This agent, Gliadel®, delivers the chemotherapeutic drug carmustine (BCNU) from a biodegradable polymer placed in the resection cavity after brain tumor surgery. Gliadel® represents the first clinical application of polymer delivery for brain tumors, but the potential for this new methodology is far greater. In this review, we will briefly summarize the development of Gliadel® from a laboratory idea to its current role as an approved treatment for gliomas. Then we will present the most recent work being done to expand the potential benefits of polymeric delivery for brain tumors. This work includes trials for its use as the initial therapy for gliomas, as well as its use against metastasis. Further clinical trials exploring the maximum-tolerated dose and the combination of Gliadel® with systemic chemotherapeutic treatments such as temozolamide and O^6–benzylguanine will be reviewed. Finally, we will present preclinical work on the efficacy of polymeric methods for delivering other chemotherapeutic agents, and a variety of novel compounds that modify brain tumor biology. This latter work represents potential future clinical applications of local polymeric drug delivery to the brain and other sites where cancers can occur.

Introduction

The development of controlled release polymers is changing medical therapy, with applications in a number of diverse clinical areas [1]. Polymer-based drug delivery also has great promise for advancing the treatment of primary malignant gliomas. This disease has a median survival of under 1-year despite aggressive therapy with surgery, radiation, and chemotherapy [2]. Since 80% of gliomas recur within 2 cm of the original tumor, improved local control is needed [3]. The US Food and Drug Administration (FDA) approval of Gliadel® in 1996 represents the first new treatment approved for brain tumors in over 20 years. Gliadel® has also been approved by numerous regulatory agencies worldwide. Gliadel® is a polymer–drug combination that delivers the chemotherapeutic agent carmustine (BCNU) directly to the site of a brain tumor via controlled release from a biodegradable matrix. Drug-polymers are implanted directly into the brain in the tumor resection cavity. The promise of local delivery, however, lies in its potential to increase the therapeutic options for brain tumors by greatly expanding the number of drugs available for use. Currently, most systemically delivered drugs do not adequately penetrate brain tumor tissue because of residual blood–brain barrier function. Other drugs may enter, but require concentrations that result in systemic toxicity. Polymeric methods release drug at the tumor site for a prolonged period without significant systemic exposure. In addition to chemotherapeutic agents, a variety of other biologically active agents can be released in active form, further increasing the potential benefit to brain tumor patients. In

this review, we will first present the development and use of Gliadel®. Then, we will present developments in delivery of other compounds for brain tumors. Gliadel® is an example of a concept developed in the laboratory and brought to clinical practice. The newer agents are currently being investigated in the laboratory, and show great potential for future clinical use.

Review of Gliadel® development and current approved use

Gliadel® represents a successful collaboration between industry and academics. Funded through a NCI National Cooperative Drug Discovery Grant, the initial preclinical laboratory studies evaluated feasibility, toxicity, biodistribution, and efficacy. Clinical trials then evaluated safety initially, followed by randomized trials for efficacy. The data were evaluated by regulatory agencies, and Gliadel® is now available for use. Gliadel® is composed of 3.85% carmustine (BCNU) in PCPP-SA (PCPP-SA = poly-[bis-p-(carboxyphenoxy)propane-sebacic acid] copolymer in a 20:80 formulation; dimensions: diameter 1.4 cm; thickness 1.0 mm).

Preclinical testing

The first issue to be addressed was whether the polymer material itself was toxic to brain tissue. When compared to other standard neurosurgical implants (Gelfoam and Surgicel®; i.e. hemostatic materials routinely implanted in the brain during surgery), PCPP-SA in rat brain was nontoxic and biocompatible [4]. The localized inflammatory reaction was comparable to the Surgicel® resolved over 5 weeks, and was not associated with behavioral or neurological deficits or significant pathological changes in the animals.

Toxicity was further assessed in primates [5]. These animals received either empty polymers, or polymer containing carmustine (1,3-bis(2-chloroethyl)-1-nitrosourea; i.e. BCNU). A subset of animals also received radiation therapy because most brain tumor patients receive radiation after surgery. Animals were followed up to 6 months by clinical exam, computed tomography (CT) and magnetic resonance (MR) brain imaging, and eventual autopsy. No neurological or general deleterious effects were seen in any animal. Imaging studies did show early brain edema that later resolved. Pathology showed only the expected localized inflammatory changes. Concurrent radiation did not cause any adverse effects. Thus, the polymer–BCNU combination appeared nontoxic and biocompatible.

The biodistribution of chemotherapeutic agents released from polymer was determined in rabbit brain [6]. Using quantitative autoradiography, BCNU was detected in over 50% of the area of brain sections 3 days after implantation. BCNU tissue concentrations of 6 mM were generated 10 mm from the polymer at 3 and 7 days after implantation. Thus, polymeric delivery sustained significant drug concentrations at a localized site for an extended period [7].

Finally, preclinical efficacy was assessed in a standard rat model, the intracerebral 9L glioma [8]. Local polymer based-BCNU delivery was compared to standard systemic dosing and untreated controls. Local release resulted in a 5.4–7.3-fold increase in median survival, compared to 2.4-fold for systemic treatment (Figure 1). Moreover, approximately one-third of animals treated with polymer showed no viable tumor at scheduled autopsies at 4 months. Based on all the foregoing studies, the first clinical trials of local intracerebral chemotherapy for brain tumors were planned.

Rationale behind choice of drug and dose

One of the most common questions currently asked about Gliadel® development concerns drug choice. BCNU is lipophilic and thus has a favorable profile for brain tumor delivery by the systemic route. The polymer itself was a new drug, or at least a new device, and its effects on the brain were unknown. BCNU was a known quantity in that it was effective to some degree and had FDA approval for brain tumors. However, the local concentrations of drug were log orders higher than previous clinical usage and therefore needed to be explored clinically [7,9]. Thus, the basic scientific principle of minimizing unknowns led to the choice of BCNU for initial development. We have now learned that polymer-based delivery can be safe and effective. As will be seen later in this review, BCNU is only the beginning of polymer-based brain tumor therapy, with many other drugs in preclinical development.

The other common current question concerns the dose approved for use. This choice also results from the requirement of prospective decision-making. The next section will delineate this more fully, but the

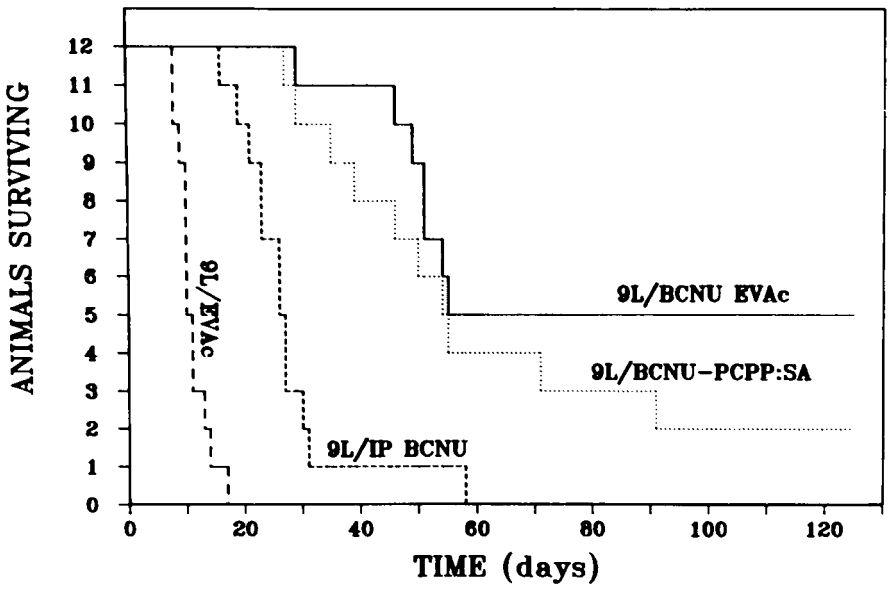

Figure 1. Survival curves of the groups bearing i.c. tumors treated with either systemic (9L-i.p. BCNU) or interstitial i.c. (9L-BCNU-PCPP:SA) BCNU. (Can Res, 53:329–333, 1993 reprinted with permission by Amer Assoc for Can Research, Inc.)

basic points are straightforward. Although higher doses had been used in laboratory animals, initial human uses started at much lower doses as is standard for a dose-escalation trial. Three doses were evaluated; the intermediate dose, 3.85% BCNU loaded, was chosen as the safest and potentially most effective dose [9]. Therefore, this dose was studied in the Phase III trial and subsequently received regulatory approval. Later in this review, we will present the rationale and some of the current data on the safety of further dose escalation.

Clinical trials for recurrent malignant glioma

The initial human study was a multi-institutional Phase I–II trial that included 21 patients treated at three different doses (1.93%, 3.85%, and 6.35% BCNU-loading) [9] (Figure 2A and B). All patients had recurrent unifocal, unilateral malignant gliomas after prior radiotherapy, with or without prior chemotherapy. No systemic effects of this local chemotherapy treatment were seen, and there were no adverse reactions attributable to the BCNU-polymer itself. Mean survival for increasing dosage groups was 65, 64, and 32 weeks, respectively. The overall mean period of survival was 48 weeks from implantation and 94 weeks from the initial operation. The only significant difference between groups was histology: 60% of the first two groups had glioblastoma, whereas all patients in the highest dose group had glioblastoma. This study showed the 3.85% loading to be safe and apparently effective, and therefore it was studied in a Phase III trial.

The Phase III prospective, randomized, placebo-controlled trial was conducted at 27 centers and studied 222 patients [10]. Patients were randomized to receive, at the time of surgery, polymer with BCNU or empty polymer. The rationale for this study randomization was to be able to identify the benefit of BCNU loaded polymers, Gliadel®, on survival. Since this was the first controlled, randomized trial looking at locally delivered chemotherapy, the investigator's goal was to evaluate the benefit of this therapy alone, thus it was not compared to another treatment, that is, systemic BCNU.

In the two study groups, there were no significant differences in histology, age of the patients, Karnofsky performance score, or other variables. Eligible patients: had unifocal, unilateral recurrent malignant glioma (verified pathologically during the trial surgery), required debulking as determined by the surgeon, had prior radiotherapy with or without prior chemotherapy, and had a Karnofsky score of at least 60 (i.e. independent function). Patients received debulking surgery followed by placement of either empty or 3.85% BCNU-loaded polymers.

Results showed a median posttreatment survival of 31 weeks for patients treated with BCNU-polymer

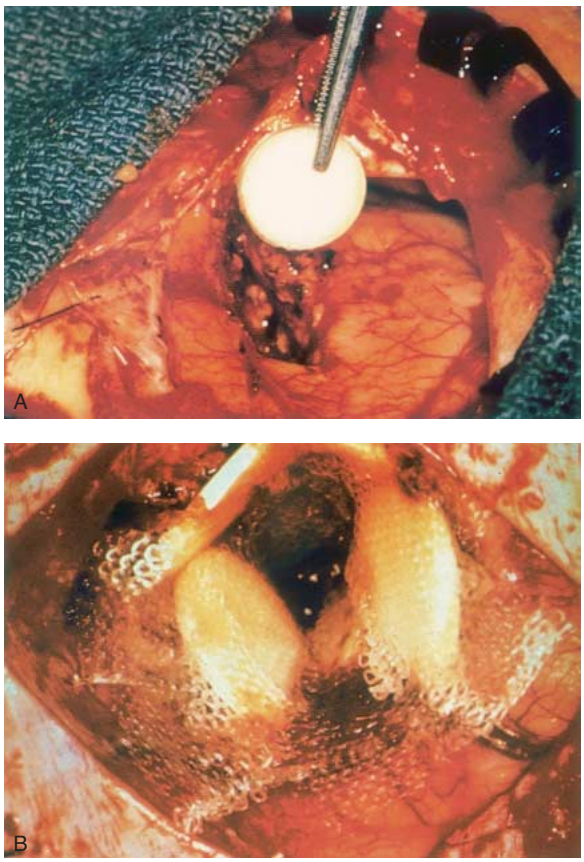

Figure 2. (A) A polymer wafer with BCNU being placed into a tumor resection cavity. (B) Multiple polymer wafers lining the surface of a resection cavity and being secured in place with Surgicel®. (Scientific American: Science & Medicine, 3: 52–61, 1996 reprinted with permission.)

versus 23 weeks for blank polymer (hazard ratio 0.67, $p = 0.006$). In the subgroup of patients with glioblastoma, 6-month survival was increased 60% in the BCNU-polymer group (64% vs. 44%, $p = 0.02$). There were no clinically significant adverse effects attributable to the BCNU-loaded polymers.

Gliadel® for initial glioma therapy. As a general principle of oncology, treatments effective at recurrence are usually more effective when used as initial therapy [11]. For gliomas, an added variable during initial treatment is radiation, which is recommended in all cases. While the primate study noted above showed no adverse interaction of radiation and BCNU-polymers, these animals did not harbor tumors. With this in mind, a Phase I study of Gliadel® used at initial craniotomy was performed at three centers in 22 patients [12]. All but one had glioblastoma. All received standard radiation therapy postoperatively, and none received additional chemotherapy in the first 6 months. There was no increased toxicity above that normally seen in patients receiving radiation after glioma surgery. Thus, initial therapy appeared safe, leading to the initiation of a Phase III placebo-controlled randomized blinded study [13].

Valtonen et al. [13] reported a prospective, randomized placebo-controlled study from Finland and Norway using Gliadel® or placebo as part of initial treatment, followed by standard radiotherapy. Thirty-two patients were enrolled in the study equally divided between the groups, and all completed the study. All placebo patients had glioblastomas. In the Gliadel® group 11/16 had glioblastomas. The treatment group had a lower initial median Karnofsky score (75 vs. 90 for placebo). Median survival was 58.1 weeks for the Gliadel® group, versus 39.9 weeks for placebo (hazard ratio 0.27, $p = 0.012$). When considering only the 27 patients with glioblastomas, median survival was 53.3 weeks with Gliadel® and 39.9 weeks with placebo (hazard ratio 0.28, $p = 0.008$). Moreover, of six patients alive at 2 years, five were in the Gliadel® group (31% 2-year survival vs. 6% for the control group), and four of these had glioblastomas. At 3 years, 25% of patients in the Gliadel® group were alive as compared to one of sixteen in the control patients. These studies strongly suggest that Gliadel® is safe and effective as initial therapy [13,14]. Based on the cumulative evidence above, Gliadel® was approved for use as initial treatment in the US by the FDA on February 25, 2003.

A second, larger placebo-controlled Phase III study to evaluated Gliadel® as the initial therapy of gliomas has been completed by the European Association of Neurological Surgeons [14]. In this study, 240 patients were randomized to treatment with Gliadel® or empty polymer at the time of initial treatment. Median survival was significantly increased to 14 months in the Gliadel®-treated patients compared to 11.6 months in the placebo arm.

Current approved use

These studies led to the 1996 US FDA approval of Gliadel® for use as an adjunct to surgery for treating recurrent glioblastoma patients and the 2003 US FDA approval of Gliadel® as initial therapy for patients with glioblastoma. This was the first new treatment for gliomas approved by the FDA in 23 years.

Numerous other countries have approved Gliadel® for initial treatment and recurrent treatment of brain tumors. Tumors should be unifocal and unilateral to benefit from this local therapy. Although the trials showed no differences in steroid requirements, BCNU-polymers do exacerbate cerebral edema after surgery. Thus, rapid taper of steroids postoperatively (p.o.) is not recommended. We typically continue high-dose steroid therapy (generally dexamethasone 4 mg p.o. qid) for 2 weeks postsurgery before beginning to taper the dose.

Recent advances in local intracerebral polymeric delivery

Metastases

Single brain metastases have been shown in randomized trials to respond to local treatment (surgical resection) followed by whole brain radiation [15]. Yet even in these cases a significant number of patients recur at the original metastatic site [16].

To begin investigating the potential role of local polymer-based chemotherapy, Ewend, et al. performed an extensive experimental study in a rodent model of brain metastasis [17,18]. Five histological types that commonly metastasize to brain in humans were studied: lung, breast, renal cell and colon carcinomas, and melanoma. PCPP-SA polymer was used to deliver three different chemotherapeutic agents: BCNU, carboplatin, and camptothecin. Each tumor–drug combination was tested both with and without radiation.

Several interesting findings were noted. First, a toxicity experiment (no tumor inoculum) showed that increasing the percentage of BCNU loading in combination with radiation could become toxic. Twenty percent loaded polymers alone were well-tolerated, but added radiation required a reduction to 10% loading to avoid toxicity. Analogous findings were seen with carboplatin. Second, while there was some variation among tumor–drug combinations, combined polymer chemotherapy and radiation was generally more effective than either modality alone. As expected, certain tumor lines were more sensitive to certain drugs, although all responded to BCNU-radiation.

Based largely on this study, two multicenter clinical trials of Gliadel® in metastatic disease have been initiated. The first is a Phase I study involving 25 patients and will determine the safety of Gliadel® treatment and radiation therapy in metastasis. The second study, funded by the NIH, will determine the safety and efficacy of interstitial chemotherapy for treatment of metastases without radiation therapy. The goal is to determine Gliadel's effectiveness and whether radiation therapy can be safely withheld in these patients. This study also highlights the promise of polymer-based therapy for delivery of a variety of agents that might ultimately be tailored to the chemosensitivity of an individual tumor, which we will discuss further below.

Dose escalation

Newer laboratory data led to reconsideration of the clinical dosing regimen. On re-evaluation of the initial Phase I dose escalating study, certain observations were noted. Since the highest dose group in the trial differed significantly in histology (all glioblastomas), a poorer outcome would be expected. Further statistical analysis showed no significant difference between the 6.8% loaded dose (11 patients) and the 10 patients treated with 3.85% loaded in the subsequent randomized study. Thus, we were uncertain whether we had achieved the maximum tolerated dose. As an initial means of addressing this issue, further investigative work was undertaken. In a study by Sipos et al. [19] two approaches were used to improve interstitial delivery of BCNU by polymers in the intracerebral 9L glioma model. First, the polymer half-life was prolonged by increasing the ratio of carboxyphenoxypropane (CPP) to sebacic acid (SA). Second, the percent drug loading was increased. All formulations were nontoxic to rat brain except the highest BCNU loading of 32%. Efficacy was not different between the two polymer ratios (20:80 as in Gliadel®, vs. 50:50 ratios). The best results were seen with 20% BCNU polymers, with a 75% long-term survival rate (>120 days) and 40-fold longer median survival than controls.

To determine whether further clinical trials were appropriate, we initiated primate studies with the highest dose chemotherapy polymer. Twenty percent BCNU polymers (20:80 CPP:SA ratio) were implanted into primates for short-term study of brain reaction in four animals, and long-term study in one [19]. One animal developed intermittent neurological symptoms with a small hematoma at the operative site. All other animals showed no sign of toxicity, and only the expected postoperative changes on brain histology. The long-term animal remained

behaviorally normal, and brain MRI at 150 days showed only expected postoperative changes. Fung et al. [7] reported a study of 20% BCNU polymer pharmacokinetics in primates. This analysis included thin layer chromatography to determine actual BCNU tissue concentrations. Significant BCNU tissue concentrations (0.1–7.5 μM) were found up to 2 cm from the polymer for up to 30 days. This 2-cm region is particularly relevant because 80% of gliomas recur within this volume. Tissue exposure to the BCNU area under concentration–time curve (AUC) was 4–1200 times higher (depending on distance from the implant) than that produced by intravenous administration.

With this information, a new human dose-escalation trial was begun [20]. Forty-four patients have been enrolled. Polymer loads were increased from 6.5% loading by weight to 28% loading by weight. Toxicity was assessed 1 month after implantation. Three of four patients treated with 28% loaded polymers developed severe brain edema and seizures. For this reason, nine additional patients were treated at the previous dose level, 20% loaded polymer, which confirmed this as the maximum tolerated dose (MTD). Maximum BCNU plasma concentrations with the 20% loaded polymers were 27 ng/ml. A Phase III trial is being planned.

5-Fluorouracil

Menei et al. [21] has recently reported that 5-fluorouracil (5-FU) delivered locally by a biodegradable polymer (poly D,L, lactide-co-glycolide) [PLAGA] is safe and achieves significant concentration in the cerebrospinal fluid. The median survival in their patients with glioblastomas was 98 weeks. Further clinical studies are planned. This work expands the role of polymeric treatment of brain tumors [22].

Preclinical studies: Polymer-chemotherapy

All of the above applications—recurrent glioma, initial glioma therapy, brain metastases, and further dose escalation—have shown how the idea of polymer-based drug delivery has been taken to clinical trials based on bench laboratory results. This process has already led to regulatory approval for recurrent glioma (U.S.A. Canada, Europe, South America, Israel, and South Korea), and initial use (Canada). Now we will review newer developments that have great potential to benefit patients by expanding polymer-based brain tumor therapy to other compounds.

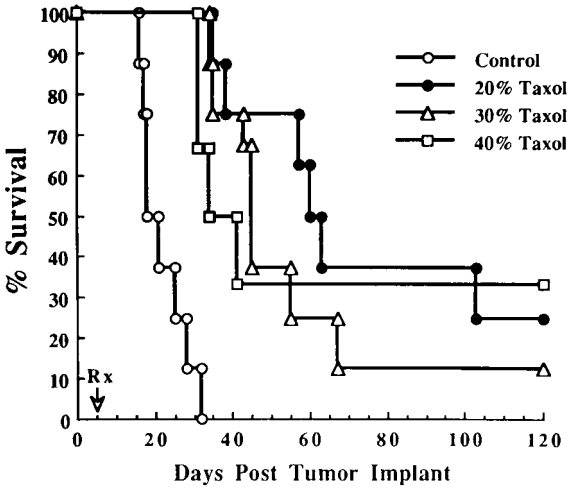

Figure 3. Kaplan-Meier survival curves for polymer-taxol efficacy. Rats received an intracranial 9L gliosarcoma tumor implant on day 0 and were treated on day 5 with an intratumoral implant consisting of a 10 mg dose of PCPP:SA (20:80) loaded with 20%, 30%, or 40% taxol by weight. Control animals received a 10 mg PCPP:SA (20:80) implant with no loaded drug. (Can Res, 54:2207–2212, 1994 reprinted with permission by Amer Assoc for Can Research, Inc.)

Taxol. Taxol binds microtubules and is another promising antineoplastic agent whose application to brain tumors is hindered by its inability to significantly enter brain tissue [23,24]. Using 20%–40% polymer loading, Walter et al. [25] reported that local taxol prolonged the survival of rats bearing intracerebral 9L gliomas by 1.5–3.2 fold, (Figure 3). Brain tissue taxol concentrations were several orders of magnitude higher than the 90% lethal dose *in vitro*, even at the brain periphery. Furthermore, these high concentrations were maintained at these distances for at least 30 days. Taxol in polymer was shown to be beneficial in treating intracranial tumors; whereas, systemic treatments of taxol were not effective. Thus, taxol is an example, in the laboratory, of a useful drug that is not effective when given by conventional methods, but is effective when delivered locally to the brain with polymer. Clinical trials with taxol microspheres are being initiated.

Camptothecin. This promising topoisomerase I inhibitor had demonstrated unexpected systemic toxicity in early human trials for malignancies in the 1970s [26–28]. Polymer-based application may allow its use by minimizing systemic exposure, and was investigated by Weingart et al. [29]. A variety of rat and human glioma lines were found to be sensitive

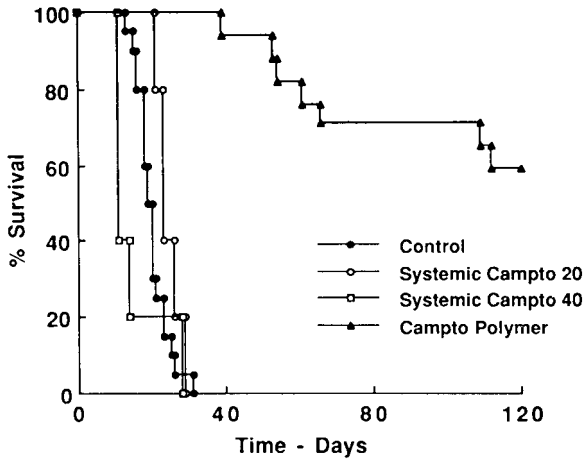

Figure 4. Kaplan-Meier survival curves comparing systemic delivery of camptothecin with local delivery with polymers. Rats received an intracranial (9L gliosarcoma implant on day 0 and treatment was initiated on day 5. Control animals and those treated with i.p. camptothecin received a 9 mg polymer implant with no loaded drug. Systemic camptothecin (campto) at 20 or 40 mg/kg/day was administered i.p. over 4 days, beginning on day 5. The campto polymer group received an intratumoral implant of EVAc containing 4.4 mg of camptothecin. Dosing was based on polymers weighting 8.8±0.5 mg, loaded with 50% camptothecin by weight. (Int J Cancer, 62(5): 605–609, 1995 reprinted with permission by John Wiley & Sons, Inc.)

to camptothecin *in vitro*. In the intracerebral 9L model, systemic administration was no different than control. Intracerebral injection was also ineffective. When treated by local polymer delivery, median survival in two experiments was 50 days and >120 days (59% still alive) (Figure 4). Newer camptothecins have been synthesized and some of which are being evaluated in the treatment of primary brain tumors are even more potent and may be candidates for polymer delivery to treat brain tumors.

Carboplatin. Platinum drugs crosslink DNA and have shown promise for a variety of brain neoplasms and are currently used to treat intracranial tumors in children, but are limited by systemic toxicity [30–33]. They are also water-soluble and thus do not enter brain tissue well. Local delivery minimizes both of these problems, making drugs like platinum ideal candidates for this new methodology. Using the intracerebral rat F98 glioma, the efficacy of polymer-based carboplatin was investigated [34]. The basic protocol is similar in all the experimental studies of local delivery discussed in this review. Animals receive intracerebral tumor implants, followed by placement of polymer at the tumor site, typically several days later. When compared to systemic delivery, polymer-based carboplatin was significantly more effective. The best median survival with systemic dosing was 36.5 days using 30 mg/kg/week compared to 53 days with 5% polymer.

4-hydroperoxycyclophosphamide (4HC). Cyclophosphamide is another water-soluble drug whose use for brain tumor is limited by systemic toxicity [35]. It is an alkylating agent that requires hepatic activation. 4HC is a pre-activated hydrophilic derivative of cyclophosphamide that spontaneously generates active metabolites. Judy et al. [36] investigated this derivative for efficacy by polymer release. 9L and F98 glioma cells were more sensitive *in vitro* to 4HC than to BCNU. Intracerebral gliomas responded best to 20% loaded 4HC polymer, with a median survival of 77 days (vs. 21 days for systemic BCNU treatment) and 40% survived for >80 days.

Local polymer-chemotherapy. These four examples demonstrate how polymer-based chemotherapy may be expanded to increase the armamentarium for glioma therapy. Each case suggests potential clinical usefulness for a promising drug that heretofore has not been effective because of poor drug delivery and/or unacceptable systemic toxicity. While still at the bench level, they represent one aspect of the future for clinical application.

Preclinical studies: Novel agents for brain tumor therapy

Another aspect of future applications regards novel compounds that alter brain tumor biology in a variety of ways. The potential number of such agents is unlimited, but each must be properly investigated to

determine the actual benefits and risks of local use. We will review a few of these novel approaches below.

Angiogenesis inhibitors. Recently, interest in agents that block tumor vascularization has been increasing with the discovery of more potent inhibitors [37,38]. The list of antiangiogenic compounds is now sizable [39]. However, most have biochemical characteristics that predict brain tumor delivery problems analogous to that seen with many chemotherapy drugs. Tamargo et al. [40] have shown that subcutaneous glioma growth can be inhibited by local polymer release of the antiangiogenic combination heparin–cortisone. As a technical issue, this study also demonstrated that two drugs can be released from the PCPP-SA polymer with biological efficacy.

Weingart et al. used polymer-based delivery to treat intracerebral rat gliomas with the established angiogenesis inhibitor minocycline [41,42]. This agent's antiangiogenic activity correlates with inhibition of matrix metalloproteinases, and thus it may also block tumor invasiveness [43,44]. Systemic minocycline administration was ineffective. Polymer treatment as monotherapy proved quite effective, but only if implanted simultaneously with the tumor, where it extended median survival from 13 to 69 days. In fact, half the animals survived till the study end at 200 days. In a more clinically relevant model, animals bearing intracerebral tumors underwent surgery for tumor resection followed by minocycline polymer implantation. (This model is directly analogous to the current clinical use of Gliadel®.) Median survival was increased 43% compared to empty polymer treatment (Figure 5).

A large number of papers now support a primary role of antiangiogenic therapy as an adjunct to chemotherapy or radiotherapy [45–49]. Along these lines, Weingart et al. [41] also studied the ability of local minocycline to enhance the effect of standard systemic BCNU chemotherapy. In this experiment, polymers were not implanted simultaneously, but rather into established tumors. Survival was increased 93% over that seen with BCNU alone. Thus, local delivery of antiangiogenic agents may retard glioma growth alone and synergistically with more standard treatments.

Radiosensitizers. Drugs capable of increasing tumor-cell radiation sensitivity have been known for many years. Their application to the brain also suffers from systemic toxicity and poor blood–brain barrier

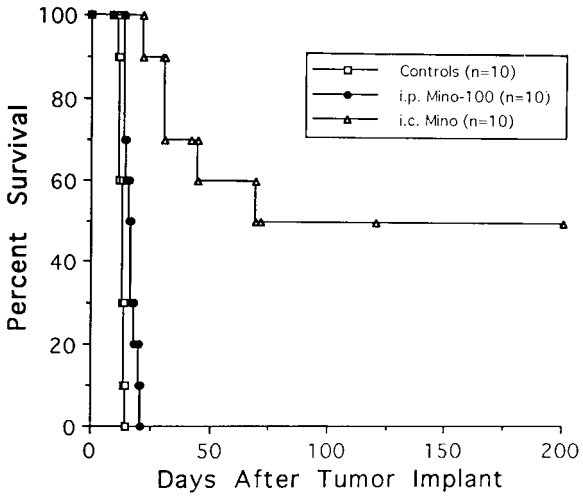

Figure 5. Graph illustrating survival curves for animals treated at the time of tumor implantation: i.p. Mino = intraperitoneal minocycline; i.c. Mino = intracranial minocycline in polymers. (J Neurosurgery, 82: 635–640, 1995 reprinted with permission.)

penetration [50]. Williams et al. [51] studied the potential for polymeric delivery of the halogenated pyrimidine IUdR (5-iodo-2′-deoxyuridine) to improve its efficacy. In a flank model, radiation caused a growth delay in U251 human glioma xenografts, but with implantation of IUdR polymers tumors actually regressed. Polymers adjacent to tumor were more effective than contralateral polymer implants. Since the extent of radiosensitization increases with the percentage of thymidine replacement in replicating DNA, Williams et al. [52] further investigated the ability of polymers to improve IUdR delivery to intracerebral gliomas [52]. Implantation of polymers at the intracerebral tumor site resulted in over 30% of cells being labeled with IUdR. In contrast, extracranial polymer implants labeled less than 15% of intracerebral tumor cells. In a related study, Cardinale et al. [53] showed that local polymer release of tirapazamine enhanced the effect of concomitant systemic tirapazamine in glioma radiosensitization. These studies suggest that clinical trials with local radiosensitizer treatment may show increased efficacy.

Immunomodulators. Immunotherapy is an evolving area of active research in brain neoplasms. Wiranowska et al. [54] reported polymeric release of interferon, a potent immunomodulator with anti-glioma activity. As a protein, interferon entry into brain tissue is severely restricted by the blood–brain barrier. This study showed that

interferon could be released from polymers into brain parenchyma and retain its bioactivity (the latter determined by the inhibition assay of viral cytopathic effect). Thus, intracerebral release of bioactive immunomodulators (and other proteins) is feasible.

Cytokine in combination with local chemotherapy. Sampath et al. [55] have reported that the combination of paracrine immunotherapy, with nonreplicating genetically engineered tumor cells that produce IL-2, and local delivery of chemotherapy by biodegradable polymers act synergistically against a murine brain tumor model. Microsphere polymers may also be used to release the cytokines. These findings are the basis of a planned clinical trial combining chemotherapy and immunotherapy.

Steroids. Though not a novel compound, corticosteroids do represent the drug most commonly used in the care of brain tumor patients. Steroids reduce brain edema, and many patients become chronically dependent to minimize their symptoms. Chronic systemic steroids cause many deleterious side effects including diabetes, hypertension, osteoporotic fractures, opportunistic infections, myopathy, and weight gain among others. Tamargo et al. [56] investigated local release of dexamethasone as a means of achieving the desired effect, brain edema reduction, without systemic drug exposure. Animals with intracerebral gliomas received dexamethasone polymer implants 5 days after tumor inoculation. Edema reduction by polymer was as effective as systemic dosing. However, the plasma steroid level was 16 times lower with polymeric delivery, and brain tissue levels were 19 times higher. Thus, this method may ultimately be developed to minimize the steroid-related morbidity seen in brain tumor patients.

Conclusion

A major problem limiting new drug treatment of brain neoplasms is poor tissue penetration. Drugs administered systemically may not reach effective concentrations in tumor tissue. Polymeric delivery directly to the tumor site is one solution to this problem. Local concentrations are dramatically increased, while systemic toxicity is minimized. The current use of Gliadel® as a new, effective agent in brain tumors demonstrates the feasibility of this approach. The ongoing challenge is to expand local delivery to the many other drugs (chemotherapy and myriad biological therapies) that may benefit these patients for whom no long-term survival can be reasonably expected with current treatments.

Disclosure

Under a licensing agreement between Guilford Pharmaceuticals and the Johns Hopkins University, Dr. Brem is entitled to a share of royalty received by the University on sales of products described in this work. Dr. Brem and the University own Guilford Pharmaceuticals stock, which is subject to certain restrictions under University policy. Dr. Brem also is a paid consultant to Guilford Pharmaceuticals. The terms of this arrangement are being managed by the Johns Hopkins University in accordance with its conflict of interest polices.

References

1. Brem H, Langer R: Polymer-based drug delivery to the brain. Sci Med July/August 3(4): 52–61, 1996
2. Black P: Brain tumors. Part 1 [see comments]. N Engl J Med 324(21): 1471–1476, 1991
3. Hochberg FH, Pruitt A: Assumptions in the radiotherapy of glioblastoma. Neurology 30(9): 907–911, 1980
4. Tamargo RJ, Epstein JI, Reinhard CS, Chasin M, Brem H: Brain biocompatibility of a biodegradable, controlled-release polymer in rats. J Biomed Mater Res 23(2): 253–266, 1989
5. Brem H, Tamargo RJ, Olivi A, Pinn M, Weingart JD, Wharam M, Epstein JI: Biodegradable polymers for controlled delivery of chemotherapy with and without radiation therapy in the monkey brain. J Neurosurg 80(2): 283–290, 1994
6. 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(4): 640–647, 1992
7. Fung L, Ewend M, Sills A, Sipos E, Thompson R, Watts M, Colvin O, Brem H, Saltzman W: Pharmacokinetics of interstitial delivery of carmustine, 4-hydroperoxycyclophosphamide, and paclitaxel from a biodegradable polymer implant in the monkey brain. Cancer Res 58(4): 672–684, 1998
8. Tamargo RJ, Myseros JS, Epstein JI, Yang MB, Chasin M, Brem H: Interstitial chemotherapy of the 9L gliosarcoma: Controlled release polymers for drug delivery in the brain. Cancer Res 53(2): 329–333, 1993
9. Brem H, Mahaley MS Jr, Vick NA, Black KL, Schold SC Jr, Burger PC, Friedman AH, Ciric IS, Eller TW, Cozzens JW, et al.: Interstitial chemotherapy with drug polymer implants for the treatment of recurrent gliomas. J Neurosurg 74(3): 441–446, 1991
10. 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 [see comments]. Lancet 345(8956): 1008–1012, 1995
11. Ettinger D: Evaluation of new drugs in untreated patients with small-cell lung cancer: Its time has come [comment]. J Clin Oncol 8(3): 374–377, 1990
12. 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(2): 111–123, 1995
13. 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(1): 44–48; discussion 48–49, 1997
14. 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-Oncology 5(2), 2003
15. Patchell R, Tibbs P, Walsh J, Dempsey R, Maruyama Y, Kryscio R, Markesbery W, Macdonald J, Young B: A randomized trial of surgery in the treatment of single metastases to the brain [see comments]. N Engl J Med 322(8): 494–500, 1990
16. Sawaya R, Ligon B, Bindal A, Bindal R, Hess K: Surgical treatment of metastatic brain tumors. J Neurooncol 27(3): 269–277, 1996
17. Ewend MG, Williams JA, Tabassi K, Tyler BM, Babel KM, Anderson RC, Pinn ML, Brat DJ, Brem H: Local delivery of chemotherapy and concurrent external beam radiotherapy prolongs survival in metastatic brain tumor models. Cancer Res 56(22): 5217–5223, 1996
18. Ewend M, Sampath P, Williams J, Tyler B, Brem H: Local delivery of chemotherapy prolongs survival in experimental brain metastases from breast carcinoma. Neurosurgery 43(5): 1185–1193, 1998
19. Sipos E, Tyler B, Piantadosi S, Burger P, Brem H: Optimizing interstitial delivery of BCNU from controlled release polymers for the treatment of brain tumors. Cancer Chemother Pharmacol 39(5): 383–389, 1997
20. Olivi A, Tatter S, Bruce J, Judy K, Engelhard H, Burak E, Hilt D, Grossman S, Fisher J, Piantadosi S: Toxicity and pharmacokinetics of interstitial BCNU administered via wafers: results of a Phase I study in patients with recurrent malignant glioma. 1999 Annual Meeting of the American Society of Clinical Oncology, 1999
21. Menei P, Venier MC, Gamelin E, Sant-Andre JP, Hayek G, Jadaud E et al.: Local and sustained delivery of 5-fluorouracil from biodegradable microspheres for the radiosensitization of glioblastoma: A pilot study. Cancer 86: 324–329, 1999
22. Brem H, Lawson HC: The development of new brain tumor therapy utilizing the local and sustained delivery of chemotherapeutic agents from biodegradable polymers. Cancer 86: 197–199, 1999
23. Rowinsky E, Burke P, Karp J, Tucker R, Ettinger D, Donehower R: Phase I and pharmacodynamic study of taxol in refractory acute leukemias. Cancer Res 49(16): 4640–4647, 1989
24. Klecker R, Jamis-Dow C, Egorin M, Erkmen K, Parker R, Collins J: Distribution and metabolism of 3H-taxol in the rat. Proc Am Assoc Cancer Res 34: 381, 1993
25. Walter KA, Cahan MA, Gur A, Tyler B, Hilton J, Colvin OM, Burger PC, Domb A, Brem H: Interstitial taxol delivered from a biodegradable polymer implant against experimental malignant glioma. Cancer Res 54(8): 2207–2212, 1994
26. Gottlieb J, Guarino A, Call J, Oliverio V, Block J: Preliminary pharmacologic and clinical evaluation of camptothecin sodium (NSC-100880). Cancer Chemother Rep 54(6): 461–470, 1970
27. Moertel C, Schutt A, Reitemeier R, Hahn R: Phase II study of camptothecin (NSC-100880) in the treatment of advanced gastrointestinal cancer. Cancer Chemother Rep 56(1): 95–101, 1972
28. Muggia F, Creaven P, Hansen H, Cohen M, Selawry O: Phase I clinical trial of weekly and daily treatment with camptothecin (NSC-100880): correlation with preclinical studies. Cancer Chemother Rep 56(4): 515–521, 1972
29. Weingart J, Thompson R, Tyler B, Colvin O, Brem H: Local delivery of the topoisomerase I inhibitor camptothecin sodium prolongs survival in the rat intracranial 9L gliosarcoma model. Int J Cancer 62(5): 605–609, 1995
30. Hannigan E, Green S, Alberts D, O TR, Surwit E: Results of a Southwest Oncology Group Phase III trial of carboplatin plus cyclophosphamide versus cisplatin plus cyclophosphamide in advanced ovarian cancer. Oncology 50(2): 2–9, 1993
31. Williams P, Henner W, Roman -GS, Dahlborg S, Brummett R, Tableman M, Dana B, Neuwelt E: Toxicity and efficacy of carboplatin and etoposide in conjunction with disruption of the blood–brain tumor barrier in the treatment of intracranial neoplasms. Neurosurgery 37(1): 17–27; discussion 27–28, 1995
32. VonHoff D, Schilsky R, Reichert C, Reddick R, Rozencweig M, Young R, Muggia F: Toxic effects of cis-dichlorodiammine-platinum(II) in man. Cancer Treat Rep 63(9–10): 1527–1531, 1979
33. Poisson M, Pereon Y, Chiras J, Delattre J: Treatment of recurrent malignant supratentorial gliomas with carboplatin (CBDCA). J Neurooncol 10(2): 139–144, 1991
34. Olivi A, Ewend MG, Utsuki T, Tyler B, Domb AJ, Brat DJ, Brem H: Interstitial delivery of carboplatin via biodegradable polymers is effective against experimental glioma in the rat. Cancer Chemother Pharmacol 39(1–2): 90–96, 1996
35. Allen J, Helson L: High-dose cyclophosphamide chemotherapy for recurrent CNS tumors in children. J Neurosurg 55(5): 749–756, 1981
36. Judy KD, Olivi A, Buahin KG, Domb A, Epstein JI, Colvin OM, Brem H: Effectiveness of controlled release of a cyclophosphamide derivative with polymers against rat gliomas. J Neurosurg 82(3): 481–486, 1995
37. O'Reilly M, Holmgren L, Shing Y, Chen C, Rosenthal R, Moses M, Lane W, Cao Y, Sage E, Folkman J: Angiostatin: A novel angiogenesis inhibitor that mediates the suppression of metastases by a Lewis lung carcinoma [see comments]. Cell 79(2): 315–328, 1994
38. O'Reilly M, Boehm T, Shing Y, Fukai N, Vasios G, Lane W, Flynn E, Birkhead J, Olsen B, Folkman J: Endostatin: An endogenous inhibitor of angiogenesis and tumor growth. Cell 88(2): 277–285, 1997
39. Folkman J: Angiogenesis and angiogenesis inhibition: An overview. EXS 79: 1–8, 1997
40. Tamargo RJ, Leong KW, Brem H: Growth inhibition of the 9L glioma using polymers to release heparin and cortisone acetate. J Neurooncol 9(2): 131–138, 1990
41. Weingart J, Sipos E, Brem H: The role of minocycline in the treatment of intracranial 9L glioma. J Neurosurg 82(4): 635–640, 1995
42. Tamargo RJ, Bok RA, Brem H: Angiogenesis inhibition by minocycline. Cancer Res 51(2): 672–675, 1991

43. Guerin C, Laterra J, Masnyk T, Golub LM, Brem H: Selective endothelial growth inhibition by tetracyclines that inhibit collagenase. Biochem Biophys Res Commun 188(2): 740–745, 1992
44. Liotta L, Steeg P, Stetler-Stevenson W: Cancer metastasis and angiogenesis: An imbalance of positive and negative regulations. Cell 63: 327–336, 1991
45. Teicher B, Sotomayor E, Huang Z: Antiangiogenic agents potentiate cytotoxic cancer therapies against primary and metastatic disease. Cancer Res 52(23): 6702–6704, 1992
46. Teicher B, Dupuis N, Robinson M, Emi Y, Goff D: Anti-angiogenic treatment (TNP-470/minocycline) increases tissue levels of anticancer drugs in mice bearing Lewis lung carcinoma. Oncol Res 7(5): 237–243, 1995
47. Teicher B, Holden S, Ara G, Dupuis N, Liu F, Yuan J, Ikebe M, Kakeji Y: Influence of an anti-angiogenic treatment on 9L gliosarcoma: Oxygenation and response to cytotoxic therapy. Int J Cancer 61(5): 732–737, 1995
48. Brem H, Gresser I, Grosfeld J, Folkman J: The combination of antiangiogenic agents to inhibit primary tumor growth and metastasis. J Pediatr Surg 28(10): 1253–1257, 1993
49. Mauceri H, Hanna N, Beckett M, Gorski D, Staba M, Stellato K, Bigelow K, Heimann R, Gately S, Dhanabal M, Soff G, Sukhatme V, Kufe D, Weichselbaum R: Combined effects of angiostatin and ionizing radiation in antitumour therapy. Nature 394(6690): 287–291, 1998.
50. Kinsella T, Russo A, Mitchell J, Collins J, Rowland J, Wright D, Glatstein E: A Phase I study of intravenous iododeoxyuridine as a clinical radiosensitizer. Int J Radiat Oncol Biol Phys 11(11): 1941–1946, 1985
51. Williams J, Dillehay L, Tabassi K, Sipos E, Fahlman C, Brem H: Implantable biodegradable polymers for IUdR radiosensitization of experimental human malignant glioma. J Neurooncol 32(3): 181–192, 1997
52. Williams J, Yuan X, Dillehay L, Shastri V, Brem H, Williams J: Synthetic, implantable polymers for local delivery of IUdR to experimental human malignant glioma. Int J Radiat Oncol Biol Phys 42(3): 631–639, 1998
53. Cardinale R, Dillehay L, Williams J, Tabassi K, Brem H, Lee D: Effect of interstitial and/or systemic delivery of tirapazamine on the radiosensitivity of human glioblastoma multiforme in nude mice. Radiat Oncol Investig 6(2): 63–70, 1998
54. Wiranowska M, Ransohoff J, Weingart J, Phelps C, Phuphanich S, Brem H: Interferon-containing controlled-release polymers for localized cerebral immunotherapy. J Interferon Cytokine Res 18(6): 377–385, 1998
55. Sampath P, Hanes J, DiMeco F, Tyler BM, Brat D, Pardoll DM, Brem H: Paracrine immunotherapy with Interleukin-2 and local chemotherapy is synergistic in the treatment of experimental brain tumors. Can Res 59: 2107–2114, 1999
56. Tamargo RJ, Sills AK Jr, Reinhard CS, Pinn ML, Long DM, Brem H: Interstitial delivery of dexamethasone in the brain for the reduction of peritumoral edema. J Neurosurg 74(6): 956–961, 1991

Address for offprints: Henry Brem, Johns Hopkins School of Medicine, Hunterian 817, 725 North Wolfe Street, Baltimore, MD 21205, U.S.A.; Tel.: 410-614-0477; Fax: 410-614-0478; E-mail: hbrem@jhmi.edu