A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma[1,2]

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A previous placebo-controlled trial has shown that biodegradable 1,3-bis (2-chloroethyl)-1-nitrosourea (BCNU) wafers (Gliadel wafers) prolong survival in patients with recurrent glioblastoma multiforme. A previously completed phase 3 trial, also placebo controlled, in 32 patients with newly diagnosed malignant glioma also demonstrated a survival benefit in those patients treated with BCNU wafers. Because of the small number of patients in that trial, a larger phase 3 trial was performed to confirm these results. Two hundred forty patients were randomized to receive either BCNU or placebo wafers at the time of primary surgical resection; both groups were treated with external beam radiation postoperatively. The two groups were similar for age, sex, Karnofsky performance status (KPS), and tumor histology. Median survival in the intent-to-treat group was 13.9 months for the BCNU wafer-treated group and 11.6 months for the placebo-treated group (log-rank *P*-value stratified by country = 0.03), with a 29% reduction in the risk of death in the treatment group. When adjusted for factors affecting survival, the treatment effect remained positive with a risk reduction of 28% (*P* = 0.03). Time to decline in KPS and in 10/11 neuroperformance measures was statistically significantly prolonged in the BCNU wafer-treated group ($P \leq 0.05$). Adverse events were comparable for the 2 groups, except for CSF leak (5% in the BCNU wafer-treated group vs. 0.8% in the placebo-treated group) and intracranial hypertension (9.1% in the BCNU wafer-treated group vs. 1.7% in the placebo group). This study confirms that local chemotherapy with BCNU wafers is well tolerated and offers a survival benefit to patients with newly diagnosed malignant glioma. *Neuro-Oncology 5, 79–88, 2003 (Posted to Neuro-Oncology [serial online], Doc. 02-023, February 10, 2003. URL http://neuro-oncology.mc.duke.edu)*

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[4]Abbreviations used are as follows: BCM, Brain Cancer Module; BCNU, 1,3-bis (2-chloroethyl)-1-nitrosourea; CI, confidence interval; CSF, cerebrospinal fluid; EORTC, European Organization for Research and Treatment of Cancer; GBM, glioblastoma multiforme; ITT, intent-to-treat; KPS, Karnofsky performance status; QLQ, Quality of Life Questionnaire; SPECT, single photon emission computerized tomography; SAP, Statistical Analysis Plan.

Presently, malignant gliomas are treated by resection, external beam radiation, and, in some cases, systemic chemotherapy (Cairncross et al., 1992; Chang and Prados, 1995; Cristante et al., 1992; Fine et al., 1993;

Hildebrand et al., 1997; Lesser and Grossman, 1994; Reulen et al., 1988; Shapiro et al., 1992; Walker et al., 1980). Randomized trials of radiotherapy have consistently shown an improvement in survival compared to surgery alone (Walker et al., 1980). In some cases, systemic chemotherapy (including nitrosoureas, procarbazine, carboplatin, or temozolomide) is used in addition to radiotherapy; however, none of these therapies has been shown to be effective in double-blind, randomized, controlled studies in patients with primary malignant glioma (Chang and Prados, 1995; Culver et al., 1992; Fine et al., 1993; Hildebrand et al., 1997; Lesser and Grossman, 1994; Prados and Levin, 2000; Walker et al., 1980). Nitrosoureas, especially carmustine—3-bis (2-chloroethyl 1)-1-nitrosourea (BCNU), have been used most frequently because of their demonstrated in vitro activity against glioma cell lines and their relative ability to cross the blood-brain barrier. Their clinical effectiveness, however, has been limited because of the short half-life (about 20 min), the small fraction of the systemically administered dose reaching the tumor at an effective concentration, and their systemic toxicities. Other treatment modalities, including immunotherapy, immunoradiotherapy, and gene therapy, are under development but burdened with the problem of drug delivery across the blood-brain barrier (Bigner et al., 1995; Culver et al., 1992; Fontana et al., 1992; Jachimczak et al., 1993; Köppen et al., 1991; Kramm et al., 1995; Laske et al., 1997; Liebermann et al., 1995; Martuza, 1997; Merchant et al., 1990, 1997; Mesnil et al., 1996; Rainov, 2000; Ram et al., 1997; Reist et al., 1995; Riva et al., 1997; Wersall et al., 1997). In spite of the numerous therapies administered, the median survival of patients with high-grade gliomas is approximately one year (Brada and Yung, 2000; Hildebrand et al., 1997; Levin et al., 1997).

Malignant gliomas, even when macroscopically resected, invariably recur because of the infiltrative nature of the disease (Giese and Westphal, 1996). Most of these tumor recurrences are local, occurring within 2 cm of the original lesion (Hochberg and Pruitt, 1980). Therefore, many approaches to local tumor treatment have been evaluated, such as direct introduction of chemotherapeutic agents by controlled release polymers placed in the tumor resection cavity, direct infusion of toxin conjugates into the tumor, and application of virus-producing cells for suicide gene therapy (Bigner et al., 1995; Brem et al., 1994; Culver et al., 1992; Köppen et al., 1991; Kramm et al., 1995; Laske et al., 1997; Lesser and Grossman, 1994; Mesnil et al., 1996; Rainov, 2000; Ram et al., 1997; Salcman, 1994; Westphal and Giese, 1999).

Gliadel wafers (poly [carboxyphenoxy-propane/sebacic acid] anhydride wafers containing 3.85% carmustine [BCNU]) are designed to release carmustine slowly over a 2- to 3-week period after they have been placed on the surface of the tumor resection cavity. After optimal tumor resection, the surgeon implants up to 8 wafers, depending on the size of the surgical resection cavity. Efficacy of local chemotherapy with BCNU wafers has been previously demonstrated in patients with recurrent glioblastoma multiforme (GBM) in a double-blind, randomized, placebo-controlled study (Brem et al., 1995). In patients undergoing surgery for recurrent GBM, BCNU wafers significantly increased survival compared to placebo wafers (median survival of 7.2 months for the BCNU wafer-treated patients vs. 5.4 months for the placebo wafer-treated patients) (Brem et al., 1995).

A minority of patients undergo reoperation for tumor recurrence (Salcman, 1994); therefore, the potential benefits of local chemotherapy with BCNU wafers at the time of initial surgery in the larger group of patients undergoing primary resection have been studied. In an initial small study of patients (N = 32) with primary malignant glioma, BCNU wafer-treated patients (n = 16) had a median survival of 13.4 months vs. 9.2 months for the placebo wafer-treated patients (n = 16). The BCNU wafer-treated patients had significantly improved 12-month and overall survival compared to placebo wafer-treated patients (Valtonen et al., 1997).

The clinical benefits and safety profile of BCNU wafers may differ in the primary versus the recurrent surgery setting. In patients with tumor recurrence, gliosis may prevent diffusion of drug into the brain parenchyma and thus decrease access to residual tumor cells. Also, the effects of prior radiation to the target areas of recurrent tumors and the possible effects of concomitant radiation during local chemotherapy for primary malignant glioma need to be evaluated. Therefore, a placebo-controlled, multicenter, multinational, double-blind, randomized, prospective phase 3 trial was conducted to test the efficacy of BCNU wafers as local chemotherapy for malignant glioma at the time of primary surgical resection. Overall survival of the intent-to-treat (ITT) population by the Kaplan-Meier method was the primary clinical end point; time-to-clinical decline as measured by Karnofsky performance status (KPS) and neuroperformance score and time-to-disease progression were secondary end points.

Materials and Methods

Study Design and Patient Selection Criteria

A prospective, randomized, placebo-controlled, multicenter, multinational, double-blind trial was conducted that included 240 patients with the intraoperative diagnosis of malignant glioma. A total of 38 centers in 14 countries enrolled patients from December 1997 to June 1999. To be eligible, the patient had to have the intraoperative diagnosis of malignant glioma (determined by frozen section); be between the ages of 18 and 65; have radiographic evidence on cranial MRI of a single, contrast-enhancing, unilateral, supratentorial, cerebral tumor; be treated within 2 weeks of the baseline MRI; and have a KPS of 60 or higher. Patients with prior cytoreductive therapy, multifocal disease, prior radiotherapy to the brain, known hypersensitivity to nitrosoureas, and clinically significant laboratory abnormalities (in the judgement of the investigator) were excluded. The study protocol was approved by the ethics review committee at each study site. Informed consent was obtained in writing from all patients prior to the conduct of any study-specific procedures. All patients were provided the existing standard of care for the initial treatment of malignant glioma, that is, surgical resection

followed by external beam radiotherapy. The efficacy of BCNU wafers had not been firmly established in patients undergoing initial surgery for malignant glioma at the time of this trial, nor were alternative local chemotherapeutic options available to these patients. Therefore, in order to determine the potential benefit of BCNU wafers, and to eliminate bias between study groups, placebo wafers were implanted in the comparator arm. Patients were fully informed of the potential risks and benefits of BCNU wafer treatment and the fact that they would have a 50% chance of receiving either the active BCNU wafers or identical-appearing placebo wafers. They were also fully informed that they would otherwise receive the accepted standard treatment for their disease.

Treatment Plan and Evaluations

After the intraoperative pathological diagnosis of malignant glioma, patients were randomized to receive either BCNU wafers plus limited-field radiation or identical-appearing placebo wafers plus limited-field radiation. Randomization was done within each center by providing four blinded treatment boxes containing two boxes of BCNU wafers (Gliadel wafer, Guilford Pharmaceuticals Inc., Baltimore, Maryland) and two boxes of placebo wafers. This measure was followed to attempt to force balance of treatment assignment within each center. After maximal surgical tumor resection, up to 8 wafers were implanted in each patient. Patients received a total of 55 to 60 Gy of limited-field radiation to the tumor site and surrounding margin postoperatively, starting 14 days after wafer implantation according to a standard protocol (Appendix II). The protocol specified that systemic chemotherapy was prohibited until the time of recurrence in all patients except those with anaplastic oligodendrogliomas (as determined by the local pathologist). Nine patients met this criterion (5 in the BCNU wafer group and 4 in the placebo group); of these, 4 in the BCNU wafer group and 1 in the placebo group received systemic chemotherapy prior to recurrence. In addition, there was 1 protocol violation in which a patient with anaplastic oligoastrocytoma in the BCNU wafer group received systemic chemotherapy prior to recurrence. Otherwise, patients did not receive systemic chemotherapy unless a diagnosis of tumor progression was made, at which time any therapy could be employed.

Patients were followed with clinical and radiological evaluations at prespecified intervals. All patients were followed for at least 12 months after the last patient was enrolled, with the maximum time of follow-up approximately 30 months. The vital status of all patients was determined 12 months after the last patient was enrolled.

Statistical Methods/Analyses

A Statistical Analysis Plan (SAP) was developed as part of the study protocol. The sample size for the study was prespecified and calculated on the basis of a two-tailed log-rank test with an alpha level of 0.05 and a power of 1 - ß = 0.90 to detect an 18% difference in 12-month survival rates between the two treatment groups (based on survival rates of 68% in the BCNU wafer group and 50% in the placebo group, and assuming 18 months of accrual, 12 months of follow-up time, and a 15% patient loss rate).

This study was conducted by using stratified blocked randomization by clinical center. This measure explicitly recognizes the center as a source of potential variability and requires the use of a statistical test that accounts for the stratification (for example, the stratified log-rank test). Because the study was stratified by center, it was also stratified by country (a center exists uniquely within a specific country) and the study analyses were stratified by country. The primary end point of this trial was overall survival in the ITT population by the Kaplan-Meier method (log-rank statistic stratified by country) 12 months after the final patient was enrolled. Overall survival was defined as the duration between the date of randomization and date of death from any cause, or the date of last contact if the patient was lost to follow-up (1 case). Overall survival and 12-month survival were also determined for the GBM subgroup of patients using the same methodology as that employed for the ITT population.

In order to account for the effects of prognostic factors on survival, multiple-regression analyses using the Cox proportional hazards model were employed. After fitting each model, the least significant prognostic factor was removed from the model with subsequent re-estimation of risk ratios and significance levels. This iteration was continued for each analysis until all factors remaining in the model had P-values ≤ 0.05.

A number of secondary end points were also prespecified in the SAP. Time-to-progression was assessed in 3 different ways: time-to-KPS decline, time-to-neurological progression, and radiological and clinical criteria. A decline in the KPS score was defined as a KPS <60 for 2 consecutive assessments during the short-term follow-up period (study days 7–30) or for any 1 assessment during the long-term follow-up period (study months 1–12). A KPS score of 60 was prespecified in the SAP as the lowest KPS score compatible with independent patient functioning. A decline in KPS <60 was selected as a clinically meaningful decline, as this represents a point at which patients require frequent medical care and significant assistance to perform most, if not all, activities of daily living. In the case of neurological progression, progression was determined by decline in the neurological evaluation on 11 prespecified neuroperformance measures (vital signs, level of consciousness, personality, speech, visual status, fundoscopic examination, cranial nerve examination [III, IV, VI], cranial nerve examination [other], sensory status, cerebellar examination, and other signs). These neuroperformance measures represent aspects of the standard neurological clinical examination performed by the clinician, although they do not represent a validated tool referenced in the literature. In order to detect changes over time, the responsible clinician assessed the patient's neurologic function on a 6-point ordinal scale: 1 = normal, 2 = slightly abnormal, 3 = moderately abnormal, 4 = severely abnormal, 5 = not able to perform, and 6 = not done. Deterioration was defined as decline in the scale for 2 consecutive assess-

ments during the short-term follow-up period (study days 7–30) or for any one assessment during the long-term follow-up period (study months 1–12).

An effort was made to collect quality-of-life measurements by utilizing the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire QLQ-C30 and Brain Cancer Module BCM-20 brain cancer modules. However, missing data due to attrition (death) and noncompliance with questionnaires were significant in this study. As a result, the amount of data available for analysis was insufficient to allow for meaningful conclusions to be drawn.

Assessment of disease progression (based on a composite of radiological and clinical measures) was based on the occurrence of clinical deterioration or the development of a new neurological sign or change in an imaging study. When this event was documented, a standard MRI was performed. The diagnosis of progression was based either on an increase in tumor size (at least a 25% increase in the largest cross-sectional area compared to the postoperative MRI scan) or the appearance of a new lesion; if an MRI scan was not available, progression was based on a documented clinical/neurological decline.

Neuroradiology Evaluations

MRI was the standard imaging modality for this study, except for patients for whom this procedure was contraindicated (e.g., patients with cardiac pacemakers), who received CT scans. MRI scans, with and without enhancement, were performed at baseline, within 48 h postoperatively, and at 3 months postoperatively. The postoperative scan with enhancement was used to determine the extent of resection and as a basis for documenting recurrence on subsequent scans. MRI scans could be obtained by the treating physician if there was clinical suspicion of tumor progression. All MRI data were interpreted by individual sites.

Histological Analyses

The final histological diagnosis was determined by a specified methodology. The local neuropathologist determined the presence of a malignant glioma by intraoperative frozen sections. The definitive local diagnosis was then obtained from paraffin-embedded material, according to the WHO guidelines (Kleihues and Cavenee, 2000). Slides were then sent for central neuropathological review. In cases where either the local or central neuropathologist, but not both, diagnosed GBM, a referee neuropathologist's opinion was obtained. Patients were included in the GBM subgroup when at least 2 of the 3 diagnoses (i.e., local, central, and referee) were GBM. Patients with the central diagnosis of giant-cell glioblastoma or gliosarcoma were included in the GBM subgroup. Since these subgroups are small, it is not clear that they confer any prognostic difference compared to GBM, and they have not been reported as separate pathologic categories in any previous large trials of gliomas.

Safety Evaluations

Data for adverse events and serious adverse events were collected regularly at all patient visits throughout the study. Hematology and biochemical laboratory tests were conducted during the first month after surgery and at intervals thereafter. Local healing abnormalities, indications of infections, and CSF leaks were specifically monitored during the study.

Results

Patient Population Characteristics at Baseline

A total of 240 patients were randomized to treatment (120 patients were treated with BCNU wafers and 120 with placebo wafers). GBM was the diagnosis of 207 patients (101 in the BCNU wafer group and 106 in the placebo group). The sex, age, and KPS of the patients in the 2 treatment groups are shown in Table 1, and the final histological diagnoses for the 2 treatment groups are shown in Table 2. There were no significant differences between the 2 groups. The mean ± SEM volume of the

Table 1. Baseline demographic characteristics of patients (N = 240)

Demographic characteristic		Gliadel wafer n = 120	Placebo n = 120
Sex	Male n (%)	76 (63.3)	84 (70.0)
	Female n (%)	44 (36.7)	36 (30.0)
Age (years)	Mean (SEM)	52.6 (0.8)	53.6 (0.8)
	Range	21–72	30–67
Karnofsky performance score			
60		16	16
70		21	17
80		25	24
85*		2	0
90		31	40
95*		0	1
100		25	22

* The baseline Karnofsky performance score was recorded as 85 or 95 in 3 patients representing an intermediate level of function in the judgement of the responsible clinician.

Table 2. Final histological diagnosis

	Treatment group	
Tumor type	Gliadel wafer n = 120	Placebo n = 120
Anaplastic astrocytoma	1	1
Anaplastic oligodendroglioma	5	4
Anaplastic oligoastrocytoma	7	3
Glioblastoma multiforme	101	106
Metastasis/Brain Metastasis	2	1
Other*	4	5

* "Other" diagnoses consisted of a variety of histological types including astroblastoma, pleiomorphic xanthoastrocytoma, gemistocytic astrocytoma, and oligoastrocytoma.

tumor was larger in the BCNU wafer group (66.8 ± 5.9 cm^3) than in the placebo group (50.8 ± 5.3 cm^3, $P = 0.047$). The mean ± SEM percent tumor resection (as measured by comparing the preoperative to postoperative MRI scans) did not differ significantly and was 89.9 ± 1.3% for the BCNU wafer group and 88.3 ± 1.6% for the placebo group.

Primary End Point: Overall Survival of the ITT Group

All patients randomized in this study (120 patients in each of the BCNU wafer and placebo wafer groups) were included in the ITT overall survival analysis. Three patients were censored alive at the time of last contact: 2 patients were lost to follow-up, and 1 patient withdrew consent. All other patients either died during the course of follow-up or were known to be alive at the end of the study follow-up period. Survival time was significantly increased in the BCNU wafer group compared to the placebo wafer group. The median survival time in the ITT population was 13.9 months for the BCNU wafer group and 11.6 months for the placebo wafer group, with 1-year survival rates of 59.2% and 49.6%, respectively. The difference between the ITT survival curves, by the Kaplan-Meier method (Fig. 1), was statistically significant ($P = 0.03$, stratified log-rank statistic), with a 29% (95% CI, 4%–48%) reduction in risk of death in the BCNU wafer-treated group compared to the placebo wafer-treated group.

In order to determine if the baseline prognostic-factor imbalance between the 2 treatment groups might have influenced the survival results, a stratified Cox proportional hazards model was performed after a determination that the prognostic factors met the proportional hazards assumption. Prognostic factors included in this model were baseline KPS (≤70 vs. >70), age (≥60 vs. <60), final histological diagnosis (GBM vs. non-GBM), sex, and number of wafers implanted. Age ($P = 0.001$) and baseline KPS ($P = 0.0002$) were shown to be strong indicators of survival (with tumor histology falling out of the final model). Patients ages ≥60 years had a higher risk of death than patients <60 years of age, and patients with a low KPS (≤70) had a higher risk of death than patients with a high KPS (>70). When the overall survival was adjusted for these prognostic factors, the BCNU wafer-treated patients still had statistically significantly longer survival than the placebo wafer-treated patients ($P = 0.03$). Reduction in risk of death for the BCNU wafer-treated group was 28% (95% CI, 2%–47%) compared to the placebo wafer-treated group. This analysis demonstrates that the survival difference between the BCNU wafer group and the placebo wafer group (a 28% reduction in risk of death) is clinically significant and convincingly independent of other prognostic factors.

One of the assumptions at the initiation of this study was that the number of patients undergoing reoperation at the time of disease progression would be low, as this study was predominantly conducted within the European Union, and the clinical management of patients typically involves reoperation for tumor progression at a lower frequency than in the United States. However, 29% of

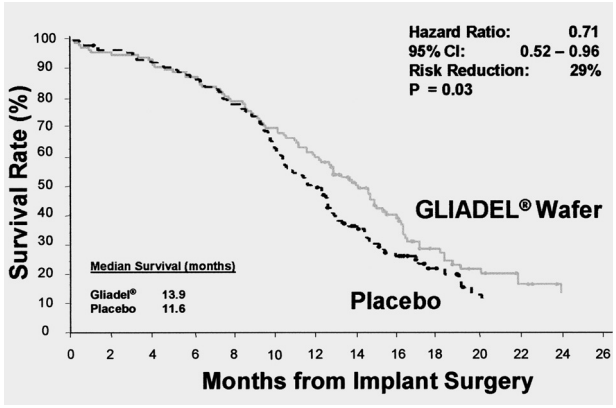

Fig. 1. Kaplan-Meier survival curve (ITT population)

the BCNU wafer patients and 25% of the placebo wafer patients had reoperation for tumor progression (based on the treating physician's clinical decision for reoperation). Reoperation was a delayed event and may have confounded the primary survival end point by providing treatment to patients who might otherwise have died. To test this possibility, in the placebo group a Kaplan-Meier analysis was done in which patients were censored at the time of reoperation. As seen in Fig. 2, the median survival in placebo patients undergoing reoperation was prolonged relative to those who did not undergo reoperation, thus confirming that reoperation would confound the primary end point in this trial.

Therefore, an analysis of the ITT population in which those undergoing reoperation were censored at the time of reoperation was performed, and the resulting Kaplan-Meier curve is shown in Fig. 3. Overall, when living patients undergoing reoperation for disease progression were censored, the BCNU wafer group survived longer ($P = 0.02$, stratified log-rank statistic) than the placebo group (median survival of 14.8 months vs. 11.4 months), with a risk reduction of 36% (95% CI, 8%–55%). The mean time to reoperation for the BCNU wafer-treated patients who underwent second surgery was 272 days versus 218 days for the placebo wafer-treated patients ($P = 0.10$).

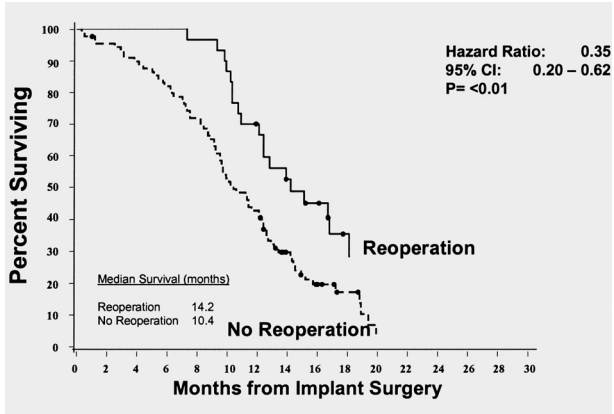

Fig. 2. Kaplan-Meier survival curve: Effect of reoperation in placebo group (ITT population)

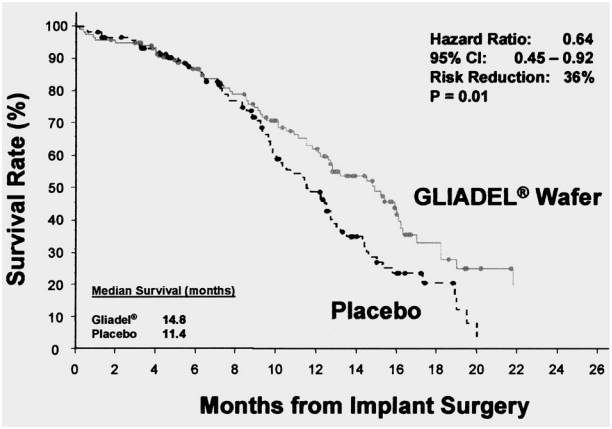

Fig. 3. Kaplan-Meier survival curve censoring patients with reoperation for tumor progression (ITT population)

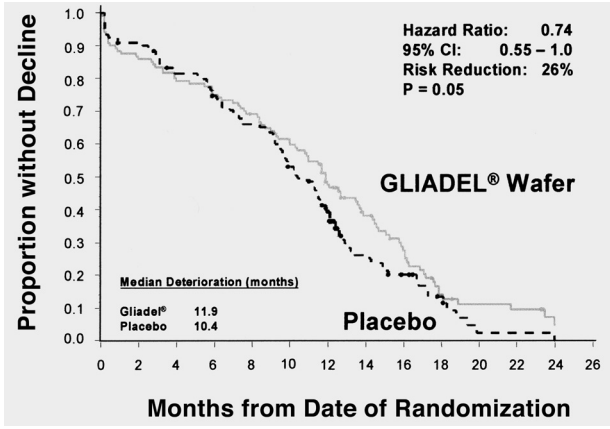

Fig. 5. Karnofsky performance score decline (ITT population)

Patients were also allowed to receive chemotherapy at the time of tumor recurrence. Thirty-five of 36 patients who underwent reoperation at the time of recurrence also received chemotherapy; in the placebo group, 28 of 30 patients undergoing reoperation received chemotherapy. Therefore, the analysis done to account for the effect of reoperation at the time of recurrence effectively accounted for the effect of chemotherapy given at the time of recurrence; no separate analysis was performed.

GBM Subgroup Analysis

Median survival in the BCNU wafer-treated GBM group (n = 101) was longer (13.5 months) than in the placebo wafer-treated GBM group (n = 106; 11.4 months). The comparison of the survival curves by the Kaplan-Meier method showed that the difference was not statistically significant ($P = 0.10$, stratified log-rank statistic; Fig. 4). However, the GBM group represents a selected subgroup of the entire randomized study population, thus introducing the possibility that imbalance between the treatment groups in terms of significant prognostic factors may have occurred because of the selection process. The use of a Cox proportional hazards model is an accepted method to adjust for the possibility of this imbalance and to determine if the treatment effect seen is a result of an independent treatment effect or the existence of more patients in the treatment group with more favorable prognostic factors. When corrections were made for these prognostic factors, BCNU wafers significantly prolonged survival in the GBM subgroup ($P = 0.04$, stratified log-rank statistic), with a risk reduction of 31% (95% CI, 3%–51%).

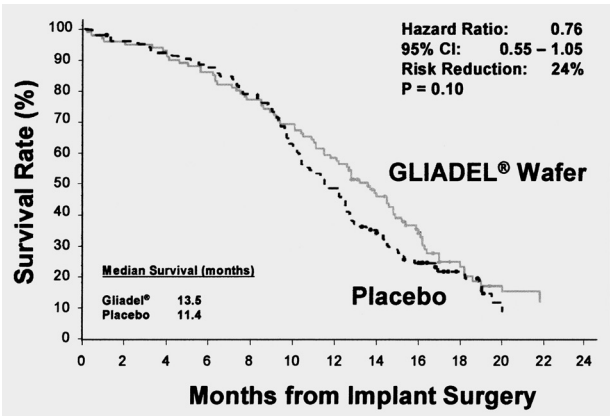

Fig. 4. Kaplan-Meier survival curve (GBM subgroup)

KPS Decline

In the ITT population, the median time to KPS deterioration was longer (11.9 months vs. 10.4 months; 95% CI, 10.4 months–13.7 months), and more patients were deterioration-free at 1 year after initial surgery (47.5% vs. 39.3%) in the BCNU wafer-treated group than in the placebo wafer-treated group (Fig. 5). This difference was statistically significant ($P = 0.05$, stratified log-rank statistic), with a risk reduction of 26% (95% CI, 0%–45%).

Neuroperformance Measures Deterioration

The time to deterioration for each of 11 individual neuroperformance measures was calculated from the date of randomization to the date of neurological deterioration by the Kaplan-Meier method. In the ITT population, the difference between the BCNU wafer-treated group and the placebo wafer-treated group was statistically significant ($P < 0.05$, stratified log-rank statistic) for all but one neuroperformance measure (Table 3). The exception was visual status ($P = 0.09$), although in this measure the median time to deterioration was also longer in the BCNU wafer group than the placebo wafer group.

Progression-free Survival

Determination of progression-free survival was based on a composite measure using radiological and clinical decline criteria and was calculated by the Kaplan-Meier method. Progression-free survival was similar in both treatment groups (5.9 months) ($P = 0.90$, stratified log-rank statistic).

Table 3. Time to neuroperformance decline (ITT Population)

Neuroperformance measure	Median time without deterioration (weeks) Gliadel wafer n = 120	Placebo n = 120	*P*-value*
Vital signs	54.9	49.1	0.010
Level of consciousness	52.1	45.4	0.016
Personality	51.7	40.0	0.008
Speech	49.6	36.7	0.003
Visual status	44.0	42.4	0.087
Fundus	55.1	46.3	0.007
Cranial nerves II, IV, VI	54.9	49.1	0.016
Cranial nerves, other	54.3	46.3	0.003
Motor status	45.4	31.4	0.013
Sensory status	51.6	44.1	0.024
Cerebellar status	54.1	46.7	0.011

* Stratified by country

Table 4. Neurologic adverse events

Adverse event	Gliadel wafer n = 120 n (%)	Placebo n = 120 n (%)
Nervous system		
Abnormal gait	6 (5.0)	6 (5.0)
Amnesia	11 (9.2)	12 (10.0)
Aphasia	21 (17.5)	22 (18.3)
Ataxia	7 (5.8)	5 (4.2)
Brain edema	27 (22.5)	23 (19.2)
Confusion	28 (23.3)	25 (20.8)
Convulsion	40 (33.3)	45 (37.5)
Depression	19 (15.8)	12 (10.0)
Dizziness	6 (5.0)	11 (9.2)
Facial paralysis	8 (6.7)	5 (4.2)
Grand mal convulsion	6 (5.0)	5 (4.2)
Hemiplegia	49 (40.8)	53 (44.2)
Incoordination	3 (2.5)	8 (6.7)
Intracranial hypertension	11 (9.2)	2 (1.7)
Neuropathy	8 (6.7)	12 (10.0)
Speech disorder	13 (10.8)	10 (8.3)

Adverse Effects and Safety

Although the numbers of deaths, adverse events, and laboratory abnormalities were high in this study, as may be expected in this patient population, the safety results were comparable for the BCNU wafer and placebo wafer groups. The adverse event profile for the BCNU wafer group was similar to that of the placebo wafer group. The most common adverse events were tumor progression, neurological progression, and general clinical deterioration. There were no statistically significant differences between groups in the number of patients reporting any nervous system adverse event or in any adverse event occurring in >5% of the safety population, with the exception of intracranial hypertension, which was reported by 11 patients in the BCNU wafer group and 2 patients in the placebo wafer group ($P = 0.019$). Intracranial hypertension was a late event, occurring at greater than 6 months following implantation in 9 of the 11 patients in the BCNU wafer-treated group. Therefore, it is unlikely that any of these late-occurring events were directly related to the BCNU wafers. Rather, they were likely related to recurrence of the primary tumor and an associated increase in intracranial pressure caused by edema or mass effect from the tumor. Convulsions (both frequency and time-to-seizure), intracranial infections, and healing abnormalites were not more common in the BCNU wafer group than in the placebo wafer group. CSF leak was more common in the BCNU wafer group than in the placebo wafer group (6 patients compared to 1 patient), although CNS infections were not more common in BCNU wafer-treated patients. Nervous system adverse events occurring in ≥5% of either of the treatment groups are shown in Table 4.

Discussion

This large, international, placebo-controlled, multicenter, double-blind, randomized, prospective phase 3 trial for malignant glioma has demonstrated the efficacy of local chemotherapy using BCNU wafers (Gliadel wafers) for the treatment of malignant glioma at the time of primary diagnosis and surgery. In addition to the overall survival benefit (29% reduction in risk of death in the ITT group), BCNU wafers produced a clinical benefit in time-to-decline in KPS and 10/11 neuroperformance measures. The large trial size (240 patients) and blinded conduct of this trial increase the likelihood that any potential confounding factors were evenly distributed between the 2 treatment groups. However, to ensure that the survival benefits observed in the study were not due to an imbalance of baseline prognostic factors that could affect outcome (e.g., age, KPS, and tumor histological type), a Cox proportional hazards model analysis was performed confirming that the treatment effect is present when adjusting for baseline prognostic factors affecting survival. The mean percent resection for the 2 treatment groups was comparable, as was the frequency and type of postoperative radiotherapy and posttumor recurrence chemotherapy (data not shown). The BCNU wafer-treated patients had significantly larger tumors at baseline than the placebo wafer-treated patients.

Approximately 86% of the patients enrolled in this study received a diagnosis of GBM. The subgroup analysis for survival in the GBM subgroup yields a treatment benefit for BCNU wafer group that barely misses statistical significance ($P = 0.10$) in the unadjusted analysis but becomes statistically significant ($P = 0.04$) when adjusted for baseline prognostic factors (age and KPS). The hazard ratios in the ITT population and the GBM subset were 0.71 (representing a 29% mortality risk reduction) and 0.76 (representing a 24% mortality risk reduction), respectively, thus indicating that the drug has a treatment effect in both patient groups.

This study was undertaken in 14 different countries with 38 enrolling centers that are not part of a specific study consortium, yet all are regional centers of excellence in brain tumor patient care. Therefore, the results of such studies may be taken as an indication of what may be predicted in general clinical practice in a number of countries.

This study had an age eligibility criterion of up to 65 years old. This requirement was specified in order to minimize the impact of comorbidities, common in patients over the age of 65, on the primary end point of survival.

In the present study, the BCNU wafer-treated group had a benefit in time-to-decline in KPS and 10/11 neuroperformance measures. However, time-to-disease progression, as primarily measured by imaging studies, was no different in the 2 treatment groups. The optimal end point and time-to-disease progression measures in clinical trials of malignant glioma therapies are debated issues (Brada and Yung, 2000). While survival is the firmest end point and virtually all patients with this disease who expire do so because of CNS tumor progression, time-to-progression based on imaging studies has been used with mixed results in the past (Brada and Yung, 2000). Difficulties faced with using an imaging measure to detect disease progression include the diffuse and invasive nature of this disease (Andrews et al., 1997), the effects of concomitant steroids on image-based indications of disease recurrence/tumor progression and on clinical signs (both of which may respond to increased steroid doses) (Bigner et al., 1995), and establishing a firm correlation between the imaging evidence of disease recurrence and survival (Brada and Yung, 2000). In addition, at the time of the initial surgery, the clinical goal is to perform a gross total resection. Thus, in the immediate postoperative period there is optimally no residual tumor enhancement from which to make a comparison of tumor regrowth. Therefore, clinical parameters such as time-to-KPS decline are widely used as an indicator of disease progression.

The present study may illustrate a disparity between a radiological/imaging disease-progression end point and a completely clinically based end point. The imaging/radiological-clinical composite time-to-progression result was not positive, although both the time-to-progression for the KPS and the neuroperformance evaluations were positive. Interestingly, the imaging/radiological-clinical composite time-to-progression end point, when reached, was based on the imaging/radiological component in approximately 70% of the patients. Thus, the time-to-progression analysis was based on nonclinical (imaging) evidence in the majority of cases. Image-based, time-to-progression analysis in the presence of the BCNU wafer may be confounded by the immediate postoperative edema and enhancement that these wafers may produce (Brem et al., 1995). This effect may have the result of suggesting progression/recurrence by imaging when, in fact, it has not occurred. This BCNU wafer-specific effect, coupled with the previously mentioned factors, suggests that time-to-progression based on imaging alone should be used with caution in these patients. Utilization of PET or SPECT methods may increase the sensitivity and specificity of imaging to detect disease progression in glioma patients.

The profile and frequency of adverse events are similar for the BCNU wafer and placebo wafer groups. This is not unexpected given that BCNU wafers do not produce detectable systemic (plasma) exposure of BCNU, and thus systemic toxicities of BCNU are avoided. When BCNU wafers were studied in the treatment setting of recurrent GBM, convulsions in the immediate postoperative period, healing abnormalities, and infections were noted to occur more frequently (Brem et al., 1995). In the present study, these complications were not observed to be more frequent in the BCNU wafer-treated patients. This may be due, in part, to the fact that patients in the recurrent setting have had extensive previous radiotherapy (potentially leading to local healing difficulties) and are performing clinically at a lower level than primary malignant glioma patients at the time of initial diagnosis and surgery. In any case, the safety profile of BCNU wafers in primary malignant glioma surgery appears to be more benign than in recurrent GBM.

The role of chemotherapy in the treatment of malignant glioma was recently reviewed in a meta-analysis published by the GMT group (Stewart, 2002). This group performed a systematic review of the literature and selected 12 randomized trials comparing radiotherapy alone to radiotherapy plus systemic chemotherapy in patients with high-grade glioma. Overall, the results showed a significant prolongation of survival associated with chemotherapy, with a hazard ratio of 0.85 (95% CI, 0.78–0.91, $P < 0.0001$), or a 15% relative decrease in the risk of death. This effect is equivalent to an increase in 1-year survival of 6% (CI, 3%–9%) from 40% to 46% and a 2-month increase in median survival. There was no evidence that the effect of the chemotherapy differed in any group of patients defined by age, sex, histology, performance status, or extent of resection. The authors concluded that there is a small, but clear, benefit in survival from chemotherapy. The results of the current trial compare favorably to those obtained by the Glioma Meta-analysis Trial, further supporting the role of chemotherapy in the treatment of these tumors.

With respect to additional data on the benefit of local chemotherapy, 2 previous placebo-controlled, double-blind studies of BCNU wafers in malignant glioma have been conducted (Brem et al., 1995; Valtonen et al., 1997). In all 3 studies, BCNU wafers have shown a survival benefit compared to placebo wafers, with a mortality risk reduction of 31% (Brem et al. in recurrent malignant glioma), 63% (Valtonen et al. in primary malignant glioma), and 29% (the present study).

Taken as a whole, the results of the present trial coupled with those of the previous smaller trial (Valtonen et al., 1997) demonstrate the efficacy and safety of BCNU wafer treatment in malignant glioma patients at the time of primary surgery. Local BCNU wafer therapy can safely provide clinical benefits to the larger group of patients with primary malignant glioma at the time of initial surgery, in addition to the smaller group treated with BCNU wafers who undergo reoperation for recurrent glioblastoma multiforme. The implantation of BCNU wafers at the time of primary surgical resection can be performed with ease, does not require additional surgery, and is not associated with any systemic toxicities or side effects. Therefore, BCNU wafers should be considered as a treatment option in all patients with malignant glioma undergoing primary surgical resection.

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Appendix I: Study Investigators and Neuropathologists

Investigators

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Appendix II: Radiation Therapy Protocol

1. General
   Patients should be treated with involved/limited-field radiotherapy to the planning target volume (PTV), including the tumor (gross tumor volume [GTV], clinical target volume [CTV]) and a defined margin with localized radiotherapy technique.
2. Patient positioning
   Patients should be immobilized in an immobilization device in use in the radiation therapy center.
3. Volumes of treatment
   - 3.1 Tumor volumes should be defined on the basis of preoperative imaging.
   - 3.2 GTV should be defined as the region of enhancement presumed to represent tumor (on preoperative imaging—either CT or MRI). In unenhancing tumors GTV should be defined by the region of low density on CT or high signal intensity on T2-weighted MRI.
   - 3.3 The definition of CTV is not mandatory and may include GTV plus 1- to 3-cm margin in 3 dimensions or the region of low signal intensity (CT)/high signal intensity (T2W MRI) in enhancing tumor, or other definition specific to the radiation therapy center. Exception for the margin definition can be made for bone and meningeal structures, which are considered anatomical barriers to tumor spread.
   - 3.4 PTV definition may be related either to GTV or CTV. Overall it is recommended that PTV be defined as GTV/CTV plus 2- to 5-cm margin in 3 dimensions as used in the radiation therapy center. Exception for the margin definition can be made for bone and meningeal structures, which are considered anatomical barriers to tumor spread.
   - 3.5 The radiation therapy may be carried out to a single PTV throughout or by a two-phase technique reducing at 40 to 45 Gy to a smaller PTV.
   - 3.6 It is recommended that the planning volumes be defined by each radiation therapy center prior to commencing the study.
4. Treatment planning
   - 4.1 Treatment planning should be performed on a planning computer, and dose homogeneity within and coverage of the PTV should conform to the ICRU 50 criteria.
   - 4.2 The aim of treatment planning is to minimize the amount of normal brain irradiated and to minimize the dose to normal brain. Multiple field arrangements are preferred. Parallel opposed lateral field arrangements and whole-brain radiotherapy should be avoided. The use of custom blocking is optional.
5. Dose fractionation
   - 5.1 Dose should be prescribed according to the ICRU 50 criteria.
   - 5.2 The total dose to the PTV should be 55 to 60 Gy in 30 to 33 daily fractions. All fields should be treated daily, Monday to Friday.