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Safety and Effectiveness of Bis-Chloroethylnitrosourea Wafer Chemotherapy in Elderly Patients with Recurrent Glioblastoma

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Keywords

Glioblastoma · Carmustine · Bis-chloroethylnitrosourea · Wafers · Elderly · Chemotherapy

Abstract

Objective: To assess the safety and effectiveness of bis-chloroethylnitrosourea (BCNU) wafers in elderly patients with recurrent glioblastoma (GBM). **Methods:** Patients with recurrent GBM operated on between 2007 and 2014 were divided into 3 groups: >65 years with BCNU wafer implantation, >65 years without BCNU wafer implantation, and ≤65 years with BCNU wafer implantation. We compared survival and complications. **Results:** A total of 79 patients were identified: 24 in the older BCNU group (median age 68.2 years, 33.3% with a methylated *MGMT* promoter), 16 in the older non-BCNU group (median age 68.6 years, 31.3% with a methylated *MGMT* promoter), and 39 in the younger BCNU group (median age 56.8 years). Survival after progression was 9.2 months in the elderly BCNU group and 7.6 months in the elderly non-BCNU group ($p = 0.34$); overall survival was 17.2 and 15.9 months, respectively ($p = 0.35$). We found a tendency toward a higher rate of seizures and pneumonia in the older BCNU group. **Conclusion:** BCNU wafer implantation

after resection of recurrent GBM is a reasonably safe treatment in patients aged >65 years. Seizures and systemic infections may occur more frequently, but the trade-off is still favorable as survival may be influenced positively. Higher age should not be regarded as a contraindication for BCNU wafers.

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Introduction

Glioblastoma (GBM) is the most frequently occurring primary brain tumor. It is most likely to affect older patients, with the highest incidence between 65 and 84 years [1]. The prognosis is dismal in any scenario, yet elderly patients have a particularly poor prognosis and often require treatment, which differs from the therapeutic standards in younger individuals [2]. Gross total resection, whenever achievable, is the mainstay of surgical treatment [3], while hypofractionated radiation therapy with 40 Gy appears to be favorable compared to the 60-Gy regimen recommended for younger patients [4, 5]. As combined radiochemotherapy seems to provide diminishing effects with increasing age, radiotherapy alone or chemo-

therapy alone may be advocated in elderly GBM patients [6]. Currently, chemotherapy alone has been recommended for elderly GBM patients (>65 years) with a methylated *MGMT* promoter [7]. However, the prognosis remains very poor, with a 1-year survival rate of 26.2% for patients aged 65–74 years and 11.0% for patients aged ≥75 years [8]. Hence, there is a strong need for new or additional therapeutic strategies in the treatment of elderly GBM patients to improve their survival.

Bis-chloroethylnitrosourea (BCNU) was introduced in the form of wafers for local chemotherapy after resection of high-grade gliomas a quarter century ago [9]. Since then, randomized controlled trials have demonstrated increased overall survival (OS) in patients suffering from high-grade glioma both after implantation of BCNU wafers for recurrent tumor and after the initial diagnosis [10–12]. The benefits of BCNU wafers have been consistently recognized in clinical trials, reviews, and meta-analyses [13–15]. On the other hand, complications after BCNU wafer implantation have been repeatedly reported. Still, the addition of BCNU wafers to the therapeutic standard in GBM has become an established option.

To date, the effectiveness of BCNU wafers in elderly patients has not been studied. Thus, we sought to compare the survival and complication rates of patients with first recurrent GBM aged >65 years who had undergone BCNU wafer implantation intraoperatively as an adjunct therapy with those of elderly patients who had been treated for a first recurrent GBM without BCNU wafers. Additionally, the complication rates of patients aged ≤65 years who had been treated with BCNU wafers were compared with those of the older group who received BCNU wafers.

Methods

We searched our tumor database for patients who had been diagnosed with a GBM between 2007 and 2014, had received tumor resection both at diagnosis and after recurrence, with available magnetic resonance images, and in whom the *MGMT* promoter methylation status was known. The survival in patients >65 years who had received BCNU wafer implantation at recurrence was compared with the survival in patients of the same age without local BCNU therapy. These groups were matched for factors associated with survival, including age, extent of resection, adjuvant treatment, and *MGMT* promoter methylation status.

In addition, to evaluate safety, patients aged ≤65 years who had received BCNU wafers at surgery for recurrent tumor formed a control group for comparison of complication rates; individuals aged ≤65 years who had not received BCNU wafers were not included. The complications considered in our analysis were newly

developed hydrocephalus, pseudocysts, cerebral abscess, increase in cerebral edema, pseudoprogression, deep vein thrombosis or pulmonary embolism, symptomatic increase in intracranial pressure, systemic infection (e.g., pneumonia), seizures, cerebrospinal fluid leak, and wound healing disturbances. In case of missing information about the occurrence of complications, the respective patients were excluded from analysis of the complication in question. Hence, for some items, the number of patients studied is lower than the total in their group. The study was approved by the local ethics committee (number EK179082004).

For statistical evaluation, we performed a multivariate analysis which included age, sex, *MGMT* promoter status, number of implanted wafers, extent of resection, and radiochemotherapy after first and after second surgery (yes or no) with log-rank test and Kaplan-Meier curves for survival analysis. Complications were compared with the Fisher exact test. OS was defined as the time from the first surgery until the last follow-up. Progression-free survival (PFS) was defined as PFS1 for the time between the first and second surgery and as PFS2 for the time between the second surgery and the last follow-up.

Results

Patient Population

We identified a total of 79 subjects: 24 patients aged >65 years (older BCNU group) who had undergone BCNU wafer implantation for their first recurrent GBM (17 male [70.8%], median age 68.2 years, range 65.3–76.6, 8 with a methylated *MGMT* promoter [33.3%], average number of wafers 5.9), 16 patients aged >65 years with a first recurrent GBM (older non-BCNU group) who had not received BCNU wafers (12 male [75.0%], median age 68.6 years, range 65.7–81.9, 5 with a methylated *MGMT* promoter [31.3%], average number of wafers 5.3), and 39 patients aged ≤65 years (younger BCNU group) who had been treated with BCNU wafers for recurrent GBM (25 male [64.1%], median age 56.8 years, range 38.1–64.7). The Karnofsky performance score in all operated patients was ≥70.

All patients in the younger group (≤65 years), 91.7% of elderly patients with BCNU wafers, and 93.8% of elderly patients without BCNU wafers received systemic chemotherapy after the first tumor resection, with temozolomide being by far the most commonly used drug. Adjuvant radiotherapy was applied to all younger patients, 95.8% of elderly patients with BCNU, and 93.8% of elderly patients without BCNU. Complete tumor resection at first diagnosis was achieved in 56.4, 58.3, and 68.8% of patients in the younger BCNU, older BCNU, and older non-BCNU groups, respectively. Patients' characteristics in all 3 groups are shown in Table 1.

Table 1. Characteristics of the patients in each group

Patient characteristics	≤65 years with BCNU	>65 years with BCNU	>65 years without BCNU	p value between BCNU groups	p value between older groups
Number of patients	39	24	16		
Males	25 (64.1%)	17 (70.8%)	12 (75.0%)	0.40 ^a	0.53 ^a
Median age, years	56.8	68.2	68.6		0.92 ^b
Age range, years	38.1–64.7	65.3–76.6	65.7–81.9		
MGMT promoter methylation	12 (30.8%)	8 (33.3%)	5 (31.3%)	0.52 ^a	0.59 ^a
Complete resection at first diagnosis	22 (56.4%)	14 (58.3%)	11 (68.8%)	0.49 ^a	0.44 ^a
Complete resection at first recurrence	19 (48.7%)	11 (45.8%)	10 (62.5%)	0.50 ^a	0.28 ^a
Mean number of BCNU wafers	5.9	5.3	0		
Right tumor side	22 (56.4%)	10 (41.7%)	12 (75.0%)	0.27 ^c	0.10 ^c
Tumor localization					
Frontal	13 (33.3%)	8 (33.3%)	4 (25.0%)	0.6 ^a	0.42 ^a
Temporal	10 (25.6%)	4 (16.7%)	5 (31.3%)	0.3 ^a	0.24 ^a
Parietal	2 (5.1%)	2 (8.3%)	1 (6.3%)	0.49 ^a	0.65 ^a
Occipital	5 (12.8%)	1 (4.2%)	1 (6.3%)	0.25 ^a	0.64 ^a
Involvement of two lobes	9 (23.1%)	9 (37.5%)	5 (31.3%)	0.17 ^a	0.42 ^a

BCNU, bis-chloroethylnitrosourea. ^aOne-sided Fisher exact test. ^bTwo-sided Mann-Whitney U test. ^cPearson χ^2 test.

Patients following BCNU wafer implantation were considered for systemic chemotherapy the same as patients without BCNU wafers. As there is no consensus on chemotherapy in the recurrent setting, the decision was made for each patient individually during interdisciplinary tumor boards. Temozolomide was the most commonly used agent, while ACNU (nimustine), CCNU (lomustine), bevacizumab, and irinotecan were used in fewer cases, including combinations of agents. For an overview of the adjuvant treatments provided to elderly patients without BCNU wafer implantation, see Table 2.

Comparison of Adverse Effects in Younger versus Elderly Patients with Wafer Implantation

One of 39 younger patients (2.6%) and 2 of 24 elderly patients (8.3%) with BCNU wafer implantation developed a hydrocephalus. Pseudocysts were not observed in any patient. One of the younger patients (2.6%) suffered from a cerebral abscess, while none of the elderly patients did. A general progression of postoperative cerebral edema occurred in 26 out of 36 younger patients (72.2%) and in 12 out of 22 elderly patients (54.5%). Two patients of each group (5.1 vs. 8.3%) developed a symptomatic increase in intracranial pressure. Pseudoprogression was observed in 2 of 38 younger patients (5.3%) and 1 of 24 elderly patients (4.2%). Deep vein thrombosis or pulmonary embolism arose in 1 patient of the

Table 2. Adjuvant treatment of elderly patients without BCNU wafer implantation

MGMT promoter methylation	RT after first surgery	CT after first surgery	RT after second surgery	CT after second surgery
1	1	TMZ	0	ACNU/TMZ
1	1	TMZ	0	TMZ
0	1	TMZ	0	ACNU/TMZ
0	1	TMZ	0	0
0	1	TMZ	0	TMZ
0	1	TMZ	0	TMZ
0	1	TMZ	0	TMZ
1	1	TMZ	0	ACNU/TMZ/BV
0	1	TMZ	0	0
0	1	TMZ	0	0
0	1	TMZ	0	TMZ
1	1	TMZ	0	0
0	1	TMZ	1	TMZ
0	0	0	0	TMZ
1	1	TMZ	0	TMZ
0	1	TMZ	0	0

All but 1 patient (whose condition was deemed too bad for adjuvant treatment following a pulmonary embolism) received radiation and TMZ after the first surgery. After the second surgery, 1 patient underwent stereotactic radiotherapy. Most patients received chemotherapy after the second tumor resection, with TMZ being the most frequently used drug. ACNU, nimustine; BCNU, bis-chloroethylnitrosourea; BV, bevacizumab; CT, chemotherapy; RT, radiotherapy; TMZ, temozolomide.

Table 3. Complications upon implantation of BCNU wafers for recurrent glioblastoma in patients ≤65 years (older BCNU group) and >65 years (younger BCNU group)

Complications	Younger BCNU group	Older BCNU group	<i>p</i> value
Hydrocephalus	1/38 (2.6%)	2/22 (8.3%)	0.322
Pseudocysts	0/39 (0%)	0/24 (0%)	–
Cerebral abscess	1/38 (2.6%)	0/22 (9%)	1
Progression of edema	26/36 (72.2%)	12/22 (54.5%)	0.255
Pseudoprogession	2/38 (5.3%)	1/24 (4.2%)	1
Deep vein thrombosis/pulmonary embolism	1/39 (2.6%)	3/24 (12.5%)	0.15
Symptomatic intracranial pressure increase	2/39 (5.1%)	2/24 (8.3%)	0.632
Systemic infections (e.g., pneumonia)	1/39 (2.6%)	4/24 (16.7%)	0.065
Seizures	2/39 (5.1%)	5/24 (20.8%)	0.095
Cerebrospinal fluid leak	3/39 (7.7%)	2/24 (8.3%)	1
Wound healing disturbances	7/39 (17.9%)	2/24 (8.3%)	0.462

The *p* values are given for the 2-sided Fisher exact test; the significance level was set at *p* = 0.05. BCNU, bis-chloroethylnitrosourea.

younger group (2.6%) and in 3 patients of the older group (12.5%). A cerebrospinal fluid leak developed in 3 younger (7.7%) and 2 elderly patients (8.3%). Seven of the younger patients (17.9%) and 2 of the elderly patients (8.3%) experienced wound healing disturbances. None of these differences in complications yielded statistical significance. One of the younger patients (2.6%) and 4 of the elderly patients (16.7%) suffered from a systemic infection, with a borderline statistical significance. None of the elderly patients treated without BCNU wafers developed systemic infections. Comparison of the rate of systemic infections between the groups >65 years with and without BCNU wafers yielded a nonsignificant result in the Fisher exact test. Seizures occurred in 2 of the younger (5.1%) and 5 of the older patients (20.8%), with a borderline statistical significance. Table 3 provides an overview of the adverse effects related to BCNU wafer chemotherapy.

Comparison of Survival in Patients ≤65 Years with Wafer Implantation versus Patients >65 Years with Wafer Implantation

The younger BCNU-treated patients had a median PFS1 of 6.7 months (95% confidence interval [CI] 4.5–8.8) after the first surgery, while the PFS1 was 7.4 months (95% CI 6.9–8.0) in the elderly BCNU group (*p* = 0.41). Median PFS2 was 9.2 months (95% CI 5.8–12.6) in the younger group and 9.2 months (95% CI 7.5–10.9) in the older group (*p* = 0.35). Mean OS was 19.0 months (95% CI 15.0–23.1) in the younger group and 17.2 months (95% CI 13.7–20.8) in the older group (*p* = 0.41).

Comparison of Survival in Patients >65 Years with Wafer Implantation versus Patients >65 Years without Wafer Implantation

Patients in the older BCNU group (>65 years) had a median PFS1 of 7.4 months (95% CI 6.9–8.0) after the initial tumor resection compared with 10.4 months (95% CI 8.0–12.8) in older patients without BCNU (*p* = 0.44). Median PFS2 was 9.2 months (95% CI 5.2–13.2) in the older BCNU group compared to 7.6 months (95% CI 2.8–12.3) in the group without BCNU, but this was not significant (*p* = 0.34, Fig. 1). The median OS was 17.2 months (95% CI 13.7–20.8) in the older BCNU group versus 15.9 months (95% CI 13.0–18.8) in the non-BCNU group (*p* = 0.35, Fig. 2).

Comparison of Survival Depending on MGMT Methylation Status

The median OS in patients with an unmethylated MGMT promoter was 18.7 months (95% CI 16.0–21.4) in the younger and 15.6 months (95% CI 11.1–20.2) in the older BCNU group (*p* = 0.9). In patients with a methylated MGMT promoter it was 21.7 months (95% CI 16.6–26.8) and 18.3 months (95% CI 12.9–23.7), respectively (*p* = 0.14).

Comparing both groups aged >65 years, median OS after surgery with BCNU wafer implantation did not differ significantly, with 18.3 months (95% CI 12.9–23.7) in patients with a methylated MGMT promoter versus 15.6 months (95% CI 11.1–20.2) in those with an unmethylated MGMT promoter (*p* = 0.78).

Fig. 1. The survival after progression in patients aged >65 years who were implanted bis-chloroethylnitrosourea (BCNU) wafers at their surgery for recurrent glioblastoma was 9.2 months, compared to 7.6 months in patients aged >65 years who did not receive BCNU wafers ($p = 0.34$).

Fig. 2. The overall survival in patients aged >65 years who were implanted bis-chloroethylnitrosourea (BCNU) wafers at their surgery for recurrent glioblastoma was 17.2 months, compared to 15.9 months in patients aged >65 years who did not receive BCNU wafers ($p = 0.35$).

When considering patients aged >65 years without BCNU wafer implantation, the median OS was 15.9 months (95% CI 13.0–18.7) in those with an unmethylated and 16.7 months (95% CI 11.7–21.7) in those with a methylated *MGMT* promoter ($p = 0.80$).

Discussion

The concept of local delivery of BCNU wafer directly into a tumor resection cavity was developed in the 1990s and was approved in 2003 by the US Food and Drug Administration as part of the management of patients with GBM. However, to date, data about the safety and the clinical effect of wafer implantation in patients aged >65 years are lacking. Hence, the aim of our study was to address these issues regarding safety following BCNU wafer implantation in elderly patients with recurrent GBM and to evaluate their effectiveness as an adjunct treatment option in the recurrent setting.

Our study demonstrates a favorable adverse effect profile of BCNU wafers in elderly patients when implanted for the treatment of recurrent GBM. The overall compli-

cation rate in the latter cohort was 66.7%, with postoperative progression of edema being by far the most common adverse effect; yet, interestingly, no complication was significantly more common when compared with elderly patients who did not receive BCNU wafers. Nevertheless, the comparison of BCNU-related complications in younger versus elderly patients demonstrated a slightly higher rate of systemic infections (pneumonia) and seizures in elderly patients as the only remarkable difference between both groups. However, the latter finding was not statistically significant.

Of note, the complication rate in our study was somewhat lower than that reported by Subach et al. [16], who found complications in 76.6% of patients with recurrent GBM treated with BCNU wafers – mostly wound infections, sepsis, cerebrospinal fluid leak, and seizures. In a further study, Bock et al. [17] reported a complication rate of 52% in a retrospective study of BCNU wafer implantation for primary resection of high-grade glioma – mostly cerebral edema, healing abnormalities, cerebrospinal fluid leak, seizures, and alteration of mental status. New seizures developed in 16% of patients. Notably, in the large trials by Brem et al. [10] and Westphal et al. [12],

seizures were not more frequent among BCNU-treated patients than in the placebo groups.

Considering the short survival time in GBM, especially in elderly patients, a possible higher risk of systemic infection (which can be sufficiently managed with antibiotics) and seizures (which can usually be controlled with medication) may be an acceptable trade-off for the chance of a slightly prolonged survival, as shown in our current analysis. Some considerable studies failed to detect a higher complication risk in patients treated with BCNU wafers [15, 18]. With regard to treatment effectiveness, we could not determine a significant effect of the BCNU wafers on the survival of patients aged >65 years after implantation in comparison to their counterparts who did not receive the wafers (PFS2 9.2 vs. 7.6 months). Although the difference in survival is not statically significant, these survival times are considerably longer than those in the literature, which are reported to be approximately 7 months in a patient population with a median age of 56 years [19]. As patients aged >65 years who were not treated with BCNU wafers had a numerically higher rate of complete resection at surgery for recurrent GBM (62.5 vs. 45.8%), yet a lower PFS2 than elderly patients with BCNU wafer implantation (7.6 vs. 9.2 months), we argue that the comparability of the groups may be flawed and that the positive effect of BCNU on survival may be underestimated in our study.

The 1.6-month improvement in median survival after implantation of BCNU wafers for first recurrent GBM and the 1.3-month improvement in OS in the older BCNU group over the control older non-BCNU group are roughly comparable with the available data, which showed an improvement in OS of 2–2.4 months [10, 20]. Curiously, comparing survival data between the younger and the older BCNU group, there was no significant difference in OS (19.0 vs. 17.2 months), which might be explained by the fact that only patients in good condition (Karnofsky performance score ≥ 70) underwent a second tumor resection with wafer implantation, independent of age. This may be a considerable factor blurring the difference in survival which would be expected with regard to age because the fraction of patients not receiving surgery upon tumor recurrence may have been much higher in the elderly group. Thus, we suspect a selection bias as the main reason for the lack of difference in survival after surgery for recurrent GBM with BCNU wafer implantation between the younger and older patients.

As expected, the median OS was numerically longer in patients with a methylated *MGMT* promoter, although no statistical significance could be detected in our patient

population. This observation held true both for patients with BCNU wafer implantation and those without. Hence, in this study, we cannot confirm an enhanced effect of BCNU wafers on survival in patients with *MGMT* methylated tumors as has been suggested experimentally [21].

From an economical perspective, BCNU wafer implantation remains an expensive treatment. The cost of treatment in Germany depends on the number of placed wafers. The placement of 4–6 wafers costs around EUR 7,564, whereas insertion of 7–9 wafers costs EUR 12,103 [Veelken et al., unpublished data; 13]. Thus, the question can be raised how high the monetary cost for a moderate increase in survival may be in socialized medicine. The same, however, goes for various other treatments in oncology, chiefly immunotherapy and tumor-treating fields. The latter yields a cost of USD 21,000 per month [22], while the total cost of a combination of ipilimumab and nivolumab for the treatment of melanoma has been reported to amount to USD 295,566 per patient [23]. The question of the financial sustainability of these particularly expensive therapies is a question at the border between economics and ethics and will likely be uttered more frequently and more explicitly in the near future.

Our study has several limitations, starting with its retrospective nature. As there was no randomization, there may have been differences between both elderly groups which we are not aware of. Furthermore, the patient population may be too small for detection of differences in survival and complication rates. In fact, OS, PFS2, and systemic infections as well as seizures were numerically considerably different between the groups, yet the difference did not reach statistical significance, which it might have done given a larger patient population.

Of note, BCNU wafers were already in use before temozolomide became the standard chemotherapeutic agent in GBM treatment. Skepticism about the concomitant use of both drugs has been tempered by several studies and reviews demonstrating their compatibility [24–31]. In our study, we show that the combination of both agents – even in elderly patients – is a mostly safe option in the recurrent setting. It should be mentioned that we start adjuvant treatment with temozolomide 8 weeks after BCNU wafer implantation. This is the time at which the wafers have usually dissolved [13, 32, 33]. This approach might minimize any side effects occurring due to simultaneous drug administration.

Conclusion

The use of BCNU implants after resection of recurrent GBM in the elderly is a reasonably safe and effective treatment as long as patients present in good clinical condition. Seizures and systemic infections may be more likely upon use of BCNU wafers in this patient group. These possible complications need to be taken into account, but should not be the reason for not considering this treatment option in elderly patients. Furthermore, survival

may be increased in elderly patients with recurrent GBM when BCNU wafers are implanted upon second tumor resection. For detection of statistically significant correlations, larger controlled studies are called for.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose. No funding was received for this study.

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