Cancer Chemother Pharmacol (1996) 39: 90–96

ORIGINAL ARTICLE

**Alessandro Olivi · Matthew G. Ewend
Tadanobu Utsuki · Betty Tyler · Abraham J. Domb
Daniel J. Brat · Henry Brem**

Interstitial delivery of carboplatin via biodegradable Polymers is effective against experimental glioma in the rat

Received: 25 August 1995/Accepted: 21 February 1996

Abstract *Purpose*: Carboplatin has shown promise experimentally as an antineoplastic agent against both primary central nervous system (CNS) tumors and several solid tumors that frequently metastasize to the brain. Unfortunately, carboplatin is limited in its clinical use for tumors in the CNS by systemic toxicity and poor penetration through the blood–brain barrier. Recent advances in polymer technology have made feasible the intracranial implantation of a biodegradable polymer capable of local sustained delivery of chemotherapy for brain neoplasms. This study assessed the toxicity and efficacy of carboplatin delivered from intracranial sustained release polymers in the treatment of experimental gliomas in rodents. *Methods*: Two biodegradable anhydride polymer systems were tested: a copolymer of 1,3-bis-(*p*-carboxyphenoxy propane) and sebacic acid, and a copolymer of fatty acid dimer and sebacic acid. The polymers were loaded with carboplatin and dose escalation studies evaluating toxicity were performed by implanting carboplatin-loaded polymers into the brains of rats. Next, efficacy was tested. F-98 glioma cells were injected intracranially into rats, and 5 days later polymers containing the highest tolerated doses were implanted at the site of tumor growth. The survival of animals receiving carboplatin-loaded polymer was compared with that of animals receiving intraperitoneal doses of the same agent. *Results*: Carboplatin-polymer was well tolerated at doses up to 5% loading in both polymer systems. Locally delivered carboplatin effectively prolonged survival of rats with F98 gliomas. Maximal treatment effect was seen with 5% loading of either polymer, with median survival increased threefold over control ($P < 0.004$). Systemic carboplatin also significantly prolonged survival, but the best intracranial polymer dose was significantly more effective than the best systemic dose tested. *Conclusions*: Carboplatin can be safely delivered intracranially by biodegradable sustained- release polymers. This treatment improves survival in rodents with experimental gliomas, with locally delivered carboplatin being more effective than systemic carboplatin.

Key words Carboplatin · Glioma · Polymer · Drug delivery systems · Brain tumor

A. Olivi (✉) · M.G. Ewend · T. Utsuki · B. Tyler · H. Brem
Department of Neurosurgery, The Johns Hopkins School of Medicine, Baltimore, MD 21205, USA
TEL (410) 614–0477; FAX (410) 614–0478

A. Olivi · H. Brem
Department of Oncology, The Johns Hopkins School of Medicine, Baltimore, MD 21205, USA

A.J. Domb
Department of Pharmaceutical Chemistry,
School of Pharmacy-Faculty of Medicine,
The Hebrew University of Jerusalem, Jerusalem, Israel 91120

D.J. Brat
Department of Pathology, The Johns Hopkins School of Medicine, Baltimore, MD 21205, USA

Introduction

Platinum drugs, which exert antitumor effects by binding to DNA and producing interstrand crosslinks, have shown promise in the treatment of central nervous system (CNS) tumors including malignant glioma, medulloblastoma, optic pathway glioma, brainstem glioma and ependymoma [6, 14, 33, 41, 42]. These drugs are also active against a variety of solid tumors that frequently metastasize to brain, including breast and non-small-cell lung cancer [8, 16, 19, 28, 30, 34]. Unfortunately, the use of platinum-based drugs is limited by systemic toxicity. Cisplatin (cis-diamminedichloroplatinum) has significant neurotoxicity, nephrotoxicity, ototoxicity, and gastrointestinal toxicity [17]. To minimize these toxic effects, analogs of cisplatin including

carboplatin [cis-diammine-1, 1-cyclobutane-dicarboxylate platinum(II)] were synthesized. While less toxic than cisplatin, systemic carboplatin therapy is limited by bone marrow suppression [16].

Strategies have been devised to increase the therapeutic index of platinum drugs, either by treating side effects or by reducing their occurrence. For carboplatin, hematopoietic toxicity has been treated with the use of bone marrow-stimulating growth factors or bone marrow rescue [32]. Efforts to decrease the occurrence of side effects have focused on targeted delivery. For CNS malignancies, intracarotid delivery of carboplatin and cisplatin has been attempted in order to increase the amount of drug entering the blood supply near the site of the tumor [11, 26, 37, 41]. Efficacy, however, is relatively small, and dose-limiting retinal toxicity, ototoxicity, and bone-marrow suppression are seen. Such lack of efficacy is attributed to the blood–brain barrier, which inhibits passage of the agent through the capillary wall into the brain. Since platinum-containing drugs are water-soluble, they have difficulty crossing the blood–brain barrier.

To overcome the restrictions imposed by the blood-brain barrier, local delivery of chemotherapy to brain tumors has been achieved by incorporating these agents into biodegradable polymers and implanting the polymers directly into the tumor cavity after resection [1, 5]. Carboplatin is an ideal candidate for local delivery into the brain via polymers for several reasons. The drug is effective in vitro against CNS tumors, but doses are limited clinically by hematologic toxicity. Moreover, there is a clear relationship between increasing both concentration and duration of exposure to carboplatin and likelihood of response, at least in chemosensitive tumors [18]. Carboplatin is less neurotoxic than other platinum-based compounds when delivered directly to the CNS [31]. Finally, the drug can be released in a sustained fashion from polymers [9]. We reasoned that local delivery of carboplatin directly to the CNS by either poly(carboxyphenoxy)propane and sebacic acid (CPP : SA) polymer or fatty acid dimer and sebacic acid (FAD : SA) polymer might allow treatment with high doses at the site of the tumor, yet minimize systemic toxicity. To test this hypothesis, we examined the toxicity and efficacy of polymer-delivered carboplatin against gliomas in a rat model system.

Materials and methods

Preparation of polymer implants

The FAD : SA copolymer was synthesized from dimer erucic acid and sebacic acid at a molar ratio of 18 : 78 [9]. The CPP : SA copolymer was synthesized from 1,3-bis-(*p*-carboxyphenoxy propane) (CPP) and sebacic acid (SA) at a molar ratio of as 20 : 80 as previously described [7]. Disk-shaped polymer implants (3 mm diameter, 1 mm height, 10 mg each) were prepared by melt mixing carboplatin powder (Bristol Myers Pharmaceutical Company, Syracuse, N.Y.) into the melted polymer at 70 °C for 30 s and casting the uniform mixture into a 1-mm thick film. The film was cut into disks by means of a 3-mm bore. In vitro release was measured in 0.1 *M* phosphate buffer, pH 7.4, at 37 °C as previously described [9].

Animals

Male Fischer 344 rats weighing 200–250 g were obtained from Harlan Sprague-Dawley (Indianapolis, Ind.) and kept in accordance with the policies and principles of laboratory animal care of the Johns Hopkins School of Medicine Animal Care and Use Committee.

F98 glioma inoculations

The F98 glioma has been previously characterized [15, 22, 23]. Stereotactic injection of 10 000 F98 glioma cells into the left parietal lobe of the rats was carried out as previously described [20]. Injection of cells in this manner results in the formation of intracranial tumors which, if untreated, are uniformly fatal in 16–24 days.

Toxicity of carboplatin delivered by FAD : SA polymer

To measure toxicity of carboplatin delivered intracranially from FAD : SA polymers, five animals per group received intracranial polymers containing 0%, 3%, 5%, 7% and 10% loading doses of carboplatin. The method of implantation is detailed elsewhere [20]. The animals were observed daily for signs of neurologic toxicity, for systemic toxicity as evidenced by hematologic complications such as bleeding or infection, and for survival.

Efficacy of carboplatin delivered by FAD : SA polymer and by systemic administration

The efficacy of nontoxic doses of carboplatin delivered intracranially by FAD : SA polymer was compared with the efficacy following systemic delivery, which is the current method of clinical administration. There were three arms in the study: control animals did not receive carboplatin; animals in the polymer arm received one of three escalating doses of locally delivered carboplatin; animals in the systemic dosing arm received one of three escalating doses of intraperitoneal carboplatin. The number of animals in each group is given in Table 1. All animals first received intracranial F98 glioma. On the 5th day after tumor implantation, animals in the polymer arm received a FAD : SA polymer loaded with 1%, 2%, or 5% carboplatin. Animals in the systemic chemotherapy arm received blank polymer intracranially and were subdivided into three groups for intraperitoneal injections of carboplatin once per week for 3 weeks at doses of 10 mg/kg per week (approximating human doses of 360 mg/m^2), 30 mg/kg per week, and 50 mg/kg per week. Injections began 5 days after tumor inoculation and were given as single injections weekly for 3 weeks. Animals were observed for signs of toxicity and survival was recorded. Autopsies were performed whenever possible to determine the cause of death.

Efficacy of carboplatin delivered by CPP:SA polymer

Toxicity testing defined doses higher than 10% loading of carboplatin in CPP : SA polymer as toxic; therefore efficacy testing analogous to that with FAD : SA-loaded polymer was performed with the CPP : SA polymer with carboplatin at loadings equal to and below

Table 1 Survival in rats with intracranial F98 glioma after treatment with carboplatin administered by FAD:SA polymer directly into the tumor bed or by systemic injection

Model of carboplatin delivery	Dose of carboplatin	Number of animals in group	survival > 40 days (%)	Median survival (days)	Statistical analysis of survival (*P*-value)
Control	None	28	0	16	
Intracranial delivery by polymer	1% loaded polymer	38	5	32	< 0.001vs control
	2% loaded polymer	12	33	35.5	< 0.001 vs control
	5% loaded polymer	15	60	53	< 0.001 vs control 0.0069 vs 2% polymer < 0.001 vs 10 mg/kg systemic 0.027 vs 30 mg/kg systemic < 0.001 vs 50 mg/kg systemic
Systemic delivery by intraperitoneal injection	10 mg/kg/week	13	0	23	< 0.001 vs control
	30 mg/kg/week	4	25	36.5	0.001 vs control 0.0001 vs 10 mg/kg systemic
	50 mg/kg/week	12	0	19	< 0.001 vs control

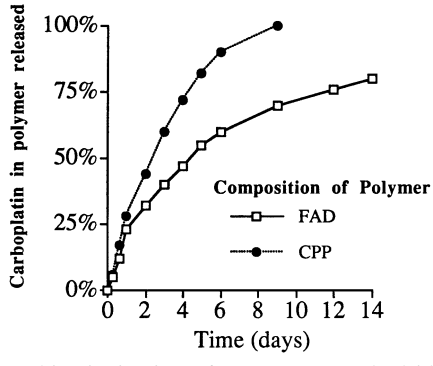

Fig. 1 Release kinetics in vitro of two separate anhydride polymers, poly(carboxyphenoxy) propane and sebacic acid (CPP:SA) polymer and fatty acid dimer and sebacic acid (FAD:SA) polymer. Each polymer weighed 10 mg and was loaded with 5% carboplatin by weight

10%. For this experiment, 32 animals underwent intracranial injection of F98 tumor and 5 days later were randomized into four treatment groups. Group 1 received intracranial implantation of blank CPP:SA polymer, and groups 2, 3 and 4 received intracranial placement of CPP:SA polymer loaded with 2%, 5% and 10% carboplatin, respectively. Toxicity and survival were again assessed. When animals died or after sacrifice if they were moribund, standard coronal sections of brain were taken. Routine hematoxylin and eosin (H&E) staining was performed. Two sections per animals were analyzed in a blinded fashion by a pathologist (DJB). Toxicity was systematically assessed in terms of neuronal injury, white matter damage, gliosis, and acute inflammation. For each category, a grade of 0, 1, 2, or 3 was assigned based on the severity. Neuronal injury was graded in the CA1, CA2, and CA3 regions of the hippocampus on the side most affected. Criteria evaluated included cytoplasmic eosinophilia, nuclear pyknosis, and neuronal dropout. White matter damage was assessed in the corpus callosum by grading edema, myelin vacuolization, and gliosis. Cerebral cortical gliosis was graded in the parietal cortex ipsilateral to the most affected hippocampus. Acute inflammation was described and graded when present at any location within the histological section. After unblinding the sections, experimental groups were analyzed for average grade of pathologic involvement.

Statistical analysis

Statistical analysis was performed using EGRET and SAS software. The primary statistical outcome variable for this study was survival time following treatment. Cumulative failure time distributions were estimated using the product limit method [21]. Because the failure times could depend on covariates such as type of polymer and drug loading, we tested the effects of covariates on failure times using proportional hazards regression models [27]. All *P*-values reported are two-sided.

Results

Drug release

Both the polymer and the drug remained stable and did not decompose during heating and mixing. The in vitro release from disks loaded with 5% by weight carboplatin is shown in Fig. 1. Carboplatin was released at a constant rate from both polymers following first order kinetics ($r^2 > 0.98$). The release from CPP:SA was faster with most of the drug being released within 7 days, while about 65% of the drug was released from the FAD:SA polymer during this period.

Toxicity

The toxicity of locally released carboplatin from FAD:SA polymer was assessed as described in Materials and methods (Table 2). The empty FAD:SA polymer showed no clinical toxicity. One animal of the five

Table 2 Toxicity of intracranial carboplatin locally delivered by FAD:SA polymers

Loading dose of carboplatin in FAD:SA polymer[a] (%)	Deaths in the first 10 days (%)	Survival more than 120 days (%)	Death days (number of animals dying on that day)
0	0	100	No deaths
3	20	80	Day 4 (1 animal)
5	20	80	Day 4 (1 animal)
7	80	20	Day 3 (2 animals) Day 4 (2 animals)
10	100	0	Day 5 (5 animals)

[a] Five animals per group

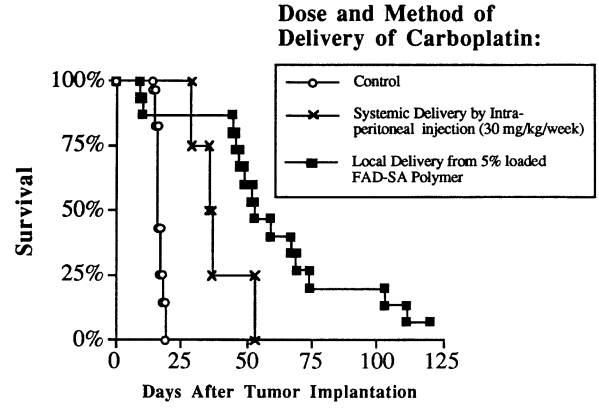

Fig 2 Efficacy of maximal local therapy (5% loaded FAD polymer) versus maximal systemic therapy (30 mg/kg/week × 3 weeks). Local therapy was significantly more effective than systemic therapy ($P = 0.027$). Both local and systemic therapy were significantly better than control ($P = 0.001$). The final death in the local therapy group (black squares) occurred on day 1933

that received 3% and one of five that received 5% loaded polymer died 4 days after polymer placement. Surviving animals were neurologically normal. Four of five animals receiving 7%, and all five of the animals receiving 10% loaded polymer died in the first 5 days after polymer placement. Thus, 5% loading of carboplatin in FAD:SA was the highest tolerated loading dose (80% long-term survival) and was chosen as the highest dose for the efficacy studies.

Efficacy of carboplatin released from FAD:SA polymer versus systemic treatment

The intracranial F98 glioma was uniformly fatal to untreated animals at a median of 16 days, and all control animals died by the 19th day. Treatment with polymers loaded with 1%, 2% and 5% carboplatin prolonged survival, with 5% loading the most effective (median survival 53 days, $P < 0.001$ vs control, Table 1). Polymer containing 5% carboplatin was significantly more effective than 1% or 2% loading doses in prolonging survival ($P = 0.007$). There were, however, two early deaths in the 5% group, one on day 9 and the other on day 10. Loadings of 1% and 2% also significantly prolonged survival over control ($P < 0.001$ for each) without early deaths.

Of the three systemic doses tested, the intermediate dose (30 mg/kg) was the most effective (median survival 36.5 days, $P < 0.001$ vs control). At higher systemic doses, animals died early in the experiment. The 5% loaded polymer was significantly more effective than the best systemic dose, 30 mg/kg per week, in prolonging survival in rats with F98 glioma ($P = 0.027$; Fig. 2).

Representative autopsies of these animals revealed large intracranial tumors with two exceptions. Two animals in the 5% polymer group had no evidence of tumor at the polymer site but died from distal spread of tumor along the neuroaxis. Animals in the 50 mg/kg per week systemic group did not have large intracranial tumors and are presumed to have died of toxicity.

Table 3 Survival in rats with intracranial F98 glioma after treatment with carboplatin locally administered by intracranial CPP:SA polymer

Treatment group[a]	Median survival (days)	Survival 40 days or more (%)	Statistical analysis (*P*-values)
Control (blank polymer)	23	0	
2% loaded polymer	46.5	75	0.01 vs control
5% loaded polymer	86.5	75	0.004 vs control
10% loaded polymer	8	12.5	

[a]Eight animals per group

Toxicity and efficacy of carboplatin released from CPP:SA polymer

Animals receiving 2% or 5% carboplatin-loaded CPP:SA polymer (Table 3) had a significantly prolonged median survival of 46.5 ($P < 0.01$) and 86.5 ($P < 0.004$) days when compared with controls (median survival 23 days). Animals receiving 10% loaded polymer had a median survival of 8 days. Two of eight animals receiving 5% loaded polymer died early (one each on day 9 and day 10). There were no early deaths in the 2% polymer group. Except for the early deaths (< 10 days) in the 5% and 10% groups, autopsies revealed that animals died of large intracranial tumors at the site of injection of F98.

Histological examination of brains from animals receiving CPP:SA polymer loaded with carboplatin revealed dose-related toxicity (Table 4). Neuronal injury in the hippocampus was increased above control levels at all concentrations used and was most significant at the 5% and 10% loadings. White matter (corpus callosum) damage was greater in animals receiving carboplatin than in controls. However, the changes were not

Table 4 Histologic findings in the rat brain after treatment with carboplatin locally administered by intracranial CPP:SA polymer. Each category was graded blindly on a 0–3 scale

Treatment group[a]	Neuronal injury in the hippocampus	White matter damage in the corpus callosum	Cerebral cortical gliosis	Acute inflammation
Control (blank polymer)	0.5	0.6	0.8	0
2% loaded polymer	1.6	2.1	1.6	0
5% loaded polymer	2.3	2.1	1.7	0.7
10% loaded polymer	2.8	2.2	2.5	1.3

[a]Eight animals per group, two H&E sections per animal

dose-dependent within the range of doses tested. Cerebral cortical gliosis increased with increasing carboplatin dose. Acute inflammation was not seen in animals receiving blank or 2% loaded polymer, but was a significant histopathologic finding in both the 5% and 10% loaded groups. Acute inflammation was found focally in regions of most severe toxicity, as well as diffusely throughout the brain parenchyma in affected rat brains.

Discussion

These results establish that in our rat model, carboplatin could be delivered safely into the brain by use of anhydride polymers. Furthermore, delivery of carboplatin from polymers, termed interstitial chemotherapy, was effective in treating an experimental intracranial glioma. Locally delivered carboplatin was more effective than systemic therapy, without apparent systemic toxicity in this model.

To date, the effect of systemic chemotherapy on the prognosis of patients with malignant gliomas has been modest. The most commonly used agent, BCNU, appears to have only a small antitumor effect when given in conjunction with radiation therapy [12, 39]. Carboplatin is highly effective against several glioma lines in vitro [10], but in clinical studies, relatively few patients with gliomas have responded to systemic carboplatin therapy [13, 14]. Potential explanations for this difference in efficacy between in vitro and in vivo observations include: failure of the drug to cross the blood–brain barrier into the tumor; systemic toxicity limiting the dose below the therapeutic level; and tumor cell resistance in vivo [35]. Interstitial chemotherapy via biodegradable polymers can increase efficacy by addressing all three of these confounding factors.

First, local delivery of drugs circumvents the blood–brain barrier by delivering the chemotherapy directly into the tumor bed. This is particularly pertinent for water-soluble compounds such as the platinum drugs, which have relatively poor penetration into the CNS. Consequently, their efficacy can be severely limited when they are delivered systemically or even via intracarotid injection.

Second, local delivery can lead to decreased systemic toxicity by minimizing the amount of drug in the circulation. In experimental animal studies of head and neck cancer, the maximal tolerable dose (LD_{50}) of platinum-based chemotherapy increased fourfold with local delivery via polymers as compared with systemic delivery. Moreover, drug levels in the tumor were high while systemic levels remained low when the drug was delivered locally with polymer [36]. For locally delivered carboplatin in the brain, the blood–brain barrier may help in preventing dissemination of the drug, which is poorly lipid-soluble, outside the CNS.

Third, local delivery via polymer may be beneficial when tumor cell resistance prevents effective therapy. Tumor cell resistance can sometimes be overcome by increasing exposure to the drug [24]. Prolonged sustained release from biodegradable polymers increases the duration and the concentration of the drug exposed to the tumor. In experimental studies, local delivery has been shown to maintain a high concentration of platinum compound in the surrounding tissue [25, 36]. In addition, platinum drugs have been shown to penetrate at least 1 cm into tumors after local delivery [36].

Local delivery of chemotherapy to brain tumors from polymers has been tested clinically in five trials, with a total of 268 patients receiving interstitial BCNU. BCNU released from polyanhydride polymer is safe and effective for the treatment of patients with recurrent malignant glioma [1, 5, 40] and safe for patients with newly diagnosed malignant glioma [4]. In these trials, there was no evidence of systemic BCNU toxicity.

The systemic toxicity of chemotherapy can be diminished by local drug delivery to the CNS [4, 5, 40]. However, high concentrations of drug within the CNS raise concerns about direct neurotoxicity. For example, neurotoxicity of carboplatin such as transient blindness after systemic dosing or high-frequency hearing loss after intracarotid injection has been reported [29, 38]. We have previously shown that direct injection of carboplatin into the CNS of animals is well tolerated at cytotoxic concentrations, and that carboplatin is less neurotoxic than cisplatin [31]. For this reason, carboplatin was selected as the first platinum-containing agent to be developed for polymer delivery.

In the present study, we examined two biodegradable polymer systems. CPP:SA has several characteristics that make it useful for delivery of carboplatin:

CPP:SA can release carboplatin in a sustained fashion in vitro; it has been shown to be nontoxic and safe for implantation both in animals and in humans [3–5]; and finally, it has been used in clinical trials to deliver BCNU to patients with malignant gliomas safely and effectively [1, 4, 5]. For these reasons, it may be very useful clinically for local delivery of carboplatin.

The FAD:SA polymer was chosen for study because it has been shown to be particularly suitable for the release of water-soluble agents, including cisplatin [36], carboplatin [9], and other hydrolytically unstable compounds [20]. In addition, it has been shown to be biocompatible with the brain of rodents [2]. FAD:SA polymer is currently being tested (under FDA supervision) in clinical trials for its efficacy in releasing gentamicin to treat osteomyelitis. It has not been used intracranially in clinical trials.

The two polymer systems appeared to be equivalent in these experiments. Their release profiles in vitro were similar although not identical. Comparisons of the 5% loading showed that both polymers increased the median survival versus control by a factor of three (CPP:SA 23.5 days control vs 86 days for 5% carboplatin; FAD:SA 16 days control vs 53.5 days for 5% carboplatin), indicating that either polymer could be used to deliver carboplatin in clinical trials.

With both polymer systems, neurotoxicity was evident in animals receiving high doses of intracranial carboplatin. The response was clearly dose-related, with an increasing number of early deaths with escalating doses of local chemotherapy. Histologic examination revealed increased neuronal toxicity in both the cortex and hippocampus with escalating doses. With both polymer systems, animals receiving 10% loaded polymer died soon after implantation, while 5% loaded polymer resulted in some early toxicity, but this loading dose appeared to be near the maximum tolerated dose. Lower doses showed no early toxicity, but were less efficacious. Possible additive toxicity between locally delivered carboplatin and concurrent radiation therapy was not explored in this model. Future studies will be needed to define either additive toxicity or beneficial radiosensitization effects of combining these two therapies.

We have demonstrated in our rat model that carboplatin is effective when delivered via polymers. Given the heterogeneity of malignant gliomas and the evidence that multiple-drug regimens are often more effective than single agents, it is important to develop multiple agents for local therapy intracranially. In the future, patients with high-grade gliomas may receive rationally designed combination local chemotherapy with agents that have different and potentially synergistic mechanisms of antitumor effect. In addition, based upon in vitro drug sensitivity testing, the most effective agent(s) for a particular patient's tumor could be selected. The selected drug or drugs loaded in polymer could either be placed at the time of craniotomy for tumor resection or placed subsequently via stereotactic techniques following careful analysis of the resected tumor specimen. Finally, polymer delivery may be used to deliver radiosensitizing agents directly into the tumor bed prior to external beam radiotherapy.

In conclusion, carboplatin delivered from polymer was effective against intracranial F98 glioma in rats. This delivery method was superior to systemic administration in this model. The delivery of carboplatin directly to the brain tumor bed by sustained release polymers may decrease systemic toxicity. Furthermore, polymer delivery can increase the duration of exposure of tumor cells to this cytotoxic agent and therefore may improve its efficacy.

Acknowledgements We wish to thank Joe Scott for his dedicated care of the animals used in these experiments, and Mike Pinn for expert technical assistance. We thank Dr. Steven Piantadosi for assistance with statistical analysis. We acknowledge Dr. Pamela Talalay, Dr. Lisa A. Carey, and Dr. O. Michael Colvin for helpful discussion. This work was supported in part by the National Cooperative Drug Discovery Group (UO1-CA52857) of the National Cancer Institute of the National Institutes of Health, Bethesda, Maryland. Dr. Ewend is a recipient of NIH National Research Service Award CA-09574. F-98 glioma was a gift of Dr. Joseph Goodman, Ohio State University, Columbus, Ohio.

References

1. Brem H, Mahaley MJ, Vick NA, Black KL, Schold SJ, Burger PC, Friedman AH, Ciric IS, Eller TW, Cozzens JW, Kenealy J (1991) Interstitial chemotherapy with drug polymer implants for the treatment of recurrent gliomas. J Neurosurg 74:441
2. Brem H, Domb A, Lenartz D, Dureza C, Olivi A, Epstein JI (1992) Brain biocompatibility of a biodegradable controlled release polymer consisting of anhydride copolymer of fatty acid dimer and sebacic acid. J Controlled Release 19:325
3. Brem H, Tamargo RJ, Olivi A, Pinn M, Weingart JD, Wharam M, Epstein JI (1994) Biodegradable polymers for controlled delivery of chemotherapy with and without radiation therapy in the monkey brain. J Neurosurg 80:283
4. Brem H, Ewend M, Piantadosi S, Burger P, Greenhoot J, Sisti M (1995) The safety of interstitial chemotherapy with BCNU-loaded polymer followed by radiation therapy in the treatment of newly diagnosed malignant gliomas: phase I trial. J Neurooncol 26:111
5. Brem H, Piantadosi S, Burger PC, Walker M, Selker R, Vick NA, Black K, Sisti M, Brem S, Mohr G, Muller P, Morawetz R, Schold SC and Polymer Brain Tumor Therapy Group (1995) Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. Lancet 345:1008
6. Charrow J, Listernick R, Greenwald MJ, Das L, Radkowski MA (1993) Carboplatin-induced regression of an optic pathway tumor in a child with neurofibromatosis. Med Pediatr Oncol 21:680
7. Chasin M, Lewis D, Langer R (1988) Polyanhydrides for controlled drug delivery. Biopharm Manufact 1:33
8. Comis RL (1993) Carboplatin in the treatment of non-small cell lung cancer: a review. Oncology 2:37
9. Domb A, Bogdansky S, Olivi A, Judy K, Dureza C, Lenartz M, Pinn M, Colvin O, Brem H (1991) Controlled delivery of water soluble and hydrolytically unstable anticancer drugs from polymeric implants. Polymer Preprints 32:219

10. Doz F, Berens ME, Dougherty DV, Rosenblum ML (1991) Comparison of the cytotoxic activities of cisplatin and carboplatin against glioma cell lines at pharmacologically relevant drug exposures. J Neurooncol 11:27
11. Dropcho EJ, Rosenfeld SS, Morawetz RB, Vitek J, Brothers M, Gorum T, Bell S, Gillespie GY, Glantz M, Mahaley M Jr (1992) Preradiation intracarotid cisplatin treatment of newly diagnosed anaplastic gliomas. The CNS Cancer Consortium. J Clin Oncol 10:452
12. Fine HA, Dear KB, Loeffler JS, Black PM, Canellos GP (1993) Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. Cancer 71:2585
13. Friedman HS, Krischer JP, Burger P, Oakes WJ, Hockenberger B, Weiner MD, Falletta JM, Norris D, Ragab AH, Mahoney DHJ, Whitehead MV, Kun LE (1992) Treatment of children with progressive or recurrent brain tumors with carboplatin or iproplatin: a Pediatric Oncology Group randomized phase II study. J Clin Oncol 10:249
14. Gaynon PS, Ettinger LJ, Baum ES, Siegel SE, Krailo MD, Hammond GD (1990) Carboplatin in childhood brain tumors. A Children's Cancer Study Group Phase II trial. Cancer 66:2465
15. Goodman JH, McGregor JM, Clendenon NR, Gahbauer RA, Barth RF, Soloway AH, Fairchild RG (1990) Inhibition of tumor growth in a glioma model treated with boron neutron capture therapy. Neurosurgery 27:383
16. Hannigan E, Green S, Alberts D, O'Toole R, Surwit E (1993) Results of a Southwest Oncology Group Phase II Trial of carboplatin plus cyclophosphamide versus cisplatin plus cyclophosphamide in advanced ovarian cancer. Oncology 50 [suppl 2]:2
17. Hoff von D, Schilaky R, Reickert C, Reddiek R, Rozencweig M, Young R, Muggia F (1979) Toxic effects of cis-dichlorodiammine platinum (II) in man. Cancer Treat Rep 63:1527
18. Jodrell DI, Egorin MJ, Canetta RM, Langenberg P, Goldbloom EP, Burroughs JN, Goodlow JL, Tan S, Wiltshaw E (1992) Relationships between carboplatin exposure and tumor response and toxicity in patients with ovarian cancer. J Clin Oncol 10:520
19. Jones AL, Holborn J, Ashley S, Smith IE (1993) CVM versus ACE in the treatment of small cell lung cancer. Oncology 2:10
20. Judy K, Olivi A, Buahin K, Domb A, Epstein J, Colvin O, Brem H (1995) Controlled release of a cyclophosphamide derivative with polymers is effective against rat gliomas. J Neurosurg 82:103
21. Kaplan EL, Meier P, (1958) Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457
22. Ko L, Koestner A, Wechsler W (1980) Characterization of cell cycle and biological parameters of transplantable glioma cell lines and clones. Acta Neuropathol 51:107
23 Ko L, Koestner A, Wechsler W (1980) Morphological characterization of nitrosourea-induced glioma cell lines and clones. Acta Neuropathol 51:23
24. Kornblith PL, Walker M (1988) Chemotherapy for malignant gliomas. J Neurosurg 68:1
25. Kroin JS, Penn RD (1982) Intracerebral chemotherapy: chronic microinfusion of cisplatin. Neurosurgery 10:349
26. Mahaley M, Hipp S, Dropcho E, Bertsch L, Cush S, Tirey T, Gillespie G (1989) Intracarotid cisplatin chemotherapy for recurrent gliomas. J Neurosurg 70:371
27. Mantel N, Haenszel W (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 22:719
28. Mottet-Auselo N, Bons-Rosset F, Costa P, Louis JF, Navratil H (1993) Carboplatin and urothelial tumors. Oncology 2:28
29. O'Brien ME, Tonge K, Blake P, Moskovic E, Wiltshaw E (1992) Blindness associated with high-dose carboplatin. Lancet 339:558
30. O'Brien ME, Talbot DC, Smith IE (1993) Carboplatin in the treatment of advanced breast cancer: a phase II study using a pharmacokinetically guided dose schedule. J Clin Oncol 11:2112
31. Olivi A, Gilbert M, Duncan KL, Corden B, Lenartz D, Brem H (1993) Direct delivery of platinum-based antineoplastics to the central nervous system: a toxicity and ultrastructural study. Cancer Chemother Pharmacol 31:449
32. Pico JL, Ibrahim A, Castagna L, Bourhis JH, Chazard M, Maraninchi D, Droz JP (1993) Escalating high-dose carboplatin and autologous bone marrow transplantation in solid tumors. Oncology 2:47
33. Poisson M, Pereon Y, Chiras J, Delattre JY (1991) Treatment of recurrent malignant supratentorial gliomas with carboplatin (CBDCA). J Neurooncol 10:139
34. Schnabel T, Zamboglou N, Kolotas C, Hartmann A, Schmitt G (1993) Combined radiochemotherapy with carboplatin in the treatment of advanced head and neck carcinomas. Oncology 2:16
35. Shapiro WR, Shapiro JR (1986) Principles of brain tumor chemotherapy. Semin Oncol 13:56
36. Shikani A, Eisele D, Domb A (1994) Polymer delivery of chemotherapy for squamous cell carcinoma of the head and neck. Arch of Otolaryngol, Head Neck Surg 120:1242
37. Stewart DJ, Belanger JM, Grahovac Z, Curuvija S, Gionet LR, Aitken SE, Hugenholtz H, Benoit BG, DaSilva VF (1992) Phase I study of intracarotid administration of carboplatin. Neurosurgery 30:512
38. Twelves CJ, Ash CM, Miles DW, Thomas DG, Souhami RL (1991) Activity and toxicity of carboplatin and iproplatin in relapsed high-grade glioma. Cancer Chemother Pharmacol 27:481
39. Walker MD, Green SB, Byar DP, Alexander EJ, Batzdorf U, Brooks WH, Hunt WE, MacCarty CS, Mahaley MJ, Mealey JJ, Owens G, Ransohoff J, Robertson JT, Shapiro WR, Smith KJ, Wilson CB, Strike TA (1980) Randomized comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery. N Engl J Med 303:1323
40. Walter KA, Tamargo RJ, Olivi A, Burger PC, Brem H (1995) Intratumoral Chemotherapy. Neurosurgery 37:1129
41. Williams PC, Henner WD, Roman-Goldstein S, Dahlborg SA, Brummett RE, Tableman M, Dana BW, Neuwelt EA (1995) Toxicity and efficacy of carboplatin and etoposide in conjunction with disruption of the blood-brain tumor barrier in the treatment of intracranial neoplasms. Neurosurgery 37:17
42. Zeltzer PM, Epport K, Nelson MJ, Huff K, Gaynon P (1991) Prolonged response to carboplatin in an infant with brain stem glioma. Cancer 67:43