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The safety of interstitial chemotherapy with BCNU-loaded polymer followed by radiation therapy in the treatment of newly diagnosed malignant gliomas: phase I trial

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Abstract

The results of a multi-institutional phase I trial evaluating the safety of surgically implanted biodegradable 1,3-bis(chloro-ethyl)-1-nitrosourea (BCNU) impregnated polymer as the *initial therapy* for malignant brain tumors are reported. This is the first study of locally delivered BCNU and standard external beam radiation therapy (XRT) given concurrently.

Twenty-two patients were treated at three hospitals. The entry criteria were: single unilateral tumor focus larger than 1 cm^3; age over 18 years; Karnofsky Performance Score (KPS) of at least 60 h; and an intra-operative diagnosis of malignant glioma.

Twenty-one of twenty-two patients had glioblastoma multiforme. After surgery, seven or eight BCNU-loaded polyanhydride polymer discs (7.7 mg BCNU each) were placed in the resection cavity. Postoperatively, all patients received standard radiation therapy; none received additional chemotherapy in the first 6 months.

Neurotoxicity, systemic toxicity, and survival were assessed. No perioperative mortality was seen. Neurotoxicity was equivalent to that occurring in other series of patients undergoing craniotomy and XRT without local chemotherapy. Systematically, no significant bone marrow suppression occurred, and there were no wound infections. Median survival in this group of older patients (mean age = 60) was 42 weeks, 8 patients survived 1 year, and 4 patients survived more than 18 months.

Interstitial chemotherapy with BCNU-polymer with subsequent radiation therapy appears to be safe as an initial therapy. Several long-term survivors in this group of older patients with predominantly glioblastoma suggests efficacy in some patients. Dose escalation and efficacy trials are planned to further evaluate interstitial chemotherapy for the initial treatment of malignant gliomas.

Introduction

Recent studies have shown that BCNU, when delivered locally with surgically implanted polyanhydride polymer wafers, is both safe [1] and efficacious [2, 3] in patients who have a *recurrent* malignant glioma. These patients all received surgery and subsequent radiation therapy as their initial treatment. Many also received systemic chemotherapy. When their tumors recurred, the patients became candidates for locally delivered BCNU, termed interstitial chemotherapy.

This study was designed to evaluate interstitial chemotherapy with BCNU in combination with surgical debulking as the *initial therapy* for malignant gliomas. While BCNU-polymer has previously been shown to have minimal toxicity in patients with recurrent gliomas [1–3], radiation therapy had been completed months prior to polymer placement in all of these patients. No patient has received BCNU-polymer and subsequently undergone external beam radiation therapy. There have been reports of demyelination and blindness when nitrosoureas were given systemically in combination with radiation therapy [4], raising concern that locally delivered BCNU with concurrent radiation therapy would have significant toxicity. We therefore initiated a phase I study of these BCNU polymer implants as the *initial therapy* for malignant gliomas in order to address two issues: 1) the safety of utilizing BCNU polymer as the first-line therapy of malignant glioma; and 2) the possibility of additive neurotoxicity between BCNU and radiation therapy because of the radiosensitizing properties of BCNU.

Materials and methods

Patient selection

Patients were enrolled in the study from July 5th, 1990 to August 14, 1991. Three hospitals (Johns Hopkins Hospital, Columbia Presbyterian Medical Center, Charlotte Memorial Hospital) participated in the study and could enroll up to 10 patients each. In order to close the study and evaluate data in a timely fashion, when one center reached 10 patients, the study was closed. The treatment protocol was approved by the appropriate institutional review boards at each site.

Patients entered in the study met the following criteria: single, unilateral supratentorial brain tumor not crossing the midline and measuring at least 1 cm^3 in size as determined by computerized tomography (CT) or magnetic resonance imaging (MRI); 18 years of age or older; Karnofsky Performance Score (KPS) of 60 or higher (indicating ability to function independently); ability to give informed consent for experimental therapy before surgery; and pathologic diagnosis of malignant glioma either by a frozen section or squash preparation made during surgery. If these criteria were met, the BCNU polyanhydride wafers were implanted during the initial surgery.

Patients were excluded from the study for any of the following reasons: renal or hepatic disease as evidenced by a value greater than twice the upper limit of normal blood urea nitrogen (BUN), creatinine, serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), lactate dehydrogenase (LDH), or bilirubin; coexistence of another life-threatening condition such that the patient could not be reasonably expected to live 6 months after surgery; fewer than 100,000 circulating platelets/mm^3; fewer than 3,500 leukocytes/mm^3; positive pregnancy test; or hypersensitivity to intravenous contrast material to the extent that contrast-enhanced CT or MRI scans could not be obtained.

Patient evaluation

Each patient underwent a thorough work-up prior to surgery including history and physical with detailed neurologic examination, mini-mental state examination (MMSE), Karnofsky Performance Score determination, tumor imaging by CT or MRI, and laboratory examination. Laboratory tests included erythrocyte count, leukocyte count with differential, hemoglobin, hematocrit, platelet count, BUN, creatinine, sodium, potassium, chloride, uric acid, glucose, SGOT, SGPT, LDH, alkaline phosphatase, total bilirubin, albumin, and total protein. Urine evaluation included pH, specific gravity, sediment, protein, glucose, appearance, color, and microscopic evaluation.

All patients had CT or MRI within 72 hours of surgery. After recovering from anesthesia on the day of surgery, each patient underwent neurologic examination, MMSE, and KPS evaluation, which were repeated on the day of discharge. After discharge, patients were evaluated on approximately postoperative days 21, 60, 120, 180, and 210. At each scheduled follow-up visit, a neurologic examination

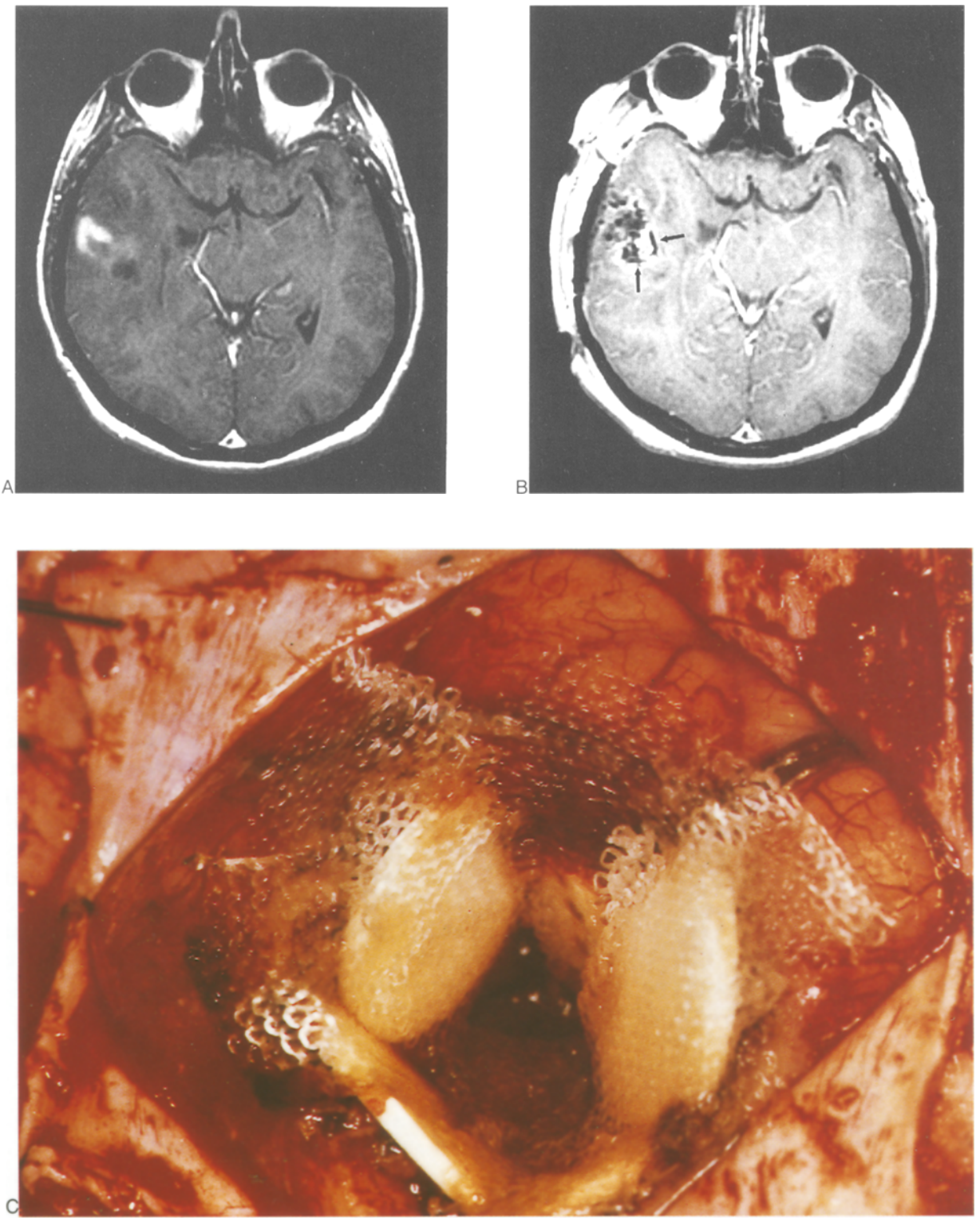

Fig. 1. Preoperative enhanced MRI (A) showing an enhancing right temporal mass. Postoperative enhanced MRI (B) showing the resection cavity with BCNU-polymer placement (arrows). Intraoperative photograph showing the resection cavity after (C) placement of the BCNU-polymer.

and laboratory evaluation was performed, KPS and MMSE were determined, and CT or MRI of the brain was obtained.

Treatment

All patients who entered the study underwent aggressive resection of the tumor mass. A resection cavity of at least 1.0 cm^3 diameter was required to place the polymer. During the surgery, frozen section or squash preparation of the tumor was obtained to establish the diagnosis of malignant glioma. Samples of all tumors were sent to the referee pathologist, Dr. Peter Burger, to confirm the diagnosis postoperatively. After maximal tumor removal was accomplished, meticulous hemostasis was achieved. A maximum of eight BCNU-loaded polyanhydride polymer wafers were placed over the resection surface (Fig. 1). Overlapping of polymers was allowed. Hemostatic agents such as microfibrillar collagen (Avitene®, MedChem Products, Inc, Woburn, Massachusetts) were used along the brain surface when necessary. Material such as absorbable gelatin sponge (Gelfoam®, UpJohn Pharmaceutical Company, Kalamazoo, Michigan) or oxidized regenerated cellulose (Surgicel®, Johnson and Johnson, New Brunswick, New Jersey) were occasionally used to cover the polymers and keep them in place on the brain surface. The dura was closed in a water-tight fashion.

Radiation therapy

All patients underwent standard external beam radiotherapy once they had recovered from surgery. In order to ensure that each study patient received optimal radiation therapy, the radiation protocol was determined by the treating radiation oncologist at each center on a patient by patient basis.

Polymer

GLIADEL®, the polyanhydride polymer used, is a copolymer of poly-carboxyphenoxypropane and sebacic acid anhydride in a ratio of 20:80. The methods of preparation are described elsewhere [5–9]. Briefly, polymer and BCNU (1,3-bis(chloro-ethyl)-1-nitrosourea) were co-dissolved in methylene chloride and spray-dried into microspheres. These microspheres were pressed into discs 1.4 cm (diameter) by 1.0 mm (thickness) by compression molding, packaged in aluminum foil pouches under nitrogen atmosphere, and sterilized by 2.2 megaRads of gamma irradiation. Loading with 50 μg BCNU/mm^2 of polymer (3.85% BCNU loading) yielded 7.7 mg of BCNU per wafer for a maximum dose to each patient of 62 mg of BCNU. The polymers were manufactured by Stolle R & D, Inc., Cincinnati, OH and were supplied by Nova Pharmaceutical Company, Baltimore, Maryland.

Analysis

The primary outcomes of this trial were neurological complications, system complications, infections, and measures of functional status including neurological examination, KPS, and MMSE. Survival was calculated as a secondary measure. Events were censored if a patient was still alive on September 14, 1994. When a patient was lost to follow-up, events were censored as of the last date of contact.

Complications incurred by individual patients were compiled and summarized. For each postoperative event, the attending physician graded the severity (severe, moderate, or mild) and determined whether or not the event could be related to the BCNU wafer. Standard Kaplan-Meier survival curves were determined for each center and for the entire patient group.

Re-operation

Patients underwent re-operation for standard clinical indications such as worsening neurological deficit or increasing steroid requirement in combination with radiographic evidence of tumor recurrence or increasing mass effect. Standard hematoxylin and eosin staining of tissue removed at re-operation was performed. In addition, any resid-

ual polymer fragments were analyzed both at the Johns Hopkins Hospital and at The Nova Pharmaceutical Company. The extent of hydrolysis of the polyanhydride polymer matrix was determined, and any active BCNU retained in the polymer was identified.

Results

Study population

A total of 22 patients were enrolled in the study. Ten were entered at Johns Hopkins Hospital and six each at Columbia-Presbyterian Medical Center and Charlotte Memorial Hospital. There were 15 men and 7 woman, and the average age was 60 (range 42–86 years). Twenty-one patients were right handed. A violation of the protocol occurred when a patient with an initial KPS of 40 was enrolled in and completed the study. Another patient was taken to the operating room after consenting to enter the study and meeting the preoperative entrance criteria. At the time of surgery, however, the intra-operative pathology appeared consistent with glioma but a definitive diagnosis of malignant glioma could not be made. That patient did not receive polymer implants and was not included in the study.

Six patients had a past medical history of hypertension, and two had diabetes mellitus.

The most common complaint at the time of presentation was headache (10/22). Patients also were noted to have aphasia (7/22), hemiparesis (6/22), seizures (5/22), dizziness (4/22), and confusion (3/22). Other complaints occurring less commonly included visual field loss, sensory changes, personality changes, lethargy, ataxia, nausea, and dysarthria.

At the time of evaluation for entry into the study, 16 of 22 patients had been started on dexamethasone. Sixteen had also been started on medication to prevent or control seizures. The 5 patients in whom seizures were a presenting symptom were all treated with anti-convulsants at the time of surgery.

Baseline preoperative neurologic examination most frequently revealed focal weakness (9/22), dysphasia (7/22), lethargy (5/22), and visual loss (3/22). Four patients had normal exams. Mean baseline KPS was 84.3, and mean baseline MMSE was 26.3/30.

Twelve of 22 tumors were in the left hemisphere; 10 were on the right. Four tumors extended into more than one lobe, with 6 tumors in the frontal lobe, 11 in the temporal lobe, 8 in the parietal lobe, and 1 in the occipital lobe. Average estimated tumor volume was 44.3 cm^3.

Surgery

Of the 22 craniotomies performed, 22 were uncomplicated. Two cases discussed below had postoperative morbidity, but made full recoveries. There were 5 lobectomies, 3 total resections, and 14 subtotal resections. The estimated percentage of resection of the enhancing tumor mass for all patients averaged 95%. Either seven (4/22 patients) or eight (18/22 patients) polymer discs were placed in each patient. The average anesthesia time was 5 hours 25 minutes, and the median length of hospital stay was 8 days.

Pathology

Review of the pathology by the referee pathologist confirmed the diagnosis of malignant glioma in all patients. No disagreements between the original pathologic diagnosis and that of the referee pathologist were seen. Pathologic examination revealed that 21 patients had glioblastoma multiforme, and one had anaplastic astrocytoma. One patient, who had a glioblastoma diagnosed at the time of his craniotomy for polymer placement, had previously had a stereotactic biopsy of the same lesion, which revealed an oligodendroglioma. The patient received no treatment at that time. When the lesion progressed radiographically, he was entered in the study and received BCNU-polymer after the frozen section revealed a Grade IV glioma.

Postoperative morbidity and mortality

There were no deaths in the perioperative period.

The earliest death occurred 132 days after surgery. Two patients had complicated postoperative courses. One patient required reoperation 2 days later to remove a hematoma which was exerting mass effect. Five of seven polymers placed during the initial craniotomy were removed along with the blood clot. This patient made a full recovery, was discharged home 20 days after surgery, and survived 58 weeks postoperatively. A second patient developed headache, seizures, and lethargy 10 days after surgery. The patient required intubation. CT scan revealed peri-tumoral edema. Medical therapy was instituted, the patient made a full recovery and survived 32 weeks after surgery.

Twelve patients had seizures during the study. Only two patients had seizures in the 1st month postoperatively when drug release is thought to be maximal. One patient, who had presented initially with seizures, had a single seizure 1 week postoperatively. The second patient, whose peri-operative course was previously discussed, had a seizure 10 days postoperatively in association with peri-tumoral edema. The average time between surgery and the first seizure was 2.7 months. In 4 patients, seizures were controlled medically within 2 weeks of onset. Three of the 12 patients with seizures after surgery had had seizures preoperatively. Four of 6 patients with frontal lobe tumors and 6 of 11 patients with temporal lobe lesions had seizures, whereas only 2 of 8 patients with parietal lobe tumors had seizures.

A total of 15 adverse events in 10 patients were graded by the attending neurosurgeon as severe (Table 1). Seizures were the most common neurologic complication. Four patients had transient decline in their neurological examination, usually a decline in mental status. This group includes the two patients who had peri-operative morbidity as described under postoperative complications. One of these patients required surgical decompression for removal of a hematoma, while the other responded to medical management. Those patients' courses are described under postoperative complications. Two additional patients had decline in mental status outside the peri-operative period. Both responded to medical therapy. No wound infections occurred in any patient. The only severe infectious complication was an aspiration pneumonia complicated by subsequent sepsis that occurred in the fourth month postoperatively.

The moderate and mild complications are listed in Table 2. Seizures were the most common neurologic complication in this group. Eight infections occurred, all of which were unrelated to the surgery or the surgical incision.

Further surgical intervention

Nine of 22 patients underwent a second craniotomy (Table 3), and 1 of these 9 subsequently had a stereotactic biopsy. The second craniotomy occurred an average of 34 weeks after the placement of the BCNU-polymer at initial surgery. Seven patients had evidence of active tumor at the second craniotomy; one had only evidence of necrosis with quiescent tumor. One patient had a hematoma. Seven patients had evidence of residual polymer at re-operation. One patient had undergone craniotomy 2

Table 1. Post-operative events graded as severe in patients treated with BCNU interstitial chemotherapy

Post-operative events	Number of patients
Neurologic:	
Seizures	3
Decline in neurologic exam:	
Postoperative stupor	1
Confusion	1
Neurologic decline with increased MRI enhancement	1
Intracranial hypertension	1
Clinically significant necrosis	1
Infectious	
Pneumonia with 2° sepsis	1
Gastrointestinal	
Gastrointestinal bleed	1
Vomiting	1
Dehydration	1
Vascular	
Deep vein thrombosis	1
Pharmaceutical complications	
Phenytoin allergy	1
Systemic disease	
Intra-abdominal lymphoma	1

days after placement of the polymer for removal of a hematoma. At that time, five of the seven polymer wafers previously placed were removed. Six other patients had residual fragments of polymer removed during re-operation, which occurred between 12 and 68 weeks after initial implantation. Analysis of the polymer fragments demonstrated that all of the polyanhydride bonds had been hydrolyzed, and no BCNU was detected within the polymer fragments. Two patients had no residual polymer at the time of reoperation. This is consistent with biodegradation and absorption of the polyanhydride material.

Table 2. Post-operative events graded as moderate or mild in patients treated with BCNU interstitial chemotherapy

Post-operative events	Number of patients
Neurologic:	
Seizures	9
Headache	3
Clinically significant necrosis	2
Confusion	1
Weakness	1
Intracranial hypertension	1
Depression	1
Ataxia	1
Hallucinations	1
Surgical:	
Subgalial fluid collection	1
Infectious	
Pneumonia	3
Urinary tract infection	3
Bronchitis	1
Costochondritis	1
Gastrointestinal	
Nausea	1
Vascular	
Deep vein thrombosis	1
Hypertension	1
Pharmaceutical complications	
Phenytoin toxicity	2
Carbamazepine allergic reactions	1
Musculoskeletal	
Back pain	1
Hip pain	1
Dermatologic	
Rash	1

Neurologic outcome

Functional evaluation was carried out by neurological examination, KPS, and MMSE. Neurological examination showed no significant changes from admission to discharge. Several patients had subtle declines in mental status postoperatively. The two more serious declines are discussed under postoperative morbidities. Other patients had small changes in neurologic examination that were consistent with having undergone craniotomy and tumor resection, but by discharge, patients had recovered to baseline. The mean KPS at initial evaluation was 82. On the night of surgery, the KPS fell to 67. By the day of discharge, the mean KPS was 78. On the first day of radiation therapy, an average of 3 weeks after surgery, the mean KPS was 80. By the final evaluation, an average of 210 days after entry in the study, KPS had declined by 23.6 points to an average of 58. Mini-mental status examination showed no significant differences in cognitive function between the initial evaluation and those on the night after surgery, the day of discharge, and the first day of radiation therapy.

Dexamethasone

All patients received dexamethasone postoperatively. The average dose on postoperative day 1 was 45 mg/day (range 16–120 mg/day). The average dose on postoperative days 7, 21, and 60 were 25 mg/day, 15 mg/day and 7 mg/day, respectively (ranges: day 7 = 1.5–120 mg/day; day 21 = 1–96 mg/day; day 60 = 0.5–32 mg/day).

Laboratory

No significant myelosuppression was seen; the lowest white blood cell count for any patient in the entire study was 3200 mm^3. The lowest postoperative hematocrit was 25.5% and the average was 37.5%. On the first day of radiation therapy, the lowest hematocrit was 27.4% and the average was 37.3%. The lowest platelet count seen in any patient was 149 platelets/mm^3. No significant increase in BUN

Table 3. Reoperations in patients receiving BCNU-polyanhydride Wafers as First Line Therapy for Malignant Gliomas: Indications, Timing of Second Surgery, and Pathologic Findings

Patient	Type of procedure	Interval from Polymer placement to Re-operation	Clinical indications for re-operation	Radiographic findings prior to Re-operation	Findings and pathology at Re-operation	Polymer fragments present
1-001	craniotomy	68 weeks	persistent left hemiparesis increased steroid requirement	increased mass effect increased enhancement	micro-foci of tumor, necrosis	yes
1-002	craniotomy	32 weeks	headaches, gait unsteadiness, dizziness, leg weakness, increased steroid requirement	increased mass effect, increased edema	rare, viable atypical cells, no active tumor	no
	stereotactic biopsy	46 weeks		increased mass effect	no active tumor	no
1-003	craniotomy	12 weeks	generalized tonic-clonic seizure	increased enhancing mass	active GBM, necrosis	yes
1-004	craniotomy	2 days	lethargy	increased edema, increased mass effect	hematoma	yes
1-007	craniotomy	29 weeks	increasing dysphasia, confusion	increased edema, increased mass effect	largely necrosis, some active tumor	yes
1-008	craniotomy	29 weeks	increasing steroid requirement, short-term memory loss, left hemiparesis, left homonymous hemianopsia, left-sided neglect	increased enhancement	active GBM, some necrosis	yes
1-009	craniotomy	28 weeks	increased left hemiparesis, balance difficulty, increased steroid requirement	increased mass effect	GBM	yes
2-003	craniotomy	39 weeks	mild speech difficulty	recurrent tumor	GBM, fibrotic wall around tumor cavity	yes
2-004	craniotomy	56 weeks	mild short-term memory loss	increased enhancement increase mass effect	GBM	no

or creatinine were seen. There were mild increases in the liver function tests immediately postoperatively (mean SGPT = 62 U/L, range = 3–284 U/L, mean SGOT = 33 U/L, range = 11–129 U/L). By 3 weeks postoperatively, these mild elevations had declined (mean SGPT = 56 U/L, range = 21–184 U/L, and mean SGOT = 26 U/L range = 14–68 U/L). Bilirubin was not significantly elevated.

Radiation

All patients underwent standard radiation therapy. The median dose was 5,580 cGy (interquartile range 5,100–6,120 cGy). All patients with glioblastoma received between 5,000–6,660 cGy to the tumor bed. The single patient who had anaplastic astrocytoma received 4,500 cGy total. This patient did not have a serious complication and is still alive more than 3 years after diagnosis and treatment.

There appeared to be no correlation between radiation dose and toxicity as assessed by mortality or by morbidity. The patients who suffered complications graded as serious had a range of radiation doses similar to the overall study population (5,100–6,660 cGy range for subset of patients with serious complications). There was no correlation between length of survival and radiation dose. The five longest survivors with GBM had a range of radiation therapy doses (5,100–6,120 cGy) similar to the five patients with the shortest survival (5,580–6,660 cGy). Overall, radiation was well-tolerated by the patients.

Survival

Eighteen patients completed the 6 month evaluation. Four patients died during the study period, three of presumed tumor progression and one of a biopsy-proven abdominal lymphoma.

Survival is presented in Fig. 2. Median survival was 42 weeks. Eight patients survived more than 1 year, and four patients survived more than 18 months. The longest survivor was the patient with the anaplastic astrocytoma, who is still alive at 169 weeks. Median survival at each center varied (182 days, 292 days, 373 days). No significant differences in age, pathology, or other prognostic factors could be identified among centers to explain the difference.

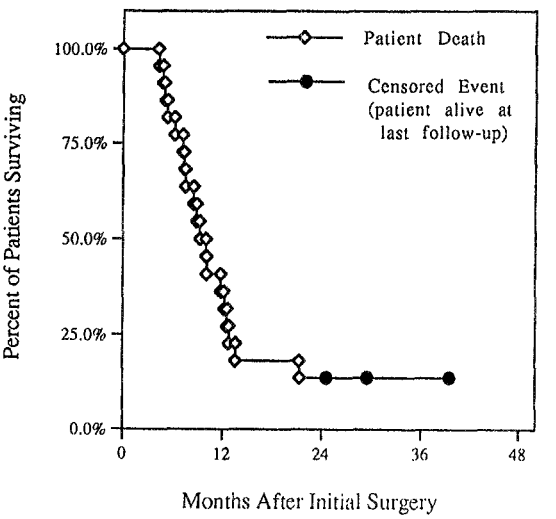

Fig. 2. Kaplan-Meier survival curve of 22 patients receiving BCNU-loaded polymer as first-line therapy for malignant glioma.

Discussion

Safety

This is the first study evaluating the safety of BCNU impregnated polymer implanted at the *initial therapy* for malignant glioma and prior to radiation therapy. No local or systemic toxicity was found that could be related directly to the polymer implants. The usual range of postoperative morbidity for initial glioma surgery was observed, but no postoperative mortality occurred. There was no evidence of increased brain toxicity from the local delivery of BCNU in this series when compared with that in other series of patients treated with craniotomy and radiation therapy with or without systemic chemotherapy [10, 11]. After recovering from the stress of craniotomy and tumor resection, patients maintained their preoperative scores for neurological examination, KPS, and mini-mental examination through the first several weeks of therapy, implying that the locally delivered BCNU did not impair their cognitive function. Incidence of perioperative

seizures was low and equivalent to that in other series of initial glioma resection [10]. Perioperative edema was well-controlled with standard doses of dexamethasone. BCNU-polymer did not exhibit significant neurotoxicity.

The patients in this study of locally delivered BCNU did not show evidence of systemic toxicity. Systemic BCNU frequently results in bone marrow suppression, hepato-renal injury, and pulmonary fibrosis in a dose-dependent fashion [12]. Analysis of peripheral blood cell counts in this study showed normal bone marrow function, and no surgical infections occurred. There was no liver or kidney dysfunction and no cases of BCNU-induced pneumonitis. Overall, no systemic side effects from the intracranial BCNU were seen. BCNU-impregnated polymer with concurrent radiation therapy appears safe when administered as initial therapy for brain tumors.

Interaction of chemotherapy and radiation therapy

In previous clinical trials with BCNU-polymer, all patients had previously received radiation therapy and more than half had failed systemic chemotherapy before polymer placement [1, 2]. No patients received external beam radiation after the implantation of the polymer. The effects of concurrent radiation therapy and locally delivered BCNU had not been previously studied. In this study, concurrent interstitial BCNU and radiation therapy given in standard fashion was well tolerated.

The synergy of external beam radiation with chemotherapy may be critical for successful therapy [12]. Studies in the rat 9L gliosarcoma model showed a synergistic effect of radiation therapy and systemic BCNU given together in prolonging survival [13]. Possible mechanisms of synergy include alterations in the cell cycle secondary to chemotherapy that increase the susceptibility of the tumor to radiation, or inhibition of the cellular mechanism by which tumor cells attempt to repair the damage done by radiation. Radiation may also increase the efficacy of chemotherapy by increasing cellular uptake of the agent or alteration of cellular mechanism of resistance [13].

Clearly, synergy between BCNU and radiation therapy is desirable, but the possibility existed that there might be additive toxicity with concurrent use of both treatments. We have previously evaluated this combination in primate brains [14]. Monkeys receiving BCNU wafers followed by radiation showed no clinical sign of neurologic compromise. Histologically, there was no difference in the pathological changes seen when they were compared with animals receiving intracranial BCNU polymer without radiation. In addition, the combination of pCPP-SA polymer or BCNU-loaded pCPP:SA polymer with radiation appears to be no more toxic in the rabbit brain than radiation alone. That study compared neurologic outcome, survival, and histopathology (A. Domb, unpublished data).

Survival

This study, like all phase I trials, was designed to test safety; efficacy was not a primary endpoint. Survival was measured in order to aid in determination of toxicity. All patients were followed until death or at least 2 years postoperatively. The median survival for this group of patients was 42 weeks, similar to previously reported series of comparable patients with malignant gliomas [15, 16]. All except one of the patients in this series had glioblastomas (95%), and as a group they were relatively old (mean age of 60 and no patients younger than 40). Both of these factors are associated with a poor outcome [15, 17, 18]. Nevertheless, four patients survived more than 18 months. Therefore, it appears that interstitial BCNU chemotherapy at the time of initial glioma diagnosis may be of benefit. Further trials will be designed specifically to establish optimal dosing and establish efficacy.

Previous clinical studies with BCNU-polymer implants

Two previous clinical trials of BCNU-polymer have been reported in patients with *recurrent malignant gliomas*. A safety and dose escalation multi-institutional study was performed in 21 patients [1]. Five

patients were treated with 1.93% BCNU-loaded polymer, five patients were treated with 3.85% loading doses, and eleven patients received 6.35% loaded BCNU-polymer. Therapy in all groups was well-tolerated and safe. The groups receiving the lower two doses had a longer median survival. On that basis, the 3.85% loading dose was selected for this study, for a Phase III trial of treatment of recurrent gliomas, and for the present trial.

In a multi-institutional, randomized, placebo-controlled, double-blinded study [3], 222 patients at 27 hospitals received BCNU-polymer (3.85% BCNU loading) at the time of reoperation for malignant glioma. All patients had previously received surgery and radiation therapy with or without chemotherapy. This therapy was safe and well-tolerated. Patients receiving BCNU polymer had a significant ($p < 0.01$) increase in survival (31 weeks) versus control (23 weeks) after accounting for prognostic variables. In patients with glioblastoma, there was a 50% increase in the number of patients surviving 6 months when BCNU therapy was compared with control. These studies demonstrated that BCNU-polymer therapy is safe and effective in the treatment of recurrent gliomas.

Choice of BCNU and its dose

BCNU was chosen for the initial trials of this delivery method for several reasons. BCNU is the current first line chemotherapy for malignant glioma [12]. Second, BCNU's short systemic half-life (< 15 minutes) makes it a good candidate for local delivery. Third, BCNU appears to be retained longer in brain tumors than in surrounding brain tissue [19].

In the initial phase I–II trial [1], several loading doses were used (1.9%, 3.85%, and 6.9% loading of BCNU). The survival was longest in the small group who received 3.85% loaded polymer, and this dose was selected for subsequent therapeutic trials. The small number of patients in that initial trial did not demonstrate a significant difference between 3.85% and 6.9% loading. Since 3.85% is quite well tolerated and increases survival in patients with recurrent gliomas, it may be possible to re-explore higher doses in search of maximal efficacy. In the laboratory, loading doses as high as 20% BCNU are consistently more effective than 3.85% in prolonging survival in a glioma model [20].

Polymeric delivery with other drugs

Many potentially beneficial chemotherapeutic agents have not been tested for effect in CNS tumors because their chemical structure prevents them from crossing the blood-brain barrier in therapeutic amounts. Local delivery of these agents from polymer would not only provide high levels but also utilize the blood-brain barrier in reverse to limit the systemic toxicity. We have shown benefit against animal tumor models of carboplatin [21], 4-hydroperoxycyclophosphamide (4–HC) [22], taxol [23], and camptothecin [24] delivered by polymers locally. In addition, the possibility of simultaneous local therapy with multiple agents is promising.

Conclusions

Interstitial chemotherapy utilizing BCNU-loaded polyanhydride polymers is safe as the initial therapy for patients with malignant glioma. Concurrent interstitial chemotherapy with BCNU and external beam radiation therapy appears to be well tolerated in brain tumor patients. Patients receiving locally delivered BCNU had perioperative infection rates, seizure rates, and steroid requirements indistinguishable from patients receiving conventional therapy. Several long term survivors in a group of older patients all but one of whom had glioblastoma suggest a potential therapeutic benefit of this treatment method. Local therapy provides high dose chemotherapy in the brain without systemic side effects. Utilization of polymer delivery of therapeutic agents at the time of initial craniotomy is demonstrated to be safe. Its potential efficacy and optimal dosing can now be explored in future clinical trials.

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