Implantable Slow-Release Chemotherapeutic Polymers for the Treatment of Malignant Brain Tumors

Prakash Sampath, MD, and Henry Brem, MD

The polymeric delivery of chemotherapeutic implants shows promise in the treatment of patients with malignant gliomas.

Introduction

Approximately 13,000 new cases of primary malignant brain tumors are diagnosed each year in the United States.\(^1\) Despite significant advances in imaging, neurosurgery, radiation therapy, and oncology, the prognosis for most patients remains dismal. For patients with glioblastoma, median survival is still less than one year even after surgical resection, conventional external-beam radiotherapy, and systemic chemotherapy.\(^2\)\(^-\)\(^4\) In recent years, our efforts to improve survival for patients harboring malignant gliomas have centered on controlling local disease. This is based on clinical and experimental observations that most malignant brain tumors recur locally, within 2 cm of the original resection field,\(^5\) and that extracranial spread is exceedingly rare.

Improving treatment for malignant brain tumors has been hindered by the unique environment of the central nervous system (CNS). New chemotherapeutic agents, angiogenesis inhibitors, cytokines, and other anticancer therapies are often unable to cross the blood–brain barrier. Furthermore, significant systemic toxicity can result from administration of these agents in doses large enough to achieve efficacious concentrations in the brain. To overcome some of these limitations, strategies at improving delivery of therapeutic agents have become a major focus of brain tumor research.

The development of implantable polymers that release chemotherapeutic agents directly into the CNS has had an impact on glioma therapy.\(^6\)\(^-\)\(^8\) This technology makes it possible to achieve very high local concentrations of anticancer agents while minimizing systemic toxicity and circumventing the need for a drug to cross the blood–brain barrier. Clinical trials with systemic nitrosoureas have shown only modest improvement in patient survival\(^2\)\(^-\)\(^4\)\(^,\)\(^9\)\(^,\)\(^10\) and were associated with significant systemic toxicity. In this paper, we review the development of biodegradable, slow-release polymers and the basis for their use in the treatment of patients with malignant brain tumors. We then discuss the clinical use of the first FDA-approved, controlled-delivery polymer, Gliadel (Guilford Pharmaceutical Corp, Baltimore, Md), and comment on ongoing and planned clinical protocols with this delivery system. Finally, we briefly discuss other therapeutic agents that are currently in development for use in biodegradable polymers to treat brain tumors.

Polymer Technology
Implantable polymer matrices loaded with chemotherapeutic agents provide a novel approach to treating patients with intratumoral therapy. A number of biocompatible polymer systems have been developed that are capable of delivering chemotherapeutic agents when implanted in tissue. For brain tumors, the polymer is surgically implanted in the tumor resection cavity (Fig 1) and allows the drug to be delivered over an extended period of time in the peritumoral region where microscopic neoplastic cells may persist.

The first polymers developed for controlled drug delivery utilized a nonbiodegradable polymer matrix with incorporated micropores. The drug diffuses out of these polymers at a rate determined by the permeability of the release matrix and the diffusion properties of the drug itself. The prototypical polymers that work in this fashion are the hydrogels and ethylene-vinyl acetate (EVAc), first described by Langer and Folkman. Although these systems have found clinical application in glaucoma, asthma, and contraceptive therapy, they have had limited use as drug delivery vehicles in the brain. One drawback is that they remain as a space-occupying foreign body in the brain once the drug is dispersed.

Polymer used in Gliadel [p(CPP-SA) 20:80]

The polyanhydride, poly[1,3-bis(carboxyphenoxy)propane-co-sebacic-acid] (PCPP-SA) matrix is an example of a biodegradable polymer that is useful in treating brain tumors (Fig 2). Polyetherhydride biodegradable polymers offer several advantages over diffusion-controlled matrices. First, since the matrix degrades at a steady rate, the drug can be released over an extended period of time with a relatively steady concentration. Second, biodegradable polyanhydrides prevent hydrolytic breakdown of the chemotherapeutic agent, thus maintaining its desired cytotoxic effects. Third, the rate of degradation can be controlled depending on the relative ratios of monomers in the copolymer matrix. Consequently, the drug can be delivered over weeks, months, or years as needed. Finally, the polymers themselves degrade as they release the drug, minimizing the need for surgical removal after the drug has been released.

There are currently a number of polymeric systems designed to optimize local delivery. A second polyanhydride, the fatty acid dimer-sebacic acid (FAD-SA) copolymer, has been developed to deliver hydrophilic agents such as platinum drugs. The introduction of poly(lactide-co-glycolide) polymer allows chemotherapeutic agents as well as larger molecules to be incorporated into microspheres that can be stereotactically injected into the brain. Polyethylene glycol-coated liposomes that encapsulate antracyclines show promise as delivery agents that both decrease systemic side effects and improve the therapeutic indices of these drugs. Also, poly(lactide-co-glycolide) nanospheres can be covalently linked to a polyethylene glycol coating that reduces opsonization and elimination by the immune system before drug release. Finally, gelatin microspheres have recently been shown to release cytokines in vivo.

Gliadel

Nitrosoureas, including carmustine (BCNU), have been widely used for the treatment of malignant gliomas. Because of their relative lipid solubility and low molecular weight, these agents can penetrate the blood-brain barrier moderately well and can achieve tumoricidal concentrations in the brain with generally tolerable systemic doses. Nevertheless, marginal efficacy is commonly associated with severe toxicity such as myelosuppression and pulmonary fibrosis. A second polyanhydride, the fatty acid dimer-sebacic acid (FAD-SA) copolymer, has been developed to deliver hydrophilic agents such as platinum drugs. The introduction of poly(lactide-co-glycolide) polymer allows chemotherapeutic agents as well as larger molecules to be incorporated into microspheres that can be stereotactically injected into the brain. Polyethylene glycol-coated liposomes that encapsulate anthracyclines show promise as delivery agents that both decrease systemic side effects and improve the therapeutic indices of these drugs.

In an effort to improve the effectiveness of nitrosoureas against malignant gliomas, BCNU has been incorporated into polymers and delivered intracranially directly at the tumor site. In the laboratory, BCNU polymer preparations have been shown to release active drug in rat and rabbit brain for up to three weeks after implantation. Moreover, BCNU has been shown to diffuse widely from the polymer. Further pharmacokinetic studies in nonhuman primates (cynomolgus monkeys) with 20%–loaded BCNU polyanhydride polymer showed that BCNU concentrations in the brain achieved by polymeric delivery were four to 1,200 times higher than that produced by intravenous administration of drug. By using quantitative autoradiography and thin-layer chromatography, tumoricidal drug concentrations were detected 4 cm from the polymer implantation site one day after surgery, 2 cm on day 7 after surgery, and 1.3 cm 30 days later.

In preclinical in vivo studies, BCNU-loaded polymer significantly prolongs survival in rats challenged either intracranially or subcutaneously with 9L glioma when compared to intraperitoneal injection of drug. In animals in which BCNU was delivered from the EVAc polymer, flank tumor growth was delayed by 44% (16.3 days; P<0.05) when compared with control animals with empty polymer implants. In an established intracranial 9L glioma, local polymer implants loaded with 20% BCNU (using both EVAc and PCPP-SA) not only prolonged the median survival of the treated animals significantly when compared to empty polymer or intraperitoneal administration of BCNU, but also produced long-term survivors in the treated groups (range of 20% to 50% in different polymer formulations). Toxicity experiments in nonhuman primates (cynomolgus monkeys) with BCNU delivered from PCPP-SA polymers implants showed no evidence of significant systemic or neurologic toxicity even in conjunction with radiation therapy. Autopsies of these same animals revealed transient, mild, localized inflammation surrounding the polymer implants.

As a result of encouraging preclinical data, clinical trials were initiated using a BCNU polymer formulation. In a phase I trial of 21 patients who had failed standard therapy for gliomas and were undergoing reoperation, escalating doses of BCNU loaded in PCPP-SA polymer showed no evidence of systemic toxicity and no deleterious effect on neurologic performance (eg, Karnofsky performance). The mean survival after reoperation and implantation of BCNU-impregnated polymer for the five patients receiving 1.9% (by weight) BCNU loading was 65 weeks; the mean survival for the five patients receiving 3.8% BCNU was 64 weeks; and the mean survival for the 11 patients receiving 6.35% BCNU was 32 weeks. On the basis of these results, 3.8% loading was selected for phase III studies.
To evaluate the efficacy of Gliadel (3.8% BCNU in polyanhydride polymer), a randomized, placebo-controlled, double-blinded, prospective phase III clinical trial was carried out in patients with recurrent gliomas who had failed standard therapy. A total of 222 patients from 27 medical centers in the United States and Canada were entered. Enrolled patients received either Gliadel or "empty" placebo polymers implanted on the surface of the resected tumor cavity. The patients were equally distributed between the two groups for all known prognostic factors (eg, median age, neurologic function, prior treatment, median interval from first operation, number of previous operations, and tumor grade). The majority of patients (65.5% for the Gliadel group and 65.2% for the placebo group) had the highest grade tumor -- glioblastoma multiforme. Before enrollment, 52.7% of the BCNU group and 48.2% of the control group had undergone previous systemic chemotherapy and all patients had received conventional external-beam whole-brain radiation therapy. A few patients had received experimental immunotherapy or brachytherapy. Postoperatively, approximately 25% of patients underwent systemic chemotherapy (equally distributed in both groups).

Clinical Principles Associated With Gliadel Use

As clinical experience with Gliadel has increased, certain lessons for its usage have emerged. First, it is important to achieve maximal tumor debulking before insertion of the Gliadel wafers into the tumor resection cavity. Released chemotherapeutic agent, which kills residual tumor cells, can result in localized increased intracranial pressure from cerebral edema. Therefore, it is important to create as much space as possible at the time of surgical debulking and to exercise caution when using Gliadel in minimally debulked tumors.

Secondly, because the effective release of chemotherapy into the brain can cause edema in the surrounding brain, high doses of corticosteroids are recommended in all patients receiving Gliadel. Moreover, corticosteroids can maintain patients for at least three weeks after surgery, since it is in this period that the maximal amount of chemotherapy is being released from the polymer. In patients where edema is of particular concern or where there is postoperative neurologic deficit, we use supra-physiologic corticosteroid doses (as high as 120 mg of dexamethasone per day) and slowly taper the dose as clinically indicated. We have found minimal deleterious effects of extremely high corticosteroid doses administered for short periods of time. Blood sugar should be carefully monitored during such administration.

In assessing the adverse effects of Gliadel in clinical trials, it was found that intracranial or wound infections occurred more commonly in patients who received BCNU (4 of 110 patients who received Gliadel vs 1 of 112 patients receiving placebo). Although this difference was not found to be statistically significant, high doses of local BCNU can adversely affect wound healing. All patients who had a serious infection were found to have a prior CSF leak. Therefore, it is recommended that a watertight closure of the dura be achieved either primarily or with a dural graft. Furthermore, if a CSF leak does develop, vigorous rapid treatment should be initiated. By utilizing these measures, the rate of infection has fallen in subsequent clinical trials. In addition, we use preoperative and postoperative antibiotics for 24 hours in all patients who undergo craniotomy and Gliadel placement.

We have found that small openings into the ventricle do not preclude the use of Gliadel. Preclinical studies in rabbits did not demonstrate a risk of direct exposure of the ventricle to Gliadel. If there is a large opening of the ventricle, however, the wafer itself could enter the ventricle system and cause mechanical obstruction of CSF pathways, possibly leading to acute hydrocephalus. In this circumstance, Gliadel is not indicated, and other adjuvant therapies should be considered.

Patients receiving Gliadel should have anticonvulsants before surgery and should remain on therapeutic levels of these medications postoperatively. Clinical studies have shown postoperative seizures overall are not more common in patients receiving Gliadel, but they occur with greater frequency in the immediate postoperative period. This underscores the need to initiate anticonvulsive therapy in all patients preoperatively and to pay particular attention to serum drug levels, especially since corticosteroids can affect the anticonvulsant dose.
Ongoing and Planned Clinical Trials

Several clinical trials are now underway to evaluate the safety and efficacy of Gliadel in a variety of different clinical situations.

Recent studies in rats have demonstrated that increasing concentrations of up to 20% BCNU are more effective in prolonging survival than are lower doses and that 20% BCNU is not associated with increased toxicity. Further studies in monkeys have shown that 20%-BCNU-loaded polymer is well tolerated and yields effective prolonged distribution of intracranial BCNU. Therefore, even though the 3.8%-BCNU-loaded polymer is effective and has received Food and Drug Administration approval, a new clinical study has been initiated to determine the feasibility of using even higher doses intracranially (a New Approaches in Brain Tumor Therapy [NABTT-NIH] study). An open-label, multicenter, dose-escalation study is currently underway to evaluate the safety of Gliadel wafers containing between 6.5% and 20% BCNU in patients with recurrent glioma and to define at which level dose-limiting toxicity occurs.

Gliadel is also being evaluated for both safety and efficacy as a therapy for radioresistant metastatic brain tumors. Preclinical studies in murine models of intracranial metastatic melanoma, colon cancer, lung cancer, breast, and renal cell carcinoma demonstrate efficacy of BCNU-loaded polyanhydride polymers. In patients, current therapies have limited ability to control CNS disease, and many die of intracranial metastases despite aggressive multimodality treatment and good systemic control of disease. Furthermore, as improved systemic therapies become available, intracranial relapse may become more common. Therefore, it is hoped that Gliadel will be a useful addition to the armamentarium available for the treatment of CNS metastases. Two multi-institutional trials are currently underway.

The application of Gliadel for pediatric patients is promising in that most pediatric patients already receive adjuvant systemic chemotherapy for brain tumors. Currently, a phase I-II study is underway for pediatric patients with supratentorial malignant CNS tumors. A clinical study of the use of Gliadel in the posterior fossa is also planned.

In recent years, much work has been focused on chemotherapeutic resistance mechanisms expressed by various tumors. Tumor cells are known to exhibit differing susceptibility to BCNU based on their ability to repair drug-induced alkylation. The major repair pathway utilizes the enzyme alkylguanine-DNA alkyltransferase (AGAT). O6-benzylguanine (O6-BG) is an excellent substrate for AGAT and irreversibly binds to AGAT, thus diminishing the cells’ ability to repair alkylation. Studies both in vitro and in vivo have shown that O6-BG potentiates the cytotoxicity of BCNU in cells expressing AGAT. Since many human gliomas have AGAT activity, we have hypothesized that O6-BG will enhance the therapeutic effectiveness of locally delivered BCNU. To test this hypothesis, a phase I multicenter trial of Gliadel with prior intravenous administration of O6-BG in patients with recurrent malignant gliomas is being initiated (through the NIH).

Other Chemotherapeutic Agents

Several other chemotherapeutic agents delivered via controlled-release biodegradable polymer technology have been investigated in the laboratory, in preparation for clinical trials.

The camptothecin (CPT) class of drugs is composed of potent antitumor agents that exert their pharmacologic effect by inhibiting topoisomerase I during the S and G2 phases of the cell cycle. The sodium analog of camptothecin has been shown to have limited systemic efficacy and to penetrate the blood-brain barrier poorly, but it can be incorporated into polymers, thus markedly improving its bioavailability. Although potent in vitro against gliomas, sodium camptothecin was found to be ineffective when administered systemically or by direct injection to treat the rat 9L glioma. By contrast, when incorporated into polymers, sodium camptothecin showed significant prolongation of survival in a 9L intracranial rat glioma model. Fifty-nine percent of implant-treated animals survived beyond 120 days, whereas median survival for the control animals ranged from 20 to 32 days. The CPTs represent the most potent drugs to date in preclinical studies using local delivery. The recent development of more cytotoxic and stable CPT analogs will allow for the development of these drugs as effective cytotoxic agents that can be incorporated into polymers.

The taxoid group of anticancer agents, including paclitaxel (Taxol) and docetaxel (Taxotere), has been linked to microtubule stabilization, cell cycle block in the G2 phase, and cell death by apoptosis. Since taxoids do not readily cross the blood-brain barrier, they may be an ideal class of drugs to use with biodegradable polymers. Preclinical studies, Taxol and Taxotere exhibited marked cytotoxicity in brain tumor xenografts in vitro and in a rat intracranial 9L glioma model, delivery by biodegradable polymers prolonged survival 3.1 times over that in control animals.

A hydrophilic derivative of cyclophosphamide (Cytoxan), 4-hydroperoxy-cyclophosphamide (4-HC), spontaneously converts to the active metabolite of cyclophosphamide, 4-hydroxy-cyclophosphamide, and does not effectively cross the blood-brain barrier. This makes 4-HC an excellent candidate for local delivery. Preclinical studies demonstrate that 4-HC incorporated into an FAD-SA polyanhydride polymer matrix significantly prolongs survival in rats challenged with intracranial P98 gliomas. When compared to control rats receiving empty polymers, the median survival was extended from 14 days to 77 days.

Platinum-based drugs such as carboplatin and cisplatin represent another class of antitumor agents that have been incorporated into biodegradable polyanhydride matrices and have shown efficacy against intracranial rat gliomas in vivo. Adriamycin, an anthracycline antitumor antibiotic, and angiogenesis inhibitors such as heparin-cortisone and minocycline also have been incorporated into polymers and have shown great promise in preclinical studies. Since many of these agents exert their antitumor effect through a variety of mechanisms, it is hoped they can be used in combination with Gliadel.

Conclusions

Interstitial drug delivery via biodegradable polymers has significant clinical implications for the treatment of malignant brain tumors. It provides an effective means for bypassing the blood-brain barrier, it produces a high concentration of desired drug directly in the region of the tumor for an extended period of time, it protects the drugs from potential degradation, and it minimizes systemic adverse effects and toxicity of the drug.

To date, large-scale clinical trials on patients with malignant brain tumors have demonstrated that improved survival can be achieved in patients receiving biodegradable implants with BCNU when compared to control “empty” implants. As newer drugs become available for local delivery either alone or in combination, the challenge will be to improve on these initial results and develop treatment strategies that further enhance patient survival and quality of life. With the development of experimental therapies such as novel chemotherapeutic agents, immunotherapy or virus-mediated gene therapy, local delivery with biodegradable polymers will play an increasing role in the management of patients with malignant brain tumors.

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References


From the departments of Neurological Surgery (P.S., H.B.), and Oncology (H.B.) at The Johns Hopkins School of Medicine, Baltimore, Md.

Address reprint requests to Henry Brem, MD, at the Department of Neurological Surgery, Hunterian 817, The Johns Hopkins School of Medicine, 725 North Wolfe St, Baltimore, MD 21205.