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Original Article

Timing of bevacizumab administration after biopsy for unresectable newly diagnosed glioblastoma

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ABSTRACT

Background: Recent studies have revealed that bevacizumab (BEV) can improve the survival of patients with newly diagnosed unresectable glioblastoma (GBM) with poor performance status. For patients who develop early clinical deterioration, early initiation of BEV would be beneficial. However, the safety and feasibility of early initiation of BEV remain to be determined because of the lack of studies addressing adverse events associated with BEV initiation <28 days after surgery. The aim of this study was to analyze the risks and benefits of early BEV administration after biopsy in patients with newly diagnosed GBM.

Methods: Thirty-one consecutive patients with newly diagnosed GBM who underwent biopsy followed by BEV administration were investigated. The relationships between the timing of BEV administration and treatment response, survival outcome, and adverse events were analyzed.

Results: Response rates based on the RANO criteria and overall survival times were similar between the early and standard BEV groups. No wound dehiscence was observed in the early BEV group, and only one case was observed in the standard BEV group. Patients in the early BEV group were more likely to have undergone biopsy with a smaller skin incision than those in the standard BEV group. Equivalent treatment effects of BEV were achieved in patients who developed early clinical deterioration and those without clinical deterioration.

Conclusion: Early BEV administration is effective in controlling early clinical deterioration and does not increase the risk of wound-healing complications. Further studies with larger numbers of patients are needed to validate our results.

Keywords: Bevacizumab, Biopsy, Newly diagnosed glioblastoma, Timing, Wound complication

INTRODUCTION

Several randomized and clinical trials have demonstrated that the addition of bevacizumab (BEV), a humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEGF) signaling, to standard chemoradiotherapy improves progression-free survival but not overall survival (OS) in patients with newly diagnosed glioblastoma (GBM).[5,9] However, recent retrospective studies have revealed the potential of BEV in improving OS in patients with newly diagnosed unresectable GBM and poor performance status (PS).[11,14] In these reports, the contribution of BEV is thought to be in preventing early clinical deterioration and facilitating continued maintenance chemotherapy.[11,14]

The manufacturer's recommendation states that BEV should not be initiated for at least 28 days following major surgery because of the risk of wound-healing complications.[1] However, in the actual clinical setting, some patients who underwent biopsy show early clinical deterioration before or immediately after the start of chemoradiotherapy, and in such cases, early initiation of BEV would be beneficial. To date, very few reports have examined the safety and feasibility of initiation of BEV <28 days after surgery in patients with GBM.[3] In our institution, we administer standard chemoradiotherapy with BEV for patients with newly diagnosed unresectable GBM 28 days following biopsy, but for patients showing early clinical deterioration, this treatment is started earlier than 28 days after biopsy. In this study, we retrospectively analyzed the timing of BEV administration in patients with newly diagnosed GBM who underwent biopsy from the perspective of risks and benefits.

MATERIALS AND METHODS

We investigated 31 consecutive patients with newly diagnosed GBM who underwent biopsy followed by BEV administration at the University of Tsukuba Hospital between December 2014 and December 2019. The surgical procedures for tumor biopsy included open biopsy via small craniotomy, endoscopic biopsy, and stereotactic needle biopsy; the most suitable method was chosen based on tumor characteristics, such as location and vascularity. Endoscopic and stereotactic needle biopsies were performed through a burr hole with a minimal skin incision. Open biopsy through small craniotomy required a large incision with a linear or curved shape, especially in cases of forehead craniotomy, and a larger skin incision was needed from a cosmetic point of view.

All patients received concurrent radiotherapy and temozolomide after the histopathological diagnosis of GBM was confirmed by biopsy. Patients with GBM treated at our institute received one of two postoperative chemoradiotherapy protocols. In the conventional protocol, a total dose of 60.0 Gy was administered in daily fractions of 2.0 Gy 5 times/week concomitant with 75 mg/m^2 temozolomide daily. For elderly patients with a low Karnofsky Performance Status (KPS) score, the elderly protocol was generally administered, in which a total radiation dose of 45.0 Gy was administered in daily fractions of 3.0 Gy 5 times/week concomitant with 50 mg/m^2 temozolomide daily.

All patients received BEV at a dose of 10 mg/kg intravenously every other week. BEV was initiated on or after 28 ± 1 days following biopsy for patients without clinical deterioration (standard BEV group), whereas for patients showing early clinical deterioration, BEV was initiated <27 days after biopsy (early BEV group). Treatment response was assessed according to the Response Assessment in Neuro-Oncology (RANO) criteria.

The study protocol was approved by the ethics committee of the University of Tsukuba Hospital (number R01-202).

Statistical analyses were performed using SPSS, version 26 (SPSS, Inc.). The primary outcome to investigate the prognostic value of the timing of BEV administration was OS, which was defined as the time from surgery to death. Survival probabilities were calculated using the Kaplan–Meier method, and differences among patient groups were evaluated using the log-rank test. Differences in normally distributed continuous variables were analyzed using Student's *t*-test, and differences in non-normally distributed continuous variables were analyzed using the Mann–Whitney U test. Differences in categorical variables were evaluated using Fisher's exact test or the Chi-square test. Statistical significance was set at $P < 0.05$.

RESULTS

The characteristics of the 31 patients are shown in Table 1. The mean age of the patients was 73.6 years (range, 38–91 years). Eighteen patients were men and 13 were women. The median KPS score before biopsy was 60 (range, 40–90). The surgical procedures included open biopsy ($n = 25$), endoscopic biopsy ($n = 4$), and needle biopsy ($n = 2$). Sixteen (51.6%) patients were treated with the conventional chemoradiotherapy protocol, and 15 (48.4%) patients were treated with the elderly protocol.

Table 1: Patient characteristics.

Characteristics	Patients (*n*=31) (%)
Age (years)	73.6±12.1
Gender	
Male	18 (58.1)
Female	13 (41.9)
KPS (preoperative)	
90	3 (9.7)
80	3 (9.7)
70	5 (16.1)
60	14 (45.2)
50	3 (9.7)
40	3 (9.7)
Biopsy method	
Open biopsy	25 (80.6)
Endoscopic biopsy	4 (12.9)
Needle biopsy	2 (6.5)
Chemoradiotherapy	
Conventional protocol	16 (51.6)
Elderly protocol	15 (48.4)
BEV administration	
Standard BEV group	18 (58.1)
Early BEV group	13 (41.9)

Data are given as mean±SD, or number (%). SD: standard deviation, KPS: Karnofsky performance status, BEV: Bevacizumab

Eighteen (58.1%) patients received BEV on or after 28 ± 1 days following biopsy (standard BEV group), and 13 (41.9%) received BEV <27 days after biopsy (early BEV group). The clinical and treatment characteristics of patients in the early and standard BEV groups are summarized in Table 2. The median durations from biopsy to BEV initiation were 21 days (range, 13–23 days) and 30 days (range, 27–40 days) in the early and standard BEV groups, respectively. The mean lengths of the skin incisions were 7.6 cm and 10.6 cm in the early and standard BEV groups, respectively. Patients in the early BEV group were more likely to have a lower KPS score at the time of BEV administration than those in the standard BEV group, although the KPS scores before biopsy were similar. However, these differences were not statistically significant. Other clinical characteristics, such as age, sex, and perioperative corticosteroid administration, did not differ between patients in the early and standard BEV groups.

According to the RANO criteria, the response rates were similar in both treatment groups: In the early BEV group, 5 patients (38.5%) had partial response (PR), 6 (46.2%) had stable disease (SD), and 2 (15.4%) had progressive disease (PD), whereas in the standard BEV group, 5 patients (27.8%) had PR, 11 (61.1%) had SD, and 2 (11.1%) had PD. The median OS for all patients was 10.3 months (95% confidence interval [CI], 9.3–11.2). The results of the analysis based on the Kaplan–Meier method are shown in Figure 1. No statistically significant difference in OS was observed based on the timing of BEV administration. The median OS of the early and standard BEV groups was 10.7 months (95% CI 6.8–14.5) and 10.3 months (95% CI 9.8–10.8), respectively.

Adverse events that fulfilled the criteria for Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher toxicities related to the administration of BEV are summarized in Table 3. No wound dehiscence was observed in the early BEV group and only one case was observed in the standard BEV group. One case of meningitis without wound complications was observed in the standard BEV group, although its correlation with BEV administration was obscure. Other complications included one case of hypertension in the early BEV group.

Case illustration

A 50-year-old man was referred to our hospital because of a suspected brain tumor. Magnetic resonance imaging (MRI) revealed a heterogeneously enhancing mass in the corpus callosum [Figure 2a]. On admission, neurological examination showed mild headache. Open biopsy was performed through small craniotomy and pathological diagnosis was GBM [Figure 2b]. Although concurrent radiotherapy and temozolomide was started 13 days after surgery, clinical deterioration such as aphasia, appetite loss, and wobbly unsteadiness was observed and progressed

Table 2: Clinical and treatment characteristics of the patients of standard BEV group and early BEV group.

Characteristics	Early BEV group (*n*=13) %	Standard BEV group (*n*=18) %	*P*-value
Age (years)	73.7±9.2	73.6±14.1	0.99
Gender			
Male	7 (53.8)	11 (61.1)	0.73
Female	6 (46.2)	7 (38.9)	
KPS			
Preoperative	60 (60–70)	60 (60–70)	0.92
Pre-BEV administration	50 (40–60)	60 (50–70)	0.08
Biopsy method			
Open biopsy	11 (84.6)	14 (77.8)	0.45
Endoscopic biopsy	2 (15.4)	2 (11.1)	
Needle biopsy	0	2 (11.1)	
Skin incision length	7.6±2.2 cm	10.6±5.8 cm	0.06
Perioperative corticosteroid use			
Yes	7 (53.8)	13 (72.2)	0.45
No	6 (46.2)	5 (27.8)	
Chemoradiotherapy			
Conventional protocol	6 (46.2)	10 (55.6)	0.72
Elderly protocol	7 (53.8)	8 (44.4)	
Response (RANO criteria)			
PR	5 (38.5)	5 (27.8)	0.71
SD	6 (46.2)	11 (61.1)	
PD	2 (15.4)	2 (11.1)	

Data are given as mean±SD, median (interquartile range), or number (%). BEV: Bevacizumab, KPS: Karnofsky performance status, PR: Partial response, SD: Stable disease, PD: Progressive disease

from before and after the start of treatment. Accordingly, BEV was administrated 22 days following surgery, then the neurological symptoms improved rapidly and improvement in MRI findings was also detected 11 days after BEV administration [Figure 2c]. After completing concurrent chemoradiotherapy, the patient was discharged home and continued outpatient maintenance temozolomide.

DISCUSSION

In the present study, we retrospectively analyzed the timing of BEV administration in patients with newly diagnosed GBM who underwent biopsy to assess the risks and benefits of early BEV administration. No increase in wound-healing complications was observed in patients who received BEV 13–23 days after biopsy (early BEV group) compared to those who received BEV more than 26 days after biopsy (standard BEV group). In addition, equivalent treatment effects were achieved in patients who developed early clinical deterioration and those without clinical deterioration, suggesting the effectiveness of early BEV initiation in controlling early clinical deterioration.

To date, the utility of adding BEV to standard chemoradiotherapy in patients with newly diagnosed GBM remains to be demonstrated, as represented by the lack of OS prolongation in two large, randomized, and clinical trials.[5,9] However, because of their strict selection criteria, these clinical trials excluded patients with poor PS, and therefore do not reflect the real clinical setting, which has substantially more patients with poor PS. The potential benefit of adding BEV to initial chemoradiotherapy has been reported in recent retrospective studies that included only patients with newly diagnosed unresectable GBM with poor PS.[11,14] In these reports, BEV administration prevented early clinical deterioration, maintained general and neurological status, and prolonged OS.

Because VEGF plays a crucial role in wound healing and tumor angiogenesis, its inhibition by BEV has the potential to affect the healing of surgical wounds. The incidences of wound complications at the craniotomy site in patients with newly diagnosed GBM or recurrent GBM were 1.5–6.9% and 4–6%, respectively, when BEV was initiated after surgery in prospective clinical trials.[5,8-10] Further, in a retrospective study of recurrent GBM, the incidence of wound complications following craniotomy was reported to be 35% when BEV was administered preoperatively.[6] In the present study, the incidence of wound complications was 3.2%, which is comparable to that reported in the previous studies.

Table 3: Adverse events following BEV administration (≥CTCAE G3).

Adverse event	All	Early BEV group	Standard BEV group
Wound dehiscence	1	0	1 (G3)
Meningitis	1	0	1 (G3)
Hypertension	1	1 (G3)	0

BEV: Bevacizumab, CTCAE: Common Terminology Criteria for Adverse Events

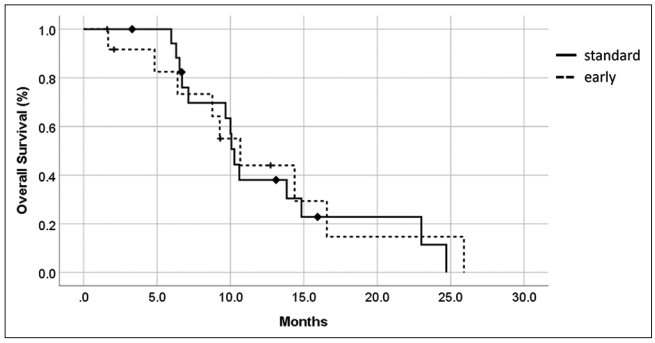

Figure 1: The result of survival analysis based on the Kaplan–Meier method.

Kaplan–Meier estimates of overall survival according to the timing of bevacizumab (BEV) administration. The dotted line indicates the early BEV group and the solid line indicates the standard BEV group.

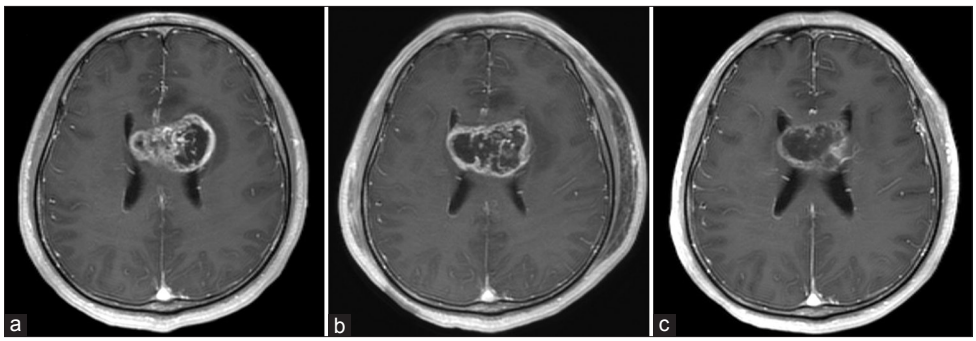

Figure 2: Axial T1-weighted images with gadolinium (a) Preoperative magnetic resonance imaging (MRI). MRI demonstrated a heterogeneously enhancing tumor located in the corpus callosum. (b) MRI the day after the biopsy surgery MRI showed mild enlargement of the heterogeneously enhancing tumor. (c) MRI 11 days after initial administration of bevacizumab MRI showed shrinkage of the heterogeneously enhancing tumor.

Notably, the incidence of wound complications did not increase in patients who received early BEV administration.

Regarding the timing of BEV initiation after surgery, the drug manufacturer recommends postponing administration of BEV for at least 28 days following surgery.[2] This interval was based on the results of the original Phase II study in which BEV was not administered within 28 days of major surgical procedures and the fact that the estimated half-life of BEV is 20 days.[3] However, few reports have analyzed the incidence of adverse events from BEV initiated <28 days after surgery. Lai *et al*. reported that the results of a Phase II study in which 70 patients with newly diagnosed GBM were treated with temozolomide and radiation therapy plus BEV initiated within 21–42 days after surgery.[12] In their report, wound complications were observed in four patients (5.7%). Based on these results, they suggested that BEV initiation 21 days after craniotomy may increase the risk of wound complications, particularly in patients with poorly healed wounds. However, the wound complication rate of 5.7% in their study was equivalent to the results of the previous prospective and clinical trials in which BEV was administered at least 28 days after surgery.[5,9] Therefore, except for patients with poorly healed wounds, BEV initiation 21 days after surgery was unlikely to increase the risk of wound complications. Furthermore, Abrams *et al*. mentioned the reasonability of BEV initiation 14 days after surgery based on basic data on wound healing in their review article.[3] It appears that the critical period for angiogenesis in capillary network formation, which plays a key role in tissue regeneration, is 14 days after surgery.[3,13] Conversely, they stated that there may be no safe interval at which the risk of wound complication is eliminated for patients who receive BEV after surgery, based on the results of a previous study with intervals of up to 5 months.[3] Moreover, in a previous study that investigated the relationship between the timing of BEV administration and the risk of wound healing in patients undergoing chest wall port placement, a significantly higher risk was observed when the interval was <14 days.[7] These authors stated that BEV was most likely to result in poor wound healing and dehiscence within the first 2 weeks after the incision. Given our results and those of these previous studies, we believe that BEV initiation 14 days after surgery can be tolerated for patients who develop early clinical deterioration when the wound condition is appropriate.

In the present study, the sizes of the surgical wound were different between the early and standard BEV groups, although the difference was not statistically significant. Notably, patients in the early BEV group were more likely to undergo surgery with a small skin incision. This may reflect a preoperative premonition based on tumor characteristics of the urgent need of early BEV initiation due to early clinical deterioration. In a previous review article, Bose *et al*. proposed different timings of BEV initiation based on the type of preceding surgery.[4] They recommended deferring BEV initiation for 2–4 weeks after stereotactic biopsy and 4–6 weeks after craniotomy to minimize the risk of wound complications. Therefore, for patients with unresectable GBM who are likely to develop early clinical deterioration, efforts to minimize the surgical biopsy wound should be considered to prepare for BEV initiation.

The present study has several limitations. First, due to its retrospective nature and potential bias in the sample, the rate of complications may be slightly underestimated. Second, this study also involved a relatively small sample size, which limit the generalizability of the findings. Although these limitations should be recognized and considered, the present findings offer useful insights into the efficacy of early BEV initiation for controlling early clinical deterioration. Further investigations with a larger number of patients are required to validate the utility of early BEV initiation.

CONCLUSION

We demonstrated that early BEV administration (13–23 days after surgery) does not increase the risk of wound-healing complications when the wound condition is good. Initiation of BEV at least 14 days after surgery can be tolerated by patients who develop early clinical deterioration to accomplish the initial chemoradiotherapy and continue subsequent maintenance chemotherapy. Further studies with larger numbers of patients are needed to validate our results.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Conflicts of interest

There are no conflicts of interest.

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