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Safety and efficacy of carmustine (BCNU) wafers for metastatic brain tumors

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Abstract

Background: Carmustine (BCNU) wafers (Gliadel) prolongs local disease control and progression-free survival (PFS) in patients with malignant gliomas. However, in metastatic brain tumors, there is a paucity of evidence in support of its safety and efficacy. The goal of this study was to assess the safety and efficacy of Gliadel wafers in patients with metastatic brain tumors.

Methods: We retrospectively reviewed the University of Washington experience with Gliadel wafers for metastatic brain tumors between 2000 and 2015.

Results: Gliadel wafers were used in 14 patients with metastatic brain tumors during the period reviewed. There were no postoperative seizures, strokes, or hemorrhages. There was one postoperative wound infection necessitating return to the operating room. The mean time to tumor progression (n = 7) and death (n = 5) after Gliadel wafer implantation was 2.5 and 2.9 years, respectively. Age was the only variable affecting PFS in patients receiving Gliadel wafers. Patients <53 years old (n = 7) had a PFS of 0.52 years, whereas patients >53 years old (n = 7) had a PFS of 4.29 years (P = 0.02). There was no significant difference in PFS in relation to presenting Karnofsky Performance Status (P = 0.26), number of brain metastasis (P = 0.82), tumor volume (P = 0.54), prior surgery (P = 0.57), or prior radiation (P = 0.41). There were no significant differences in the mean survival in relationship to any variable including age.

Conclusions: BCNU wafers are a safe and a potentially efficacious adjunct to surgery and radiation for improving local disease control in metastatic brain tumors. Larger studies, however, are needed to examine overall efficacy and tumor specific efficacy.

Key Words: BCNU, carmustine, Gliadel, gliomas, metastatic brain tumor, progression free survival

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INTRODUCTION

Patients with brain metastases have a median survival of 4–10 months, as predicted by radiation therapy oncology group (RTOG) recursive partitioning analysis (RPA) class.[10] The cause of death for the vast majority of these patients is systemic disease progression, not brain disease.[19] In a small number of patients (10–15%) with stable systemic disease and brain metastases that are recalcitrant to standard therapies (surgery, stereotactic radiosurgery [SRS], or whole brain radiation), additional therapies that enhance local control may be useful.

Gliadel is a carmustine (BCNU)-infused wafer developed in the 1970s for direct delivery of chemotherapy to the tumor bed.[20] BCNU inhibits cellular proliferation by cross-linking DNA thus preventing mitosis.[13] Prior studies have demonstrated that Gliadel wafers maintain high concentrations of the chemotherapeutic agent within the tumor bed for approximately 3 weeks following implantation.[6,9,12] This makes it an attractive way to achieve local disease control in patients with both primary and metastatic brain tumors.[1,7,8,14,20] In patients undergoing surgery for recurrent glioblastoma multiforme (GBM), Gliadel wafers have been shown to improve median survival compared with placebo (5.4–7.2 months).[3] For patients undergoing initial resection of GBM, Gliadel also improves survival compared with placebo-wafers (9.2–13.4 months).[21] These findings, in addition to other studies,[2,22] led to the Food and Drug Agency approval of Gliadel wafer implantation for malignant gliomas in 1996. However, in metastatic brain tumors, there is a paucity of evidence in support of its safety and efficacy.[7]

We retrospectively reviewed 14 patients with metastatic brain tumors resection who underwent concomitant placement of Gliadel wafers. We report local toxicity (wound infections, postoperative seizures, and wound breakdown) as well as progression-free survival (PFS) and mean survival following Gliadel wafer implantation.

MATERIALS AND METHODS

Study design

Following approval by the University of Washington Institutional Review Board, the medical records of patients undergoing metastatic brain tumor resection between 2000 and 2015 were reviewed. Fourteen cases with Gliadel wafer placement were identified and retrospectively reviewed. We documented demographic information, prior surgical intervention or radiation therapy, maximum tumor diameter, primary cancer type, postoperative complications, PFS (where progression is defined as the presence of nodular enhancement within/adjacent to the tumor bed based on follow-up imaging and/or clinical deterioration due to a neurological cause), and mean survival.

Tumor resection and BCNU wafer implantation

Surgery was performed by a single neurosurgeon (Daniel L. Silbergeld). Following resection of gross tumor, neuronavigation, and ultrasound were used to assess the tumor bed for any residual tumor. Eight Gliadel wafers were used to line the tumor bed. Postoperatively, a noncontrast head computed tomography was obtained to assess for immediate complications. A repeat magnetic resonance imaging was also performed within 48 h to determine the extent of resection. Length of stay and postoperative complications were documented.

Statistics

Statistical analysis was performed by J. B. Peto-Peto and Tarone-Ware exact tests were used to determine statistical significance among the covariates of interest. PFS for all patients (n = 14) was calculated using Kaplan–Meier estimates. All analyses were carried out in StatXact (Cytel Incorporated, Cambridge, Massachusetts, U.S.A.).

RESULTS

Demographics, symptoms, and radiographic characteristics

Patient demographics are presented in Table 1. The median age of patients in the series was 51.7 (range 31–73). About 43% (n = 6) were male and 57% (n = 8) were female. The most common primary tumors in the series were lung (n = 4), breast (n = 3), and melanoma (n = 2). There was one case of each of the following: Renal cell, testicular, leiomyosarcoma, colorectal, and bladder. The most common presenting symptoms were seizures (n = 6) and weakness (n = 5) [Table 2]. Other presenting symptoms included visual disturbances (n = 4) and headaches (n = 2). The average presenting Karnofsky Performance

Table 1: Patient demographics

Variable	*N* (%)
Median age (range)	52.1 (31-73)
Gender, *n* (%)	
Male	6 (42)
Female	8 (57)
Primary tumor site, *n* (%)	
Lung	4 (28)
Breast	3 (21)
Melanoma	2 (14)
Renal cell	1 (7)
Testicular	1 (7)
Leiomyosarcoma	1 (7)
Colorectal	1 (7)
Bladder	1 (7)

Table 2: Clinical characteristics

Patient ID	Primary	Sex	Age	Symptom	KPS	Lesions	Location	Adjuvant radiation	RTOG RPA	PFS (months)
1	Lung	Male	52	Cognitive decline	40	1	Right frontal and temporal	No	3	7.3
2	Lung	Female	52	Difficulty reading	70	3	Left temporal	No	1	
3	Lung	Male	48	Seizure	90	1	Right parietal	No	1	14.1
4	Lung	Male	73	Seizure, right hemiparesis	80	1	Left parietal	Yes	2	
5	Breast	Female	42	Headache, left paresthesia	90	1	Right parietal	No	2	18.2
6	Breast	Female	36	Visual disturbance	90	2	Right temporal	Yes	1	34.1
7	Breast	Female	53	Seizure	90	1	Left parietal	No	1	
8	Melanoma	Male	57	Seizure, left hemiparesis	60	2	Right frontal, left parietal	Yes	2	
9	Melanoma	Female	34	Seizure, right hemiparesis, aphasia	40	1	Left frontal	No	3	
10	Renal cell	Female	68	Confusion, right foot weakness	80	1	Left frontal	Yes	2	
11	Testicular	Male	31	Right homonymous hemianopsia	90	1	Left parietooccipital	No	1	2.4
12	Leiomyosarcoma	Female	63	Seizure	90	1	Right frontal	Yes	1	
13	Colorectal	Female	54	Left hemiparesis, visual field neglect	80	1	Right parietal	Yes	2	20.4
14	Bladder	Male	61	None	90	1	Right temporal	No	1	20.3

KPS: Karnofsky Performance Status, RTOG: Radiation therapy oncology group, RPA: Recursive partitioning analysis, Progression free survival

Status (KPS) score was 71.1. Most patients had one lesion (n = 10), whereas a small fraction had either two (n = 3) or three (n = 1) lesions. The average tumor diameter (maximum dimension) was 3.6 cm.

Treatment

Criteria for Gliadel use included failure to achieve local control, good performance status, and stable systemic disease. All patients had received at least one form of therapy before recurrence and Gliadel wafer placement. Most patients (n = 10, 71%) had undergone a prior craniotomy for resection of a metastatic lesion before repeat craniotomy for recurrent tumor resection and Gliadel wafer placement. The average time between prior craniotomy and Gliadel wafers placement was 12.7 months (range 4.6–18.4). Twelve patients (86%) had also undergone prior radiation for the same metastatic lesion (85% gamma knife (GK) (Elekta, Stockholm, Sweden), 15% received both whole brain and GK). The average time between prior radiation treatment and Gliadel wafers placement was 13.3 months (range 3.5–25.3).

Postoperative complications and adjuvant therapy

There were no postoperative seizures, strokes, or hemorrhages. There was one wound infection [Table 2, patient #5] that necessitated return to the operating room for treatment 10 weeks after Gliadel implantation. There was transient oculomotor nerve palsy in patient #1, which was likely due to surgical manipulation and not the BCNU wafers. The average length of stay was 3.6 days. Four patients received adjuvant SRS on an outpatient basis with GK, one patient (#13) received whole brain, and another received proton beam irradiation (#4).

Progression and death

Tumor recurrence occurred in seven patients (2/4 lung, 2/3 breast, 1/1 colorectal, 1/1 bladder, and 1 testicular; Table 2). No progression was seen in the melanoma, renal cell, or leiomyosarcoma group during the follow-up period (mean time to latest follow-up 18.7 months). All recurrences were local except for the colorectal and bladder recurrences where new distant metastasis occurred. The mean time to progression was 2.5 years. At the time of publication, 5 patients who demonstrated progression had died (mean survival 2.9 years). RTOG RPA survival data for each patient was calculated, and results are shown in Table 2 (except for leiomyosarcoma and bladder cancer).

Age was the only factor that affected PFS after BCNU wafer placement [Table 3]. Patients <53 years old had a PFS of 0.52 years, whereas patients >53 years old had a PFS of 4.29 years (P = 0.02). There was no significant difference in PFS based on presenting KPS (P = 0.26), number of brain metastases (P = 0.82), tumor volume (P = 0.54), prior surgery (P = 0.57), or prior radiation (P = 0.41). There were no significant differences in the mean survival based on these variables.

DISCUSSION

The management of brain metastasis continues to be an important topic as the incidence of brain metastases increases along with better control of systemic malignancies. Historically, a single metastasis treated with surgical resection and postoperative radiation as local recurrence rates is as high as 40% and distant recurrence in approximately 21%.[1,16-18] Local recurrence is speculated

Table 3: Survival data

	n (%)	Mean time to progression (years)	*P*	Mean time to death (years)	*P*
Age					
Mean±SD	51.7±12.6				
<53	7 (50)	0.52	0.02	1.8	0.062
53+	7 (50)	4.29		3.79	
Sex					
Male	6 (43)	2.48	0.579	2.92	0.46
Female	8 (57)	1		3.15	
Presenting KPS					
Mean±SD	77.1±18.2				
<90	7 (50)	3.81	0.259	3.59	0.67
90+	7 (50)	0.76		2.51	
Brain mets					
Mean±SD	1.4±0.6				
1	10 (71)	0.86	0.816	1.17	0.357
2+	4 (28)	2.69		4.71	
Tumor volume					
Mean±SD	185±170				
<100	6 (43)	0.76	0.537	2.35	0.664
100+	8 (57)	3.58		4.05	
Prior surgery					
No	4 (29)	2.02	0.565	2.68	0.442
Yes	10 (71)	0.99		3.44	
Prior radiation					
No	2 (14)	3.69	0.406	4.57	0.418
Yes	12 (86)	0.85		2.75	

KPS: Karnofsky Performance Status, SD: Standard deviation

to occur from microscopic tumor spread beyond the immediate resection cavity. The blood–brain barrier (BBB) prevents systemic chemotherapy from targeting these cells. Even in the setting of a disrupted BBB, there are variable concentrations of chemotherapeutic drugs within metastatic lesions.[23] Several studies have shown that metastatic brain tumors have different levels of multidrug-resistance genes compared with systemic lesions.[1,5,11] Thus, for a select group of patients a treatment paradigm that focuses beyond traditional surgery and postoperative radiosurgery may be beneficial. Gliadel wafers are a potential adjunctive therapy that can be given at the time of resection to enhance local control.

In 1996, Ewend *et al*. published the first report of BCNU wafers with radiotherapy in various animal models of metastatic models.[8] They found that BCNU wafers prolonged survival in the melanoma and renal cell carcinoma murine models. When used in combination with radiotherapy, it prolonged survival in all cancer models. In 2007, a phase I human clinical trial evaluating the safety of BCNU wafers in 25 patients was also conducted by Ewend *et al*.[7] They found that the median survival was 33 weeks with 33% of patients surviving past 1 year and 25% of patients surviving past 2 years. There were no local recurrences reported at follow-up (median 36 weeks). Two patients did develop seizures, but there were no wound breakdowns reported. These findings suggested that BCNU wafers were safe to use in humans.

Here, we report results from a retrospective analysis conducted to assess the efficacy of BCNU wafers for metastatic brain lesions. Most patients underwent craniotomy and BCNU wafer placement for tumor recurrence following previous treatments. We found that patients in our cohort >53 years had a significantly longer PFS compared with patients <53 years following BCNU wafer implantation. This may be a statistical aberration due to the small number of patients, or may suggest that this treatment regimen may be more effective for achieving local disease control in a specific subset of patients. This age-related phenomenon has also been reported for recurrent GBM patients >55 years receiving bevacizumab (Avastin).[4,15] In this study, a similar retrospective analysis demonstrated that the effect of bevacizumab was more significant in the older patient group. Bevacizumab improved both PFS ($P = 0.02$) and overall survival ($P = 0.03$) in older patients compared with the control group. The findings suggest that in the older patient population with reportedly worse outcomes following a diagnosis of either primary or metastatic brain tumors, specific therapy regimen such as bevacizumab (for recurrent GBM) and BCNU (for metastatic lesions) may have a role in curbing local disease progression. The mechanism for this, however, remains unknown.

Limitations

As with any retrospective analysis, this study has significant limitations. The cohort is too small for any significant statistical analysis. Another limitation of our study is the small and heterogeneous sample size that precludes drawing conclusions about the differential sensitivity of various cancer types to BCNU wafers. Furthermore, without a control group, these results should be viewed as having potential selection bias. Future prospective double-blinded studies with a larger cohort will provide more insights into the impact of BCNU on patient PFS and overall survival compared with placebo. These large studies may also uncover other variables that could be relevant for survival in response to BCNU wafer implantation.

CONCLUSIONS

BCNU wafers (Gliadel) are a safe adjunct to surgery and radiation for prolonging local disease control in patients with metastatic brain tumors. In our series, patients >53-year-old with metastatic brain tumors showed a higher PFS compared with patients <53 years following

Gliadel wafers administration. Gliadel wafers may provide an effective means of prolonging local disease control for patients with metastatic brain tumors. Larger studies, however, are needed to examine overall efficacy and tumor specific efficacy.

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Conflicts of interest
There are no conflicts of interest.

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