

Local Treatment of Malignant Brain Tumors Using Implantable Chemotherapeutic Polymers

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Key Words

Brain tumor, chemotherapy, drug delivery, carmustine, Gliadel[®], glioblastoma, glioma, polymer

Abstract

Malignant gliomas are among the most devastating human cancers. The infiltrating nature of these malignancies makes complete surgical resection nearly impossible. Conventional therapy for malignant gliomas consists primarily of surgical debulking followed by radiation therapy and possibly chemotherapy. The major factor limiting intracranial therapeutic levels of systemically administered chemotherapeutics is the physiologic barriers of the brain. This has led to the development of novel methods of drug delivery such as implantable polymers containing chemotherapeutic agents. Several phase III clinical trials show that implantation of carmustine-containing biodegradable polymers prolongs survival in patients with both recurrent and newly diagnosed malignant gliomas. In this article, we summarize these trials and discuss ongoing clinical trials involving implantable chemotherapy-containing polymers in the treatment of patients with malignant gliomas. (*JNCCN* 2005;3:721–728)

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The World Health Organization recognizes over 100 different types of brain tumors.¹ These tumors can be classified broadly into primary or secondary tumors, depending on whether they originate in the central nervous system (CNS) or involve the CNS via secondary spread. In 2005, an estimated 18,500 new cases of primary brain and nervous system neoplasms will be diagnosed in the United States, and 12,760 patients will die of their disease.²

Approximately half of the newly diagnosed primary brain tumors are of glial origin. Astrocytomas are the most common glial cell neoplasm and represent a heterogeneous group of tumors that can vary from low-grade gliomas to the most common and most malignant primary brain tumor, glioblastoma multiforme (GBM). In addition to GBM, the term *malignant glioma* encompasses several different tumors, including anaplastic astrocytoma, gliosarcoma, anaplastic oligodendroglioma, and anaplastic oligoastrocytoma.

Conventional systemic chemotherapy for brain tumors has been limited by a lack of effective methods of drug delivery. The blood-brain and blood-cerebrospinal fluid barriers prevent therapeutic intracranial concentrations of chemotherapeutics despite toxic systemic levels. The limitations presented by these physiologic barriers of the CNS have led to the development of novel methods of drug delivery in the treatment of CNS malignancies.³ This article reviews the development of chemotherapy impregnated biodegradable polymers, summarizes the clinical trials investigating the safety and efficacy of these polymers in the treatment of patients with malignant gliomas, and highlights future developments of polymer-based chemotherapeutic approaches in the treatment of patients with malignant brain tumors.

Historical Perspective

In 1976, Langer and Folkman⁴ first reported the sustained and predictable release of macromolecules from an ethylene vinyl acetate copolymer (EVAc). A drug incorporated into this EVAc polymer is released via diffusion through the micropores of its polymeric matrix at a rate dependent on chemical properties of the drug such as molecular weight, charge, and water solubility. The primary limitation of these polymers is their non-biodegradability. After the incorporated drug is released, the matrix remains as a permanent foreign body.

Newer biodegradable polymers such as the polyanhydride poly[bis(p-carboxyphenoxy) propane-sebacic acid] (PCPP-SA) copolymer have been developed. Polyanhydride copolymers react with water to form dicarboxylic acids, leading to the sustained release of the incorporated drug. Thus, the drug is released primarily via polymer degradation. In addition to their biodegradability, these polymers exhibit several important properties. The hydrophobic nature of PCPP-SA copolymers not only protects the incorporated chemotherapeutic agents by shielding them from interactions with the surrounding aqueous environment, but also limits the breakdown of the polymer to its surface. This process, known as surface erosion, provides a nearly constant rate of drug release. Additionally, by altering the ratio of the 2 monomers, carboxyphenoxypropane and sebacic acid, the breakdown of the polymer, and consequently drug release, can be modulated to occur over a range of days to years. Finally, because these polymers degrade as they release their incorporated drug, there is no remaining foreign body left behind, and the polymer breakdown products are nonmutagenic, noncytotoxic, and nonteratogenic.⁵ The Gliadel Wafer (Guilford Pharmaceuticals, Baltimore, MD), which is used clinically in the treatment of patients with malignant gliomas, contains 3.85% carmustine [1,3-bis (2-chloroethyl)-1-nitrosourea, or BCNU] by weight in a 20:80 molar ratio of PCPP:SA.

The choice of BCNU in the development of a polymer-based local brain tumor chemotherapeutic agent was based on the well-known activity of nitrosoureas against malignant brain tumors. BCNU, a low-molecular-weight alkylating agent, is relatively lipid soluble and, therefore, capable of crossing the blood-brain-barrier. Although, as a systemic agent, this chemotherapy modestly prolonged survival in patients with brain tumors,^{6,7} its relatively short half-life after intravenous administration (15 minutes) cou-

pled with toxicity such as myelosuppression and pulmonary fibrosis posed significant challenges to its systemic administration. Given its potential efficacy against brain tumors and undesirable systemic toxicity, BCNU was incorporated into PCPP-SA copolymers and underwent preclinical testing.

Preclinical testing established the safety and biocompatibility of the polymer within the CNS^{8,9} and biodistribution and pharmacokinetic studies showed controlled and sustained release of BCNU from the PCPP-SA copolymers.^{10,11} Efficacy studies using a rat intracranial glioma model showed that local delivery of BCNU by polymers was superior to systemic administration and led to significant prolongation of animal survival.¹² Median survival was 62 days in animals treated with BCNU polymers compared with 27 days for animals treated with systemic BCNU, and 11 days in the untreated control animals.¹² Finally, toxicity studies performed in primates showed that BCNU polymers were well-tolerated and that concomitant external beam radiotherapy did not increase toxicity.¹³ Together, these preclinical studies established the safety and efficacy of BCNU polymers and the first human clinical trial of local intracerebral chemotherapy via an implantable biodegradable polymer was initiated.

Clinical Trials for Recurrent Malignant Glioma Therapy

The initial clinical study was a multi-institutional phase I-II trial that included 21 patients with recurrent malignant gliomas treated with three different doses of BCNU in PCPP-SA copolymers (1.93%, 3.85%, and 6.35% BCNU by polymer weight).¹⁴ Enrollment criteria included the presence of a recurrent unifocal, unilateral focus of tumor in the cerebrum showing at least a 1.5 cm³ enhancing volume on computed tomography (CT) scanning; a Karnofsky Performance Scale (KPS) score of at least 60; 1 course of external beam radiotherapy; and no chemotherapy during the 6 weeks before enrollment. After tumor removal, up to 8 polymers were placed in the resection cavity. The treatment was well-tolerated at all 3 BCNU levels, and none of the patient experienced signs of local or systemic toxicity. The overall median survival was 46 weeks after implant surgery and 87 weeks from the initial surgery; 18 (86%) of the 21 patients survived more than 1 year after intracranial implantation of the polymers. Although there was no

statistically significant difference in survival between the 3 groups, the highest dose appeared to be less effective, and therefore the 3.85% BCNU-loaded polymers were chosen for further clinical studies.

A phase III prospective, randomized, double-blind, placebo-controlled clinical trial of the PCPP-SA copolymer containing 3.85% BCNU by weight was conducted in 222 patients with recurrent malignant gliomas at 27 medical centers in the United States and Canada.¹⁵ Enrollment criteria included the presence of a unilateral single focus of tumor in the cerebrum showing at least 1.0 cm³ enhancing volume on CT or magnetic resonance imaging (MRI); a KPS of at least 60; completion of external beam radiotherapy; no nitrosoureas for 6 weeks; and no other systemic chemotherapeutic agent for 4 weeks before enrollment.

Patients were randomized to receive either BCNU polymers or placebo polymers after craniotomy for maximum tumor resection. The primary endpoint of this trial was survival from the time of polymer implantation. Secondary endpoints included complication rate and toxicity. Overall, the median survival of patients who received BCNU polymers was 31 weeks compared with 23 weeks for patients who received placebo polymers (hazard ratio 0.67; $P = .006$ after accounting for the effects of prognostic factors; Table 1). In the subgroup of patients who underwent surgery for GBM, 6-month survival was 50% greater in those treated with BCNU polymers compared with placebo (56% vs. 36%; $P = .02$). No clinically significant local or systemic adverse events attributable to the BCNU polymer were reported.

Together, these studies established that BCNU polymers were safe and effective in the treatment of recurrent malignant gliomas. In 1996, the Food and Drug Administration (FDA) approved Gliadel Wafers as an adjunct to surgery for treating patients with recurrent glioblastoma multiforme (Table 2). This represented the first new treatment for gliomas approved by the FDA in over 20 years.

Clinical Trials for Initial Malignant Glioma Therapy

Several studies have investigated BCNU polymers in the initial treatment of patients with newly diagnosed malignant gliomas. The initial study was a multi-institutional phase I clinical trial that included 22 patients with newly diagnosed malignant gliomas.¹⁶ All but 1 patient had a pathologic diagnosis of GBM. At surgery, 7 or 8 polymers containing 3.85% BCNU by weight were placed in the resection cavity after maximal tumor resection. All patients received standard radiotherapy postoperatively. None of the patients received additional chemotherapy in the first 6 months after tumor resection and polymer implantation. No perioperative mortality was seen, and none of the patients experienced any local or systemic adverse effects attributable to the implanted polymers. This study not only showed the safety of surgically implanted BCNU polymers as initial therapy for patients with malignant gliomas, but also established the safety of combining local chemotherapy and postoperative radiation therapy. Subsequently, two phase III clinical trials have been conducted.^{17,18}

Table 1 Selected Phase III Studies of Patients with Malignant Gliomas

Phase III Trial	Malignant Glioma	Schedule	n	GBM (%)		Median Survival		P value
				Treatment	Control	Treatment	Control	
Brem et al. ¹⁵ 1995	Recurrent	BCNU polymer vs. control polymer	222	66%	65%	31 wk	23 wk	.006
Valtonen et al. ¹⁷ 1997	New diagnosis	BCNU polymer + XRT vs. control polymer + XRT	32	69%	100%	14.5 mo	10 mo	.012
Westphal et al. ¹⁸ 2003	New diagnosis	BCNU polymer + XRT vs. control polymer + XRT	240	84%	88%	13.9 mo	11.6 mo	.03
Stupp et al. ³⁵ 2005	New diagnosis	Temozolamide + XRT vs. XRT	573	93%	92%	14.6 mo	12.1 mo	< .001

Abbreviations: xrt, radiation therapy.

Table 2 Current United States FDA-Approved Indications for Gliadel Wafers

Indication	Date Approved
Patients with recurrent glioblastoma multiforme as an adjunct to surgery	September 1996
Patients with newly diagnosed high grade malignant glioma as an adjunct to surgery and radiation	February 2003

Valtonen et al.¹⁷ reported on a phase III multi-institutional prospective, randomized, double-blind, placebo controlled trial of BCNU polymers in patients with newly diagnosed malignant gliomas. Inclusion criteria included a unilateral, unifocal intrinsic brain tumor not crossing the midline of at least 1.0 cm in diameter by CT or MRI; age between 18 and 65 years; KPS greater than 60; and histopathologic diagnosis of high-grade glioma on frozen section. Thirty-two patients were enrolled in this study and were randomized to receive either BCNU or placebo wafers. All but one patient in the study underwent standard postoperative radiotherapy. Although the study was originally planned to involve 100 patients, it was stopped after 32 patients because the drug was temporarily unavailable; no scientific reasons or emerging treatment differences were responsible for the study's premature termination.

The primary endpoint of the study was time from surgery to death. With all 32 patients included in the analysis, the median survival was 58.1 weeks for the active treatment group versus 39.9 weeks for the placebo group ($P = .012$; Table 1). In this study, all placebo-treated patients had a diagnosis of GBM, whereas only 11 of 16 patients receiving BCNU polymers had a diagnosis of GBM. For the subgroup of patients with GBM, the median survival was 53.3 weeks for the active treatment group and 39.9 weeks for the placebo group ($P = .008$). Three years after the termination of the study, 25% of the patients in the BCNU polymer group were alive compared with only 6% of the placebo-treated patients.

A second, larger phase III prospective, randomized, double-blind, placebo-controlled trial of BCNU polymers was conducted in 240 patients with newly diagnosed malignant gliomas at 38 centers in 14 countries.¹⁸ Eligibility criteria included an intraoperative diagnosis of malignant glioma; age between 18 and 65 years; MRI

evidence of a single, contrast enhancing unilateral, supratentorial, cerebral tumor; less than 2 weeks since baseline MRI; and KPS greater than 60. Patients were randomized to receive either BCNU or placebo wafers at the time of initial surgical resection; both treatment groups received standard radiotherapy postoperatively. In this study, 84% and 88% of the BCNU and placebo-treated groups had a diagnosis of GBM, respectively.

The primary endpoint of the trial was overall survival of the intent-to-treat (ITT) population 12 months after the final patient was enrolled. Secondary endpoints included time-to-progression, which was assessed by time-to-KPS decline, time-to-neurologic progression, and radiologic and clinical criteria.

Median survival in the ITT group was 13.9 months for the BCNU polymer group and 11.6 months for the placebo-treated group (log-rank P value stratified by country = .03), with a 29% reduction in the risk of death in the treatment group (Table 1). Time-to-decline in KPS and in 10 of 11 neuroperformance measures was prolonged in the BCNU polymer-treated group ($P < .05$). For the subgroup of patients with GBM, the median survival, when adjusted for baseline prognostic factors including age and KPS, was 13.5 months in the BCNU polymer treated group compared with 11.4 months in the placebo polymer group ($P = .04$, stratified log-rank statistic). Adverse events were comparable between the two groups except for CSF leak and late-occurring intracranial hypertension. These were more common in the BCNU polymer-treated patient population.

Meldorf et al.¹⁹ conducted an integrated analysis of the Valtonen et al.¹⁷ and Westphal et al.¹⁸ phase III clinical trials to determine the long-term efficacy of BCNU polymers in patients with newly diagnosed GBM. Of 234 patients in the combined data set, 112 received BCNU polymers and 122 received placebo wafers. Patients were matched demographically and for the number of polymers implanted. The hazard ratio for BCNU polymer treatment was 0.75 (95% confidence interval, 0.58–0.98; $P = .034$) which corresponded to a 25% reduction in the risk of dying. The median survival for patients treated with BCNU polymers was 13.1 months compared with 10.9 months for the placebo group ($P = .031$; log rank stratified by study).

Based on the above randomized clinical trial data, the FDA, on February 25, 2003, approved Gliadel Wafers for treatment of patients with newly diagnosed malignant gliomas as an adjuvant to surgery and

radiation. Currently, Gliadel Wafers are approved for use in the United States, Canada, and Europe in patients with newly diagnosed high-grade malignant gliomas as an adjunct to surgery and radiation and in patients with recurrent GBM as an adjunct to surgery (Table 2). Recently, the Centers for Medicare and Medicaid Services (CMS) announced a new Diagnosis Related Group (DRG) assignment for Gliadel Wafers. The new DRG (DRG 543), Implantation of Chemotherapeutic Agents or Acute Complex Central Nervous System Principal Diagnosis, took effect on October 1, 2004.

Ongoing and Future Clinical Trials

Dose Escalation

The above clinical trials used PCPP-SA copolymers containing 3.85% BCNU by weight. Preclinical animal studies showed that the efficacy of BCNU polymers can be improved by increasing the amount of BCNU in the polymers.²⁰ Concentrations ranging from 4% to 20% were well-tolerated in the rodent model, and primate toxicology studies confirmed that polymers with 20% BCNU by weight were well-tolerated intracranially.²⁰ Based on these data, a multi-institutional phase I trial was conducted in 44 adults with recurrent malignant gliomas.²¹ This study showed that higher amounts of BCNU given interstitially are well-tolerated and that the maximum tolerated dose of BCNU that can be implanted in polymers after resection of recurrent high-grade gliomas is 20%. A polymer with 20% BCNU provides 5 times more BCNU than the currently commercially available polymers. Maximum BCNU plasma concentrations with the polymers containing 20% BCNU were 27 ng/mL. Additional clinical trials comparing higher doses of locally delivered BCNU, either via polymers containing higher amounts of BCNU or implantation of larger numbers of polymers, will be necessary to determine the clinical effectiveness of this approach.

Brain Metastasis

Brain metastasis represents a significant source of morbidity and mortality in patients with systemic malignancies. In general, local recurrence rates after current treatment modalities including surgery, whole-brain radiation, and stereotactic radiosurgery range from 6% to 20%.²² Thus, the efficacy of local delivery of BCNU polymers is being investigated in the treatment of metastatic brain tumors. BCNU polymers have been

shown to prolong survival in animal models of metastatic brain tumors, including lung carcinoma, renal cell carcinoma, colon carcinoma, melanoma, and breast carcinoma.^{23,24} Preliminary results from a multi-institutional phase I-II trial showed that the combination of external beam radiation therapy (4,400 cGy) and the BCNU-polymer, after surgical removal of a single brain metastasis, resulted in no local recurrence in 25 patients.²⁵ In a single-institution study, 34 patients with newly diagnosed cerebral metastases were treated with MR-guided surgery, BCNU polymers, and radiation therapy (3,000–4,400 cGy).²⁶ The BCNU polymers were well-tolerated and no local recurrence was found in any of these patients, who had primary carcinoma of the lung, breast, colon, and melanoma. Taken together, these preliminary data suggest that the use of implantable polymers may provide local control superior to current approaches including surgery plus whole brain radiation therapy or radiosurgery. A phase III trial of BCNU polymers in patients with supratentorial brain metastasis is planned.

An important difference between the use of polymers for primary and metastatic tumors is the relatively smaller volume of metastatic tumors. Accordingly, 8 BCNU wafers may be required to line the tumor cavity for a primary malignant tumor, whereas 4 wafers may be sufficient for a metastatic tumor. As with malignant gliomas, the use of high-dose steroids, meticulous attention to anticonvulsant levels, and watertight dural closures reduces complications such as peritumoral edema, seizures, or CSF leaks, respectively.

Concomitant Inhibition of O⁶-Alkylguanine-DNA Alkyltransferase

Mechanisms of chemotherapeutic resistance are important factors in determining clinical response. A major mechanism of resistance to alkyl nitrosoureas is in the DNA repair protein, O⁶-alkylguanine-DNA alkyltransferase (AGT), which protects tumor cells from damage by removing DNA adducts before cytotoxic interstrand cross-linking can occur. O⁶-benzylguanine (O⁶-BG) is a substrate analogue that binds AGT, diminishing the ability of cells to repair alkylated DNA and thus potentiating the cytotoxicity of BCNU in cells expressing AGT.²⁷ The high incidence of AGT activity in human CNS tumors²⁸ coupled with the inverse relationship between survival and AGT levels in patients with malignant gliomas who receive

BCNU therapy^{29,30} provided the impetus to investigate strategies for AGT inhibition in combination with BCNU therapy.

Although O⁶-BG alone is nontoxic in humans, the combination of systemic BCNU and O⁶-BG results in dose-limiting bone marrow toxicity necessitating a reduction in the maximal dose of systemic BCNU that can safely be administered.^{31,32} In an attempt to take advantage of the potentiating effects of O⁶-BG on BCNU cytotoxicity while avoiding the systemic BCNU toxicity, Rhines et al.³³ investigated BCNU polymers in a rodent brain tumor model in which the animals were pretreated with systemic O⁶-BG. In this study, median survival was improved in the animals receiving the combination therapy compared with those receiving either O⁶-BG or BCNU polymers alone. Moreover, it was not necessary to reduce the amount of BCNU contained within the polymer when O⁶-BG was administered systemically. A phase I-II trial of BCNU polymers combined with systemic administration of O⁶-BG has been completed for patients with recurrent malignant gliomas³⁴ (J. Weingart, unpublished data), and a phase II clinical trial is currently underway (Table 3).

BCNU Polymers and Temozolomide

Recently, a phase III clinical trial showed that the addition of temozolomide to radiotherapy prolonged survival in patients with newly diagnosed GBM compared with radiotherapy alone (Table 1).³⁵ A phase I trial of BCNU polymers and temozolomide has been com-

pleted for patients with recurrent malignant gliomas,³⁶ and a phase II trial of combination therapy with BCNU polymers followed by radiation and temozolomide for patients at initial diagnosis of malignant gliomas was recently reported.³⁷ Additional studies investigating the combination of these active agents are currently underway (Table 3).

Other Studies

In addition to the clinical trials discussed previously, numerous trials involving BCNU polymers are ongoing, some of which are listed in Table 3. Moreover, the success of Gliadel Wafers has led to the development of additional other polymer-based antineoplastic treatment approaches using other conventional chemotherapeutic compounds, angiogenesis inhibitors, radiosensitizers, and immunomodulators. Other authors have provided more detailed information on preclinical analysis of these polymer-based treatment approaches for patients with brain tumors.³⁸

Conclusions

The delivery of therapeutics to CNS tumors has been a challenge. Overcoming the physiologic barriers of the brain has prompted the development of alternate routes of drug delivery. Implantable biodegradable chemotherapeutic polymers have facilitated the delivery of local therapeutic agents intracranially. Gliadel, the 3.85% (w/w) BCNU-loaded PCPP:SA copolymer, represents the first successful product of this technology. Clinical

Table 3 Selected Ongoing Phase II and III Clinical Trials with Gliadel Wafers			
Clinical Trial	Phase	Sponsor	Status
The PRECISE Trial: Study of Convection Enhanced Delivery of IL13-PE38QQR compared with Gliadel Wafer in Patients with Recurrent Glioblastoma Multiforme	III	NeoPharm, Inc.	Recruiting
Temozolamide During and Following External Beam Radiation Therapy in Patients With Newly Diagnosed Glioblastoma Multiforme Who Have Undergone Optimal Surgical Resection and Insertion of Gliadel Wafers	II	JHOC	Recruiting
Gliadel and O ⁶ -Benzylguanine in Patients With Recurrent Glioblastoma Multiforme	II	DCCC	Recruiting
Concomitant Gliadel Wafer and Iodine-125 Seed Implantation Following Surgical Resection for GBM or Gliosarcoma	II	UWMC	Completed
Gliadel and O ⁶ -Benzylguanine in Adult Patients with Recurrent Malignant Gliomas	I/II	NABTT	Completed

Abbreviations: DCCC, Duke Comprehensive Cancer Center; JHOC, Johns Hopkins Oncology Center; NABTT, New Approaches to Brain Tumor Therapy/National Cancer Institute; UWMC, University of Washington Medical Center.

trials have shown that this BCNU polymer is safe and effective in the treatment of both recurrent and newly diagnosed malignant brain tumors. Numerous clinical trials involving other new drug-polymer combinations are currently underway.

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