Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas

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Summary

Chemotherapy for brain tumours has been limited because of difficulty in achieving adequate exposure to the tumour without systemic toxicity. We have developed a method for local sustained release of chemotherapeutic agents by their incorporation into biodegradable polymers. Implantation of the drug-impregnated polymer at the tumour site allows prolonged local exposure with minimal systemic exposure. We conducted a randomised, placebo-controlled, prospective study to evaluate the effectiveness of biodegradable polymers impregnated with carmustine to treat recurrent malignant gliomas.

In 27 medical centres, 222 patients with recurrent malignant brain tumours requiring re-operation were randomly assigned to receive surgically implanted biodegradable polymer discs with or without 3·85% carmustine. Randomisation balanced the treatment groups for all of the prognostic factors examined. Median survival of the 110 patients who received carmustine polymers was 31 weeks compared with 23 weeks for the 112 patients who received only placebo polymers (hazard ratio=0·67, p=0·006, after accounting for the effects of prognostic factors). Among patients with glioblastoma, 6-month survival in those treated with carmustine-polymer discs was 50% greater than in those treated with placebo (mortality=32 of 72 [44%] *vs* 47 of 73 [64%], p=0·02). There were no clinically important adverse reactions related to the carmustine polymer, either in the brain or systemically.

Interstitial chemotherapy delivered with polymers directly to brain tumours at the time of surgery seems to be a safe and effective treatment for recurrent malignant gliomas.

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Introduction

In view of the poor outlook of patients with malignant gliomas,[1-2] we investigated the direct introduction of chemotherapeutic agents by controlled-release polymers. Our rationale behind this approach was based on the high local recurrence rate of primary brain tumours,[3] the restrictions to systemic drug delivery imposed by the blood-brain barrier, and the severe complications from systemic exposure to drugs targeted for the brain.[1] A biodegradable polymer capable of sustained local delivery of a drug might circumvent the restrictions imposed by the blood-brain barrier and allow more effective direct treatment of the tumour.

The polymer consists of poly(carboxyphenoxy-propane/sebacic acid) anhydride.[4] Carmustine (BCNU), the most effective chemotherapeutic drug for brain tumour,[1,5] can be incorporated into this hydrophobic matrix which protects the active agent from hydrolysis. We established the biocompatibility of the polymer, the kinetics of its degradation, and the pattern of drug release and distribution in animals.[6,7] Carmustine incorporated into the polymer and released over a 2 to 3 week period was more effective than systemic administration in controlling growth of experimental brain tumours.[8]

A phase I trial established the safety of implanting polymers impregnated with carmustine at the time of surgery for recurrent gliomas.[9] That study also determined the effective dose, with some patients displaying prolonged survival.[9] To determine the effectiveness and safety of this new approach to treating brain tumours, we began a multicentre, prospective, randomised, double-blind, placebo-controlled study.

Patients and methods

Patients

222 patients were enrolled at 27 clinical centres. Patients were randomly assigned to receive either polymer discs containing carmustine or empty polymer implants.

Patients with recurrent malignant glioma were candidates for enrolment if they met the following criteria: presence of a

unilateral single focus of tumour in the cerebrum showing at least 1·0 cm^3 enhancing volume on computed tomography scan or magnetic resonance imaging; a Karnofsky performance score of at least 60 (ie, ability to function independently); completion of external beam radiation therapy; and no nitrosoureas for 6 weeks and no other systemic chemotherapeutic agent for 4 weeks before enrolment. In addition, patients' surgeons made an independent determination that another tumour resection would be done irrespective of the study.

Carmustine discs

BIODEL, the polyanhydride polymer used, is a copolymer of poly-carboxyphenoxypropane and sebacic acid prepared in a 20/80 ratio.[9] Briefly, polymer and carmustine were co-dissolved in methylene chloride and spray dried into microspheres, which were compressed into discs of 1·4 cm diameter and 1·0 mm thickness, and sterilised by $2{\cdot}2\times10^4$ Gy gamma irradiation.[10] Loading with 50 μg carmustine/mm^3 of polymer (3·85% carmustine loading) yielded 7·7 mg of carmustine per wafer for a maximum patient dose of 62 mg. This dose was chosen as a result of previous experiments[8] and a phase I clinical trial.[9]

Trial design

Patients underwent a craniotomy for maximum resection of tumour. The final admission criterion for the study was either the pathologist's report of malignant glioma or the report of recurrent tumour in a patient with a previously established malignant glioma. Randomisation was stratified by institution. Investigators and study monitors did not have access to the treatment assignments. After removal of the tumour, up to eight discs were applied to the resection cavity surface. Sheets of oxidised regenerated cellulose (Surgicel, Johnson & Johnson, New Brunswick, NJ, USA) were used occasionally to secure the polymers against the brain. All patients were clinically and radiologically reassessed at least once every 2 months. Patients were eligible to receive systemic chemotherapy 2 weeks after the implant surgery.

222 patients were enrolled between March 1, 1989, and January 17, 1992. An interim analysis to assess safety was done midway through the study by an outside reviewer (MW). The first analysis of all endpoints was done after all enrolled patients had passed the 6-month post-operative point (July 17, 1992). At the time of the analysis reported here (September 4, 1993), 93% of the enrolled patients had died.

Pathological evaluation

The tissue sections of the recurrent tumours were reviewed by one of us (PCB) without any knowledge of patients' treatment or outcome. Fibrillary astrocytic tumours were classified by a modified Ringertz system.[11] As part of the study, but not as a determinant of treatment, malignant gliomas (largely glioblastomas) were further subdivided into those that were clearly actively proliferating tumours and those that showed the effects of treatment. The "active" or "recurrent" neoplasms were cellular, mitotically active tumours resembling glioblastomas as encountered routinely before radiotherapy or chemotherapy. The "quiescent" or "persistent" tumours were generally extensively necrotic, but without peripheral pseudopalisading. These tumours were paucicellular neoplasms that often contained pleomorphic cells.[12]

To study the histological effects of the polymer implants with and without incorporated carmustine, 11 brains were evaluated at necropsy: 7 were from patients who had received carmustine polymers, and 4 from patients who had received placebo polymers. Postmortem magnetic resonance images were obtained for the brains of 8 patients.[13]

Statistical methods

The primary endpoint of this trial was survival from the time of polymer implantation. Secondary endpoints included rates of complications, and toxicity and quality of life measurements. The primary efficacy analysis included all the patients randomised, and all analyses classified patients according to treatment assigned (intention-to-treat). Event times were censored if the patient was still alive on September 4, 1993. The primary endpoint represents time to death from any cause.

Event-time distributions were estimated by the product-limit method[14] and compared by the log-rank statistic.[15] To control for the effects of strong prognostic factors on outcome due to chance imbalances in the treatment groups,[16,17] adjusted analyses were done with the proportional hazards regression model.[18] Prognostic factors such as pathological type, Karnofsky performance score, extent of previous surgery, age, and previous use of nitrosoureas were thought to be important a priori.[16] In practice, we included these and other statistically significant predictors in multiple regression models to examine their influence on the estimated treatment effect. Because of inter-correlations, some factors did not remain significant and were removed from the multiple regression. The estimated hazard ratio for carmustine polymers was not affected by these factors.

Differences in complication and toxicity rates between treatment groups were tested for statistical significance by the chi-squared or *t* tests. All p values reported are two-sided.

Results

Patients

Carmustine polymer discs were implanted in 110 patients and placebo polymer discs in 112. Table 1 shows that no significant differences were found between patient groups. Half the patients entered into the study had received previous systemic chemotherapy. Treatment with the carmustine polymer did not lower the performance status or neurological condition of patients compared with those who did not receive carmustine. Within 6 months of the polymer implantation, 11·8% of the carmustine group and 11·6% of the placebo group underwent re-operation.

Characteristics	Carmustine polymer (n=110)	Placebo polymer (n=112)	p
Mean (SD) age (years)	48·1 (12·3)	47·6 (13·6)	0·75
Sex (male)	74 (67%)	69 (62%)	0·38
Race (white)	100 (91%)	103 (92%)	0·78
Mean (SD) Karnofsky performance score	77·0 (13·1)	74·6 (12·1)	0·17
Mean (SD) mini-mental state exam score	24·1 (7·2)	22·6 (8·5)*	0·16
Previous treatment			
Operations			
1	83 (75·5%)	79 (70·5%)	
2	20 (18·2%)	30 (26·8%)	
≥3	7 (6·4%)	3 (2·7%)	0·17
Median interval from first operation	12·9 mo	11·3 mo	0·19
Amount of radiation therapy			
≥45 Gy	108 (98·2%)	110 (98·2%)	
<45 Gy	2 (1·8%)	2 (1·8%)	
None	0 (0·0%)	0 (0·0%)	0·99
Type of radiation therapy			
Local	53 (48·2%)	54 (48·2%)	
Whole brain	28 (25·5%)	23 (20·5%)	
Local and whole brain	29 (26·4%)	34 (30·4%)	
Unknown	0 (0·0%)	1 (0·9%)	0·60
Chemotherapy	58 (52·7%)	54 (48·2%)	0·50
Immunotherapy	7 (6·4%)	5 (4·5%)	0·53
Brachytherapy	2 (1·8%)	5 (4·5%)	0·45
Tumour histopathology at implantation			
Glioblastoma	72 (65·5%)	73 (65·2%)	
Astrocytoma (anaplastic)	15 (13·6%)	16 (14·3%)	
Oligodendroglioma (anaplastic)	4 (3·6%)	5 (4·5%)	
Oligodendroglioma	2 (1·8%)	2 (1·8%)	
Other glial tumours	16 (14·5%)	16 (14·5%)	
Necrosis	1 (0·9%)	0 (0·0%)	
>75% resection at reoperation	88 (79·9%)	87 (78·0%)	0·54

*n=108, scores were missing for 4 patients.

Table 1: **Patient characteristics by treatment group**

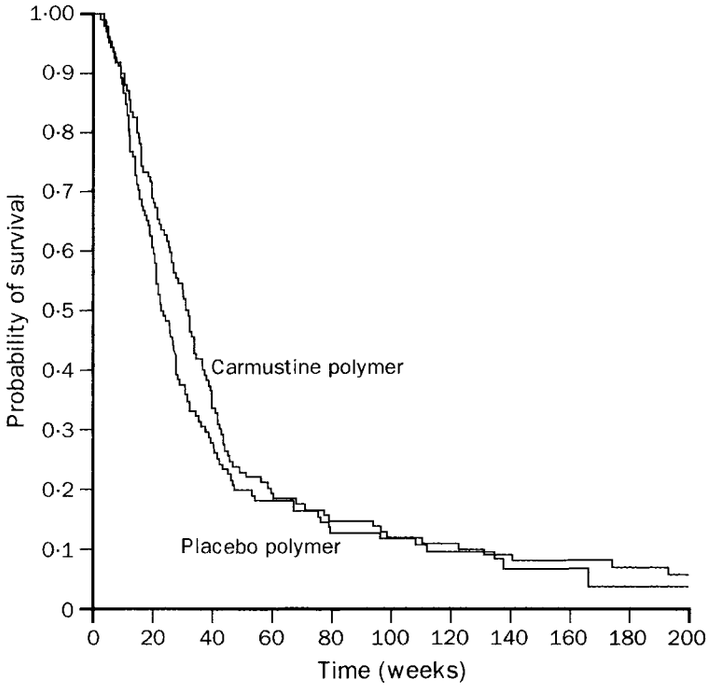

Figure 1: **Overall survival by treatment group (Kaplan-Meier curve)**

Variable	Hazard ratio (95% CI)	p*
Carmustine polymer *vs* placebo polymer	0·83 (0·63–1·10)	0 19
>75% tumour resection *vs* <75% resection	0 56 (0·41–0·76)	<0·001
Age (per decade)	1·24 (1·11–1·39)	<0·001
White *vs* other races	1·83 (1·10–3·06)	0·02
Male *vs* female	0·80 (0·61–1·07)	0·14
Interval from first surgery to index surgery (per year)	0·90 (0·84–0·96)	0·001
Karnofsky ≥70 *vs* <70	0·53 (0·40–0·70)	<0·001
Local radiation *vs* whole brain	0·76 (0 55–1 06)	0·10
Previous chemotherapy *vs* none	1·58 (1·20–2·09)	<0·001
Previous nitrosoureas *vs* none	1·61 (1·22–2·12)	<0·001
Previous immunotherapy *vs* none	1·18 (0·66–2 12)	0·57
"Active" recurrent *vs* "quiescent" tumour at implant surgery	1·25 (0·76–2·05)	0·38
Anaplastic astrocytoma *vs* glioblastoma	0 60 (0·40–0 90)	0·01
Oligodendroglioma *vs* glioblastoma	0·39 (0·26–0·59)	<0·001
All other diagnoses *vs* glioblastoma	0·31 (0·13–0·70)	0·005

*Tests the hypothesis that hazard ratio=1·0.

Table 2: **Estimated hazard ratios and 95% CIs for survival for prognostic factors (univariate regressions)**

During this initial 6-month period, 25·5% of patients in the carmustine group and 18·8% of placebo patients had systemic chemotherapy.

Laboratory analyses

Neither significant reductions in blood cell counts nor abnormalities in blood chemistry or urinalysis were found even though these frequently occur with systemic exposure to carmustine. Hyperglycaemia and glycosuria were observed in both patient groups, but these signs could be attributed to the high doses of corticosteroid used routinely to reduce cerebral swelling in these patients.

Statistical analysis

Median survival was 31 weeks in the carmustine group and 23 weeks in the placebo group. 59 (53%) of 112 patients treated with placebo implants were dead at 6 months compared with 44 (40%) of 110 patients treated with carmustine implants (p=0·061). Among patients with glioblastoma, treatment with placebo polymer led to 64% (47 of 73 patients) mortality at 6 months compared with 44% (32 of 72 patients) mortality for those treated with the carmustine implants (p=0·020).

The overall treatment effect favoured the carmustine polymer (estimated hazard ratio 0·83, p=0·19, log rank, figure 1 and table 2). Although treatment groups were balanced with respect to prognostic factors, several of these were very strong predictors of outcome. For example, resecting 75% or more of the tumour, a Karnofsky performance score greater than 70, and pathological type were all strong predictors of survival irrespective of treatment with the carmustine implants (table 2). When accounting for the effects of treatment and prognostic factors simultaneously, the estimated hazard ratio for treatment (0·67) was statistically significant (p=0·006; table 3, model A). Similar effects were seen in a multiple regression model that stratified for the effect of pathology and adjusted for the other factors (table 3, model B). These different methods of evaluating prognostic factors yielded quantitatively consistent estimates of the beneficial effect of carmustine polymer.

Because the overall survival curves (figure 1) reflect both the treatment effect and influential differences in prognostic factors, we calculated survival curves adjusted by the proportional hazards regression model for the factors listed in table 3. Adjusted survival curves (figure 2) showed an increased median survival of 9 weeks attributable to carmustine, and slightly higher long-term survival.

The clinically most important subset of patients are those with glioblastoma. In these 145 patients, carmustine polymer lowered the risk of death with an estimated hazard ratio of 0·81 (p=0·22), a finding similar to the overall effect. Factors that were significant predictors of outcome in patients with glioblastoma included age (p=0·004), interval from previous surgery (p<0·001),

Variable	Model A (all patients)		Model B (all patients, stratified for pathology)		Model C (glioblastoma patients only n=145)	
	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Carmustine polymer *vs* placebo polymer	0·67 (0·51–0·90)	0·006	0·69 (0·52–0·91)	0·01	0·67 (0·48–0 95)	0·02
Karnofsky >70 *vs* ≤70	0·65 (0·48–0·89)	0·007	0·66 (0·49–0·91)	0·01	0·62 (0·44–0·89)	0·009
Local radiation *vs* whole brain	0·60 (0·43–0·84)	0·003	0·59 (0 42–0·83)	0·003	0·64 (0·43–0·96)	0·03
"Active" *vs* "quiescent"	1·95 (1·13–3·35)	0·02	1·93 (1·26–3·78)	0·02	2·37 (1·20–4·66)	0·01
Previous nitrosoureas *vs* none	1·49 (1·11–2·01)	0·009	1·53 (1·13–2·08)	0·006	1·60 (1·12–2·28)	0·009
White *vs* other races	1·78 (1·04–3·03)	0·03	1·75 (1·03–2·99)	0·04	2·39 (1·15–4·99)	0·02
>75% resection *vs* <75% resection	0·66 (0·48–0·92)	0·01	0·67 (0·49–0·93)	0·02	..	..
Age (per decade)	1·24 (1·10–1·39)	<0·001	1·25 (1·11–1·40)	<0·001	..	..
Interval from previous operation (per year)	..	..	..	..	0·82 (0·73–0·92)	<0·001
Anaplastic astrocytoma *vs* glioblastoma	0·63 (0·42–0·95)	0·03	..	..	..	..
Oligodendroglioma *vs* glioblastoma	0·43 (0·28–0·67)	<0·001	..	..	..	..
All other diagnoses *vs* glioblastoma	0·46 (0·20–1·07)	0·07	..	..	..	..

Table 3: **Effect of carmustine polymer adjusted for prognostic factors (multiple regressions)**

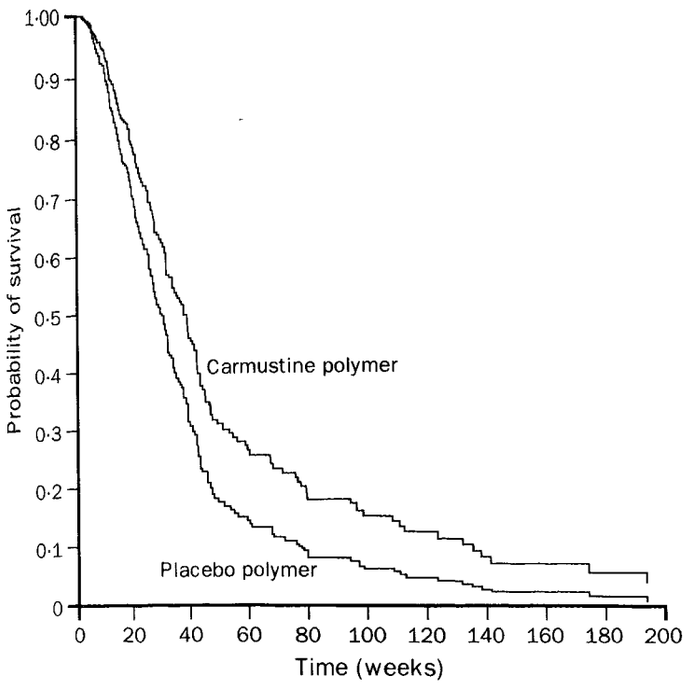

Figure 2: **Overall survival by treatment group after adjustment for prognostic factors**

The curves illustrate the treatment effect expected if all patients were about age 48, white, had performance status >70, underwent >75% resection, had local irradiation, had not previously been exposed to nitrosoureas, and had glioblastomas pathologically classified as active.

Karnofsky performance score (p=0·02), race (p=0·06), and previous nitrosourea chemotherapy (p=0·03). When treatment group and prognostic factors were considered simultaneously in a multiple regression analysis stratified by pathological type, carmustine polymer showed a significant beneficial effect in glioblastoma patients (hazard ratio 0·67, p=0·02; table 3, model C). Also, glioblastoma patients classified as having recurrent active tumours had significantly increased risk compared with those classified as quiescent (hazard ratio 2·37, p=0·01; table 3, model C). With the regression model in table 3, model C, there was no statistically significant interaction between use of carmustine polymer and active versus quiescent tumour, which indicates that the treatment benefit was not restricted only to patients with active recurrent tumour.

Adverse events

During postoperative follow-up, no deleterious effects occurred as a result of polymer implants. Anaemia occurred postoperatively in 7% of patients treated with carmustine polymers and in 11% of placebo controls; 2% of each group had thrombocytopenia and 1% of the carmustine polymer group had leukopenia. 73 patients had seizures postoperatively (41 carmustine, 32 placebo, p=0·199), which was within the expected frequency for postoperative seizures.[19]

Overall incidence of serious intracranial infection was low (5/222, 2·2%) but was more common with carmustine treatment (4/110) than placebo (1/112). This difference was not statistically significant and well within the reported range (9–13%) for recurrent glioma surgery.[2,20] Other minor infections included urinary-tract infections, pneumonia, and conjunctivitis, which were equally common in the two treatment groups and were consistent with the expected general infection rate for patients on steroids who had undergone multiple craniotomies.[2] All patients experienced cerebral oedema during the study, as is typical for postoperative craniotomy patients, and were treated with corticosteroids. There were no apparent differences between the groups in requirement for steroids.

Postmortem studies

11 brains were examined after death. The brains of 9 of the 11 patients contained large disseminated glioblastomas; in no case was there extensive necrosis. Fibrous membranes were evident in the tumour bed in several specimens. In 2 of the 11 patients, the small amount of tumour did not explain the patient's death. 1 of these patients succumbed to disseminated colon cancer and the other died after a 3-week clinical deterioration that was unrelated to the intracranial disease. Postmortem magnetic resonance scans revealed the expected increased T2 signal in the region of the tumour, which often crossed the corpus callosum. In no case did the extent of abnormal magnetic resonance signal seem remarkable or unusually large for a recurrent glioblastoma, nor were there any changes directly attributable to the implants.

Discussion

Use of biodegradable polymers to deliver prolonged, high doses of chemotherapy directly to a tumour, thereby sparing the patient from systemic exposure to the drug, represents a new tool in the armamentarium against cancer. In this study, carmustine polymer implants significantly prolonged survival. By contrast with systemic carmustine therapy, no notable untoward events were associated with the treatment.

The polyanhydride polymer used in the present trial is hydrophobic and therefore protects carmustine from decomposition until it is released into the tumour environment. Compared with systemic delivery, intracranial implantation of a carmustine-containing polymer in animals increases brain exposure to the drug 113-fold.[7]

The study was designed to isolate the effect of drug-impregnated polymer from previous treatments, so that the efficacy of implantation of the polymer-drug could be stringently evaluated. Although the study design controlled for large imbalances by randomisation, we increased the precision of the evaluation of treatment effect with adjusted analyses. Consistency in the estimated hazard ratios in favour of carmustine polymer—irrespective of the method of analysis—and the control of bias and imbalance afforded by the study design, strongly support the efficacy of this drug-delivery system. Curran et al[16] used a recursive partitioning technique to refine the stratification and design of malignant glioma trials. They observed an impact on survival of age, performance status, and tumour histopathology, independent of treatment method. Florell and colleagues[17] have emphasised the selection bias of uncontrolled trials for assessing treatment of brain tumours. The benefits of interstitial radiation implants reported in previous studies could be obtained simply by prospectively applying the entry criteria, and did not depend on the actual treatment.[17] In view of the modest but significant improvement in survival of carmustine-polymer-treated patients with recurrent gliomas, future studies will evaluate the effectiveness of higher doses of carmustine and the use of the polymer implants as the initial therapy for brain tumours.

The present results suggest that biodegradable polymers can assist delivery of other drugs. Brain tumour therapy might now be approached with agents that do not pass the blood-brain barrier. We have found that carboplatin,[21] 4-hydroperoxycyclophosphamide,[22] camptothecin,[23] and paclitaxel[24] can be effectively delivered intracranially to improve treatment of brain tumours in rats. Steroids[25] and immunotoxins such as the transforming growth factor alpha pseudomonas exotoxin fusion protein[26] may be more safely delivered by polymers. Peptides and polynucleotides including inhibitors of angiogenesis[27] and antisense oligonucleotides[28] might also be more effective when delivered locally.

Demonstration of effective polymeric delivery of carmustine directly into the brain opens the door to treatment of other diseases requiring central nervous system delivery. Solid tumours in other locations also might be treated with polymeric delivery of radiosensitisers or chemotherapeutic drugs. We suggest that, whenever local approaches such as surgery or radiation therapy are being used, consideration be given to development of biodegradable polymer delivery systems to maximize the benefit of such treatments.

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