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CLINICAL–PATIENT STUDIES

Interstitial chemotherapy for malignant gliomas: the Johns Hopkins experience

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Abstract Malignant gliomas are very difficult neoplasms for clinicians to treat. The reason for this is multifaceted. Many treatments that are effective for systemic cancer are unable to cross the blood-brain barrier and/or have unacceptable systemic toxicities. Consequently, in recent years an effort has been placed on trying to develop innovative local treatments that bypass the blood-brain barrier and allow for direct treatment in the central nervous system (CNS)—interstitial treatment. In this paper, we present our extensive experience in using interstitial chemotherapy as a strategy to treat malignant brain tumors at a single institution (The Johns Hopkins Hospital). We provide a comprehensive summary of our preclinical work on interstitial chemotherapy at the Hunterian Neurosurgery Laboratory, reviewing data on rat, rabbit, and monkey studies. Additionally, we present our clinical experience with randomized placebo-controlled studies for the treatment of malignant gliomas. We compare survival statistics for those patients who received placebo versus Gliadel® as initial therapy (11.6 months vs. 13.9 months, respectively) and at the time of tumor recurrence (23 weeks vs. and 31 weeks, respectively). We also discuss the positive impact of local therapy in avoiding the toxicities associated with systemic treatments. Furthermore, we provide an overview of newer chemotherapeutic agents and other strategies used in interstitial treatment. Finally, we offer insight into some of the lessons we have learned from our unique perspective.

Keywords Carmustine·Gliadel® · Glioblastoma multiforme · Interstitial chemotherapy · Malignant glioma

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Introduction

In recent years, an increased understanding of the etiology and pathogenesis of many types of cancer has led to the development of innovative treatments. Advances in surgical techniques have allowed for surgical ''cures'' of many benign brain tumors [1]. However, malignant brain neoplasms remain among the most rapidly fatal cancers. Median survival for patients with malignant gliomas is still less than 1 year [2]. Prognosis for those with brain tumors remains poor largely because of the inability of therapy to prevent recurrence after surgical resection. The majority of lesions recur within 2 cm of the site of the initial tumor [3]. Novel approaches have been explored to improve the effectiveness of treatment.

The Hunterian Laboratory at the Johns Hopkins Hospital (JHH) was reestablished in 1984 to investigate brain tumors, examine their biological properties, and develop surgical treatments [4]. Researchers in the laboratory have explored the fundamental properties of brain tumors, such as angiogenesis, immuno-regulation, glucose transport, imaging properties, and novel approaches to delivery of effective agents to the tumor [5–10]. Given the refractory nature of primary malignant neoplasms, recent efforts in this laboratory have been devoted to innovative approaches to the management of malignant gliomas.

This report reviews our experience with interstitial chemotherapy in malignant glioma, from its initial conception and preclinical testing to the development of a novel delivery system for the treatment of patients with brain tumors. In 1996, the Food and Drug Administration (FDA) approved the first interstitial chemotherapy for malignant glioma, carmustine (BCNU) wafer (Gliadel® Wafer, Guilford Pharmaceuticals, Baltimore, Maryland). We review the laboratory findings upon which the clinical trials for Gliadel® were based, and we discuss our clinical experience at JHH over the past 19 years. In addition, we provide insight into future developments in this rapidly expanding field.

Preclinical studies

The initial focus of our research was to address two major problems with systemic chemotherapy in the treatment of brain neoplasms: first, that most agents are unable to cross the blood-brain barrier (BBB) to achieve therapeutic concentrations; and second, that standard approaches to achieve therapeutic concentrations of any drug within the central nervous system (CNS) increase the risk of systemic toxicity [11].

The development of devices for local delivery of chemotherapeutic agents directly to the tumor site solves some of the problems encountered with systemic chemotherapy. Surgical implantation of such devices circumvents the BBB and allows for higher concentrations of a given therapeutic agent directly to the site of a tumor, thus decreasing the likelihood of systemic side effects.

Finding the most appropriate chemotherapeutic agent and mode of drug delivery were critical steps in the development of Gliadel®. The first agent chosen for local delivery was a nitrosourea, 1,3-bis (2-chloroethyl)-1-nitrosourea (BCNU), which is used systemically for the treatment of brain tumors [1, 11, 12]. The first controlled release vehicle used in the Hunterian Laboratory was an ethylene-vinyl acetate (EVAc) polymer, which releases agents embedded in its matrix via diffusion [13]. This approach served as proof of principle that effective brain tumor treatments could be delivered to a tumor in a sustained, controlled manner [14, 15].

To improve on this polymer, we then explored a newly described biodegradable controlled-release polymer, a combination of *p*-carboxyphenoxypropane (pCPP) and sebacic acid (SA) [16]. This polymer has several advantages over previous local delivery systems in that its components are polyanhydrides—biodegradable compounds containing bonds that are hydrolyzed in aqueous environments. They can release embedded agents in a controlled fashion via surface erosion. By varying the percentage of pCPP and SA in the polymer, drug release times range from a few weeks to a few months [16]. The formulation that we initially explored was a polymer that contained 20% pCPP and 80% SA, which released the drug over a 2-week period.

Studies were conducted to assess the brain biocompatibility of this polymer formulation in animals [17, 18], as well as to determine the release and distribution of BCNU around the polymer implantation site. In vitro experiments determined that BCNU could be released from 40% drug-loaded EVAc polymers for 195 h. In vivo experiments in rats determined that EVAc polymers implanted into the brain released BCNU for more than 9 days with peak drug levels of 49.6 μg/g in the ipsilateral hemisphere of the brain, and only 1.14 μg/g in the contralateral hemisphere [19]. These data were supported by autoradiography studies with New Zealand white rabbits [20].

The pharmacokinetics of drug distribution, the safety of the polymer wafer, and the effects of radiation in combination with the polymer were evaluated in non-human primates. Carmustine-impregnated (20:80) pCPP:SA polymers were implanted into the brains of cynomolgus monkeys. No neurological or general adverse effects were seen in any of the groups, and it was concluded that these polymers were safe for use in the primate brain [21]. The pharmacokinetics of drug delivery from the polymer was then analyzed and mathematically modeled using data obtained in cynomolgus monkeys. To achieve the same delivery to the brain as polymer placement, intravenous administration of BCNU would need to be four times higher at 5 cm from the polymer and 1,200 times higher at the site of wafer implantation [22]. Furthermore, the effective exposure of BCNU, i.e. the area under the curve (AUC), was 5 cm from

the polymer at 24 h post-implantation, 3 cm at 3 days, and 1 cm at 30 days.

Effectiveness of the drug-polymer combination was determined in two experimental models. Initially, brain tumors transplanted to the rat flank were utilized to determine if the drug retained its biological activity in vivo against a growing tumor. After demonstrating its in vivo activity, an intracranial transplant of a 9L glioma was treated with the polymer-drug. Not only was the drug significantly more effective than the best systemic dosing, there was 30% long-term survival with no evidence of residual tumor. By contrast, in the control animals and those treated with systemic chemotherapy, there were no long-term survivors [14]. Encouraged by these laboratory studies, which showed the BCNU polymers to be safe and effective, we initiated a series of clinical trials to parallel these laboratory findings.

Clinical development of Gliadel®

Seven multi-institutional studies were initiated to assess the safety and efficacy of the BCNU/polymer formulation. Patients with newly diagnosed (3 studies) and recurrent (4 studies) malignant gliomas were enrolled in these clinical trials. Table 1 outlines the specific studies undertaken, with reference to the total number of patients and the number of JHH patients enrolled [23–27]. Because 94 patients (10%) were enrolled at JHH, we carried out ''subgroup analyses'' of survival statistics, as well as demographic and quality of life data for the Hopkins patient population.

Phase I, II BCNU polymer study for recurrent malignant glioma

Initially, a Phase I, II trial evaluated the dose and safety, as well as secondary information on efficacy of BCNU polymers in patients with recurrent malignant gliomas who had failed other therapies [26]. A total of 21 patients from 5 centers were enrolled in this study, with 8 of the patients enrolled at JHH. Eligibility criteria included: histologic diagnosis of malignant glioma; previous external beam irradiation; radiographic evidence of recurrent cerebral disease; Karnofsky performance scale (KPS) score of ≥ 60; no chemotherapeutic agents within 1 month of surgery (or 6 weeks for nitrosoureas); and need for surgical debulking of tumor. Patients were excluded if they had multi-focal or bilateral disease, if they had diminished blood counts, or if they were pregnant. Table 2 shows the 3 patient groups and doses used in the study. The groups had comparable demographics and similar baseline levels of neurological function as quantified by their KPS score.

Following surgical resection and BCNU polymer implantation, there was no evidence of systemic toxicity in any of the three treatment groups. Computerized tomography (CT) and magnetic resonance imaging (MRI) scans were notable for increased enhancement with minimal mass effect. This enhancement decreased in approximately 50% of patients during the first 7 weeks of the study. A transient decrease in KPS scores from baseline was observed postoperatively, which returned to baseline by week 7 of the study. This temporary post-implant decrease in

Table 1 Summary of carmustine polymer safety and efficacy studies

Study	Study design	Treatment (wafer)	No. of patients/ malignant glioma	No. of hospitals	No. of JHH patients
Brem et al. [26]	Phase I	BCNU	21/R	5	8
Brem et al. [27]	Phase III RCT	BCNU vs. placebo	222/R	27	35
Brem et al. [24]	Phase I	BCNU	22/I	3	10
Toxicity evaluation of BCNU polymers for recurrent glioma (Study 9115)	Phase III	BCNU	40/R	11	7
Valtonen et al. [30]	Phase III RCT	BCNU vs. placebo	32/I	4	–
Treatment IND: safety study of BCNU polymers for recurrent malignant glioma (Study 9501)	Treatment protocol	BCNU	349/R	170	28
Westphal et al. [31]	Phase III RCT	BCNU vs. placebo	240/I	38	–
Olivi et al. [29]	Phase I dose escalation	BCNU	44/R	11	6
Total patients			970		94

BCNU: carmustine; JHH: Johns Hopkins Hospital; RCT: randomized, controlled trial; R: recurrent; I: initial; IND: investigational new drugs

Table 2 Phase I study of carmustine polymers for recurrent glioma (adopted from Brem et al. [26])

Group	No. of patients (JHH patients)	BCNU loading (mg/wafer) (%)	BCNU per 8 wafers (mg)
Group I	5 (2)	3.85 (1.93)	31
Group II	5 (3)	7.70 (3.85)	62
Group III	11 (3)	12.7 (6.35)	102

BCNU: carmustine; JHH: Johns Hopkins Hospital

KPS score is typical for patients undergoing craniotomy for tumor resection when there are no chemotherapy implants. Seizure activity was observed only in patients with a history of seizures prior to BCNU-polymer implantation. Cerebral edema and steroid use were similar to those observed in standard post-craniotomy management.

Although survival was not a primary end point of this study, median survival was 48 weeks from implantation and 94 weeks from the initial resection. For JHH patients, median survival was 47 weeks from implantation and 96 weeks from initial resection [26].

The polymers were found to be safe, with no evidence of the systemic side effects usually associated with standard chemotherapy. Therefore, a phase III study was designed to evaluate the efficacy of these BCNU polymer implants.

Phase III BCNU polymer study for recurrent malignant glioma

In order to determine if the BCNU polymer was effective, we initiated a prospective, randomized, placebo-controlled study of 222 patients at 27 centers in the United States and Canada [27]. The 7.7 mg/wafer dose (3.85% loading) was chosen for this study, based on the favorable results for this group in the Phase I, II study [26]. Entry criteria were similar to those in the previous dose-escalation study. Enrollment included patients with recurrent malignant glioma who had previously been treated with external beam irradiation.

The BCNU-polymer group consisted of 110 patients, and 112 patients were treated with the placebo polymer. Median survival was 31 weeks in the BCNU group versus 23 weeks in the placebo group [27]. Multivariate analysis estimated a 33% reduction in the risk of death for the BCNU group (hazard ratio = 0.67, $P = 0.006$). The survival benefit of the BCNU group was maintained in the subgroup of patients with recurrent glioblastoma ($n = 145$), with 6-month survival rates of 56% vs. 36% ($P = 0.01$), respectively (Fig. 1).

Although improvement in survival was modest, this approach showed promise, given the dismal outcome for these patients with highly malignant tumors. Additionally, implantation of BCNU polymers did not lower overall neurological function. There were no significant decreases in blood cell counts associated with the BCNU polymers, nor was there evidence of neurotoxicity.

Data from 35 patients enrolled at JHH were similar to the overall study population. Demographic and survival statistics for the 35 patients enrolled are presented in Table 3. Seventeen JHH patients received BCNU polymers and 18 patients received placebo polymers. Six of patients enrolled in the BCNU polymer arm and 5 patients enrolled in the placebo arm had previously been treated with chemotherapy. Median survival was 42 weeks vs. 21 weeks for the BCNU polymer and placebo treatment arms, respectively.

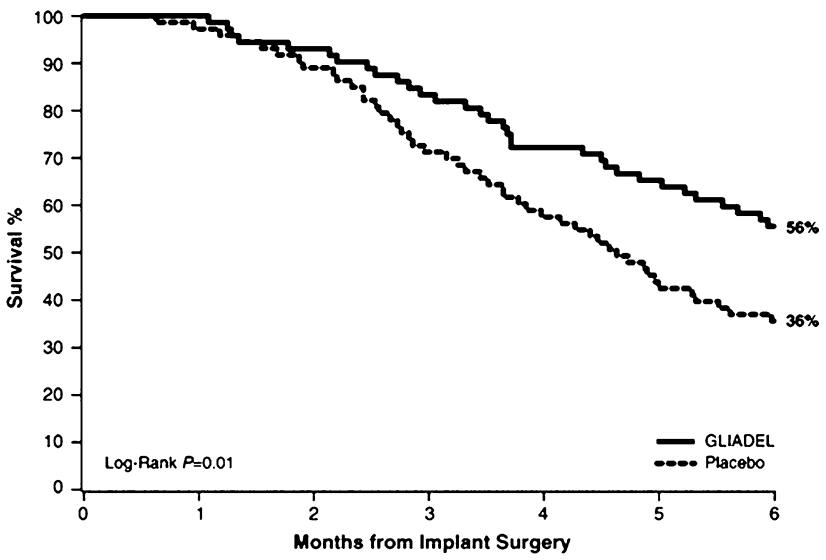

Fig. 1 Six-month Kaplan–Meier survival curves for patients with recurrent glioblastoma multiforme (Gliadel [prescribing information]: Baltimore, MD: Guilford Pharmaceuticals Inc.; 2003. Available at: http://www.gliadel.com/pdf/PI_03_01_04.pdf. Accessed September 8, 2004)

Table 3 Johns Hopkins Hospital patients enrolled in a phase III randomized, placebo-controlled study of carmustine polymers for recurrent malignant glioma: demographics and median survival

	Active group (n =17)	Placebo group (n = 18)
Mean age (years)	47	44
Mean KPS score	87	77
Mean baseline mini-mental score	28	27
Median survival (weeks)	42	21
Median survival for glioblastoma patients (weeks)	35	19

KPS: Karnofsky performance status

Eleven patients in the active group had postoperative seizures. All but one of these patients had preoperative seizures. In the placebo arm, 7 patients had postoperative seizures, 4 of whom had a history of seizures prior to surgery. Three of the patients in the carmustine group and 2 patients in the placebo group had postoperative wound or bone flap infections. These numbers are similar to those reported for patients requiring treatment for wound infections after reoperations without chemotherapy implants. Patients in both arms of the study required steroid therapy for cerebral edema. A compilation of significant adverse events in each treatment arm is shown in Table 4.

These studies validated the safety and efficacy of BCNU polymers for the treatment of recurrent malignant glioma.

Table 4 Johns Hopkins Hospital patients enrolled in a phase III randomized, placebo controlled study of carmustine polymers for treatment of recurrent malignant glioma: significant adverse events

Adverse event	No. of patient events	
	BCNU polyer arm (n = 17)	Placebo arm (n = 18)
Seizures	11[a]	7[b]
Wound infection/drainage	3	2
Headache	5	5
Lethargy	3	3
Hemiparesis/weakness	3	4
Deep vein thrombosis/pulmonary embolism	3	6
Dysphasia	2	6
Change in mental status/ confusion	4	4
Increased intracranial pressure	1	3

BCNU: carmustine

[a] Ten patients had history of seizures

[b] Four patients had history of seizures

Evaluation of toxicity: patients with recurrent malignant glioma

While the data from the previous study were being evaluated, an additional 40 patients were treated with the 3.85% BCNU polymers on a compassionate basis and for additional toxicity information. At JHH, 7 patients were enrolled and data were evaluated. Similar to the Phase III study for recurrent malignant glioma, mean age was 45 years, and mean baseline KPS was 86. Median survival was 68 weeks. One patient suffered a mild postoperative seizure, and one patient had a wound infection, treated with antibiotics.

In the period during FDA review of all study results, a Treatment IND (investigational new drugs) program was carried out to collect further safety and efficacy data. After reviewing data from the various clinical trials, on September 23, 1996, the FDA gave approval for BCNU polymers to treat recurrent glioblastoma as an adjunct to surgery. The polymers are currently commercially available as Gliadel®.

Dose escalation study of BCNU polymer wafer in patients with recurrent malignant glioma

The amount of BCNU loaded into the currently FDA-approved polymer is 3.85% or 7.7 mg/wafer. Laboratory studies have revealed that higher doses of BCNU may be even more efficacious in the treatment of malignant gliomas. In an experimental rat glioma, survival was significantly improved when doses were increased to 20 and 32% [28]. A Phase I trial for the escalation of BCNU in the polymer wafers to 28% (the maximum amount of drug that can be loaded using current commercial production techniques) has been completed. Olivi et al. [29] reported that elevated doses of up to 5 times that of Gliadel® were well tolerated. A phase III study with these higher doses is being planned.

Gliadel® wafer as initial therapy for malignant glioma

The initial studies with Gliadel® involved patients with recurrent disease who had the most advanced tumors with a poor prognosis. We then turned our attention to patients undergoing their first surgery for malignant glioma, postulating that they would receive this drug when it might have the most impact. In order to assess whether the BCNU polymers could be used as initial therapy, a Phase I, II study was conducted in the United States enrolling 22 patients from 3 hospitals, including JHH which had 10 patients enrolled. The

BCNU-polymer implants, given in conjunction with radiation therapy, were found to be safe when used as initial therapy for patients with malignant glioma [24]. Median survival was 42 weeks, with 8 patients alive at 1 year and 4 patients alive at >18 months. Bone marrow suppression or wound infection was not observed, and there were no perioperative mortalities. Median survival in this group of patients at JHH was 41.7 weeks.

Phase III European trials with Gliadel® wafer as initial therapy for malignant glioma

The FDA approved the use of Gliadel® for recurrent glioblastoma multiforme only, based on the relatively small number of newly diagnosed patients enrolled in the initial phase III trial. Therefore, two phase III, randomized trials were initiated in European patients at initial surgery for malignant glioma [30, 31]. A prospective, randomized, placebo-controlled trial was carried out by Valtonen et al. [30] in Europe to evaluate the role of Gliadel® in the initial treatment of malignant brain tumors. At the time of initial surgery, patients were randomized to receive Gliadel® or placebo polymer controls. For all patients, the surgery was followed by standard external beam radiotherapy (RT). Sixteen patients were randomized to each treatment arm. All 16 patients in the placebo arm and 11 patients in the Gliadel® arm were diagnosed with glioblastoma multiforme. Median survival improved from 40 weeks in the placebo group to 58 weeks in the treatment group ($P = 0.012$). One-, two-, and three-year survival were 56, 31, and 25%, respectively, for the Gliadel® group, and 19, 6, and 6% for the placebo group. When comparing only the 11 glioblastoma patients who received Gliadel® to the 16 patients who received placebo polymer, the median survival was 53 weeks in the Gliadel® group compared to 40 weeks for the control ($P = 0.008$).

Westphal et al. [31] conducted a large, randomized, controlled study in 240 newly diagnosed patients. Patients were randomized to treatment with surgical resection, Gliadel® wafer or placebo wafer implantation, and postoperative RT. Demographic data, including age, sex, and KPS were similar in both arms of the study. Median survival was 13.9 months for the Gliadel® group and 11.6 months for the placebo group ($P = 0.03$). There were 9 long-term survivors (>36 months from initial diagnosis) in the Gliadel® group and 2 in the placebo group. Of these long-term survivors, 7 of the patients in the Gliadel® group had anaplastic gliomas and 2 had glioblastomas. The 2 placebo patients had anaplastic gliomas.

In February 2003, Gliadel® received additional approval from the FDA for patients with newly diagnosed malignant glioma as adjunct to surgery and RT.

Initial malignant glioma: the Johns Hopkins experience

We previously reported on our experience at JHH with the use of this treatment modality for newly diagnosed tumors prior to RT [32]. Kleinberg et al. retrospectively evaluated 45 patients who had undergone Gliadel® wafer placement for newly diagnosed malignant gliomas at JHH between 1990 and 1999. They were evaluated for survival, postoperative infection, and pathology at reoperation. Twenty-eight patients received RT at Hopkins and were evaluated for toxicities during and 1 month after the completion of RT.

Median survival for glioblastoma patients was 12.8 months. Treatment for infection within 1 month of surgery and Gliadel® implantation was rare. Tissue was obtained for pathologic evaluation from 15 patients (33%) who had new contrast-enhancing lesions. Pathology revealed treatment effect or necrosis in 5 of these 15 patients (33%). Two patients with necrosis had a third surgery, which again revealed treatment effect/necrosis only. Neurologic symptoms including seizures, headache, lethargy, weakness, dysphasia, and nausea and vomiting were reported during RT by 19% of patients. Symptoms responded to steroid or anticonvulsant therapy. Thirty percent of patients experienced symptoms during steroid tapers, which resolved with increased doses. The authors concluded that Gliadel® is a safe and effective treatment for malignant gliomas in conjunction with surgery and RT. Patients require monitoring during steroid taper, and new enhancing lesions may represent tumor necrosis rather than recurrence and should be carefully evaluated prior to initiating further therapy.

Clinical lessons learned

Over the past 18 years that we have been using Gliadel® in the clinical setting, we have learned certain principles for how it can ideally benefit patients with malignant gliomas. We discuss treatment options for patients who require surgery in view of the clinical data and offer Gliadel® as a potential treatment, whether at initial presentation or for recurrent tumor.

A number of variables influence outcome and quality of life for patients undergoing surgery and Gliadel® treatment:

- Maximize tumor debulking before implantation of the polymer.
- Gliadel® should not be implanted into patients with large ventricular openings because of the potential risk of polymer dislodgment with resulting obstructive hydrocephalus.
- Watertight closure of the dura minimizes the risk of cerebral spinal fluid (CSF) leak and reduces the risk of infection.
- Prophylactic use of anticonvulsants is recommended for those patients with a history of seizures [33].

Additionally, steroids play an important role in the management of patients with Gliadel®. In the routine operation with a large decompression and no postoperative deficits, we use dexamethasone 4 mg intravenously/orally every 6 h for 2 to 3 weeks before tapering. It is important to maintain at least this level of steroids for this time period because the active chemotherapeutic drug is continuously being released and can be a source of cerebral edema. In patients who are not as well decompressed or have a neurological deficit, we increase the steroids as needed for the patients' optimal care [34]. We use doses of dexamethasone as high as 20 mg intravenously/orally every 4 h during this initial treatment period. These high doses allow patients to get through the period of maximal cerebral edema safely. Blood glucose levels need to be monitored during this treatment. This strategy has been highly effective in minimizing postoperative sequelae.

Current and future clinical studies

Laboratory studies in mice with metastatic brain tumors revealed that local chemotherapy is efficacious in the treatment of intracranial melanoma, colon carcinoma, and breast carcinoma [35]. With the addition of external beam RT, survival was prolonged in renal cell carcinoma, breast cancer, and lung carcinoma [35, 36]. Therefore, 2 multi-institutional clinical trials have been initiated for treatment of metastatic brain tumors. Thus far, results have been positive with 100% local control rates in newly diagnosed patients treated with surgery and Gliadel®, plus or minus RT [37–39].

Efforts to reduce the resistance of glioblastoma to BCNU are underway. Alkylating agents such as BCNU selectively target rapidly dividing cells by cross-linking DNA, which ultimately causes cell death. Alkyl-guanyl-DNA-alkyl-transferase (AGAT) is an enzyme that undoes cross-linking of DNA and thus provides a major mechanism of resistance to this chemotherapy. O^6-Benzylguanine (O^6BG) is a substrate analog that inhibits AGAT and defeats this mechanism of resistance [40]. However, treatment with systemic O^6BG and systemic BCNU leads to more side effects than does systemic treatment with BCNU alone [41]. Our laboratory studies have shown that BCNU-loaded polymer can become more effective with systemic delivery of O^6BG without producing additional toxicity [42]. A multi-institutional clinical trial is underway using Gliadel® in combination with systemic administration of O^6BG for treatment of recurrent gliomas.

Other laboratory investigations

Besides BCNU, other chemotherapeutic agents that could potentially be used to treat primary brain tumors cause significant systemic toxicity or do not effectively cross the blood-brain barrier. Figure 5 shows data for a number of agents used in experimental brain tumor models. For example, the microtubule stabilizer, paclitaxel (Taxol®, Bristol Myers Squibb, Princeton, New Jersey), is known to be effective against a variety of malignant cells, including glioblastoma, but does not effectively enter the brain [43, 44]. In rodent studies, this agent has been shown to be effective in treating malignant brain tumors [43]. Carboplatin, camptothecin, its analogs, 4-hydroperoxycyclophosphamide (4HC), and mitoxantrone have all had limited use in the CNS due to systemic toxicity. In our lab, these agents have been shown to prolong survival in experimental models [9, 45–49, 50].

Minocycline, a tetracycline derivative, is another agent that has been shown experimentally to have an anti-tumor effect. Local treatment with minocycline at the time of tumor implantation with use of EVAc polymers prolonged median survival time by 530% compared to treatment with placebo polymer ($P < 0.001$), and local treatment with minocycline after tumor resection increased survival time by 43% ($P < 0.002$) [10]. Treatment with minocycline delivered via pCPP:SA polymers at the time of tumor implantation resulted in 100% survival compared to the untreated controls that died within 21 days. Although treatment with the minocycline polymer 5 days after tumor implantation provided only modest increases in survival, a combination of intracranial minocycline and systemic BCNU extended median survival by 82% compared with BCNU alone [51].

In addition to the many chemotherapeutic agents that can be delivered locally to the brain, we have begun combining our drug-impregnated polymers with modulators of the immune system to stimulate a synergistic anti-tumor effect. Tumor cells that have been genetically

Table 5 Local delivery of chemotherapy in rats challenged intracranially with a lethal dose of tumor cells

Chemotherapeutic agent	Tumor line	Median survival (days)	Control median survival (days)	*P* values	References
4% BCNU	9L glioma	39.0	15.0	<0.001	Sipos et al. [28]
20% BCNU	9L glioma	[a]	15.0	<0.001	Sipos et al. [28]
32% BCNU	9L glioma	[a]	15.0	<0.05	Sipos et al. [28]
20% Paclitaxel	9L glioma	61.5	19.5	<0.001	Walter et al. [43]
5% Carboplatin	F98 glioma	86.5	23.0	0.004	Olivi et al. [45]
50% Camptothecin	9L glioma	[a]	19.0	<0.001	Weingart et al. [9]
20% 4HC	9L glioma	77.0	14.0	0.004	Judy et al. [48]
10% Mitoxantrone	9L glioma	50.0	18.5	<0.0001	DiMeco et al. [51]
10% BCNU + IL-2 Cells	B16 melanoma	[a]	15.8	0.0023	Sampath et al. [7]
10% BCNU + IL-2 Microspheres	9L glioma	45.5	18.0	<0.0001	Rhines et al. [52]

[a] For 20% BCNU, 32% BCNU, 50% Camptothecin, and 10% BCNU + IL-2 Cells, median survival was not reached. These experiments had 75, 50, 59, and 80% long-term survivors, respectively. Long-term survival is defined by animals that live > 120 days

engineered to secrete cytokines have been rendered replication-incompetent and injected stereotactically into animals challenged intracranially with a lethal dose of wild-type tumor cells. These cytokine-secreting tumor cells can produce an anti-tumor response alone or in combination with BCNU wafers [8]. In mice bearing a lethal dose of an experimental metastatic brain tumor, 10% loaded BCNU wafers in combination with replication-incompetent interleukin (IL)-2-secreting melanoma cells had a synergistic effect on median survival, compared with either therapy alone. Seventy percent of the animals treated with 10% BCNU polymers in combination with the IL-2 cells were long-term survivors while there were no long-term survivors in the control group (median survival, 15.8 days) as shown in Table 5 [7]. A synergistic effect on median survival was also noted when 10% BCNU wafers were combined with IL-2 delivered via polymeric microspheres, increasing median survival from 18 days (control) and 33 days (BCNU wafer therapy alone) to 46 days [52].

Microchip drug delivery is another method being developed. This delivery system has the potential to release multiple drugs in a controlled fashion, based on the electrochemical dissolution of anode membranes covering each drug reservoir [53]. Because the chip is an integrated circuit, thousands of combinations of drugs and kinetic release profiles can be programed into the circuit memory and delivered, providing a powerful new tool for closely modulated release of interstitial chemotherapy.

Conclusions

The preclinical studies with interstitial chemotherapy laid the groundwork for our patient clinical trials. We have demonstrated that patients with malignant brain tumors can be treated more effectively and safely with interstitial chemotherapy. The modest improvement in survival has been encouraging. However, this has also led to questions regarding what improvements can be made in drug delivery and effectiveness. With this in mind, we have continued to explore interstitial drug delivery in the following ways:

- Higher doses of BCNU (up to 5 times the current dose) in the polymer.
- Polymer preparations with different chemotherapeutic agents, antiangiogenic substances, and immune system modulators.
- Gliadel® delivered in combination with other drugs.
- Resistance modifiers (e.g., O^6BG) given systemically to enhance the effects of Gliadel®.
- Other local delivery applications, such as use of microchips.

We are encouraged that the increased clinical use of interstitial therapy will enhance our understanding of the role of this treatment and improve outcomes for patients with malignant brain neoplasms.

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