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ORIGINAL RESEARCH

Dose and Efficacy of Bevacizumab in Recurrent High-Grade Gliomas: A Retrospective Study

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Purpose: We retrospectively analyzed the effect of Bevacizumab (BEV) on recurrent high-grade glioma (rHGG) and examined the relationship between dose and efficacy.

Methods: A total of 182 patients with rHGG were included in this study. Patients were divided into a non-BEV group and a BEV group according to the treatment they received, and the BEV group was further divided into a low-dose group and a high-dose group based on the dose. Depending on the number of groups and the characteristics of numerical variables, *t*-test, ANOVA, or rank-sum test were selected. Categorical variables were compared using the chi-squared test.

Results: Progression-free survival (PFS) was lower in the non-BEV group compared to the BEV group, while overall survival (OS) was not different between the two groups. There was no difference in PFS and OS between low-dose group and high-dose group. Notably, we found that patients with longer PFS and OS were more likely to be from the BEV group. In addition, differences in Karnofsky Performance Score (KPS), steroid dose, and brain edema were observed in the non-BEV, low-dose, and high-dose groups from 3 to 12 months after treatment.

Conclusion: BEV can improve PFS in patients with rHGG, although its impact on OS is limited. There was no difference in the efficacy of different doses of BEV on rHGG. Interestingly, patients with longer PFS and OS were more likely to be from the BEV group. Based on these findings, long-term low-dose BEV appears to be an effective treatment option for rHGG.

Keywords: bevacizumab, temozolomide, recurrent high-grade glioma, progression free survival, overall survival

Introduction

The World Health Organization (WHO) classifies gliomas into grades I–IV, with grades III and IV designated as high-grade glioma (HGG).[1] These HGG are among the most aggressive neoplasms of the central nervous system, typically treated with surgical resection, radiotherapy, and chemotherapy.[2] Despite these treatments, tumor recurrence is common in recurrent high-grade glioma (rHGG). The treatment methods for rHGG include re-surgery, radiotherapy, and chemotherapy (alone or in combination). However, there is currently no established optimal treatment approach. Temozolomide (TMZ) is the most widely used chemotherapy drug for this condition.[3–5] A standard 5-day TMZ regimen, consisting of 150–200 mg/m^2 administered for 5 days out of every 28-day cycle, is typically recommended as first-line therapy for rHGG.[6]

Overexpression of vascular endothelial growth factor (VEGF), microvascular proliferation, and blood-brain barrier damage have been observed in rHGG. Bevacizumab (BEV), a humanized monoclonal antibody, exerts anti-tumor effects by inhibiting tumor neovascularization and has been applied to various tumors, including rHGG.[7] In addition to its well-documented anti-angiogenic properties, recent studies have shown that BEV can also modulate the immune system. Specifically, increased expression of VEGF can lead to immune suppression by inhibiting the maturation of dendritic cells, reducing T-cell infiltration into tumors, and promoting the presence of inhibitory cell types in the tumor microenvironment. BEV has been demonstrated to potentially reverse this immune suppression by enhancing T-cell activity.[8] Although BEV has been reported to carry a risk of side effects in treating rHGG, survival has been improved, but only in the study based on the systematic analysis of data from the published literature.[9] Two randomized clinical trials have also evaluated the efficacy of BEV in newly diagnosed glioblastoma (GBM). Despite improvements in progression-free

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survival (PFS), these trials failed to demonstrate any significant improvement in overall survival (OS).[10] Conflicting results from Phase II and Phase III clinical trials have demonstrated heterogeneity in the response to BEV in rHGG.[11] Although BEV is commonly used for rHGG, its benefits in improving quality of life and neurocognitive function remain controversial.[12] The relationship between BEV dose and adverse reactions is unclear. The purpose of this study was to investigate the effects of BEV on rHGG and explore the relationship between dose and efficacy.

Material and Methods

Patients

This retrospective study included patients based on the following inclusion criteria: (1) The first operation pathologically confirmed HGG; (2) Imaging findings or pathology from reoperation proved tumor recurrence; (3) The patient had received surgery and chemoradiotherapy, but not BEV; (4) Patients have normal coagulation, liver, and kidney function. (5) Patients have complete clinical data. The exclusion criteria are: (1) Patients with newly diagnosed HGG; (2) Patients with a history of other brain tumors; (3) The patient has a history of abnormal bleeding within the last six months. The determination of the type of resection was based on the postoperative imaging findings. A complete resection was considered when no enhanced tumor signal was observed on the imaging. If the residual enhancement signal did not exceed 5% of the preoperative signal, it was considered a subtotal resection. On the other hand, if the residual enhancement exceeded 5% of the preoperative volume, it was categorized as a partial resection.[13] A total of 182 patients were included in this retrospective study, comprising 95 males and 87 females, with a median age of 54.50 ± 16.76 years. Thirty-nine patients refused reoperation for various reasons. Imaging evaluation was conducted by two experienced neurosurgeons to exclude pseudoprogression. Table 1 presents a summary of the patients' demographic characteristics. This study adhered to the principles of the Declaration of Helsinki. Since it was a retrospective observational study that did not involve the disclosure of personal information and written informed consent had been obtained from all participants beforehand, the Ethics Review Committee of the Chinese Academy of Medical Sciences and Peking Union Medical College Hospital decided to waive the requirement for ethical approval for these reasons.

Table 1 Baseline Characteristics of All Patients

Parameter	Non-BEV (n=72)	Low-Dose BEV (n=57)	High-Dose BEV (n=53)	P-value
Age (median, years)	58±17.64	54±16.71	52±15.80	0.719
Sex (N)				0.971
Male	38	29	28	
Female	34	28	25	
Pathological grade (N)				0.682
WHO III	23	16	19	
WHO IV	49	41	34	
Extent of resection (N)				0.826
Complete resection	38	32	33	
Subtotal resection	10	10	9	
Partial resection	6	3	2	
No reoperation	18	12	9	
Tumor location (N)				0.079
Frontal lobe	19	7	9	
Temporal lobe	9	15	7	
Parietal lobe	10	4	13	
Frontotemporal lobe	15	18	9	
Parietooccipital lobe	14	9	10	
Brainstem	5	4	5	

(*Continued*)

Table 1 (Continued).

Parameter	Non-BEV (n=72)	Low-Dose BEV (n=57)	High-Dose BEV (n=53)	P-value
IDH (N)				0.413
Mutation	25	14	18	
Wild type	47	43	35	
MGMT (N)				0.998
Methylated	20	16	15	
Unmethylated	52	41	38	
Reoperation to Bev(months)	/	2±1.36	2±1.03	<0.001*
KPS	60±17.92	60±14.35	60±13.01	0.508
Edema (ccm)	24.50±12.95	31±12.40	27±11.56	0.130
Steroids (mg)	20±25.19	20±26.91	20±28.08	0.811
Steroids (day)	5±1.37	5±1.42	6±1.55	0.137

Notes: * indicates p-value < 0.05.
Abbreviations: BEV, bevacizumab; WHO, world health organization; KPS, karnofsky performance score.

Drug Administration

All patients received the standard 5-day TMZ regimen, consisting of 200 mg/m^2 administered for 5 days every 28 days. The maximum course of TMZ treatment in this study was 26 cycles. Hematological examinations were conducted prior to each cycle of treatment. Long-term TMZ therapy has the potential to enhance the prognosis of patients with HGG; however, discontinuation of the drug should only be considered when severe toxic effects emerge.[14] The recommended dose for BEV is 5–15 mg/kg, with an interval of 2–3 weeks.[15] Patients were divided into a non-BEV group (TMZ alone, n=72) and a BEV group based on whether they received BEV treatment. The decision to use BEV was influenced by several factors, including patient concerns about potential adverse reactions and financial considerations, with cost being a significant factor in many cases. The BEV group was further categorized into a low-dose group (3mg/kg, interval: 2 weeks, n=57) and a high-dose group (10mg/kg, interval: 2 weeks, n=53) depending on the dose of BEV administered. Each 28-day period constituted one treatment cycle.

Efficacy Evaluation

The therapeutic response was evaluated according to the Response Assessment in Neuro-Oncology (RANO) criteria.[16] Complete response (CR) was defined as the disappearance of the tumor signal. Partial response (PR) was defined as a ≥50% reduction in tumor area on contrast-enhanced scanning. Stable disease (SD) was defined as a decrease in tumor size of <50% or an increase in tumor size of <25%. Disease progression (PD) was defined as an increase in tumor size of ≥25%. The overall response rate (OR) included CR and PR. PFS and OS were calculated from the initiation of drug therapy. MRI was performed every 4–8 weeks. Tumor and edema volumes were obtained by accumulating the volumes on each axial image.[17] Two experienced neurosurgeons separately evaluated the patients' KPS and recorded steroid doses.

Statistical Analysis

The continuous variables are presented as the median ± standard deviation (median ± SD). All categorical variables are described as the number of patients or as a percentage (%). Depending on the number of groups and the characteristics of numerical variables, *t*-test, ANOVA, or rank-sum test were selected. Categorical variables were compared using the chi-squared test. Univariate and multivariate regression analyses were conducted to assess the impact of various factors on PFS and OS. The survival curves for PFS and OS were plotted using the Kaplan-Meier method. All data in this study were analyzed with SPSS (version 27.0, IBM). The multivariate mixed-effects model was developed using R software (version 4.4.1). A P-value of < 0.05 was considered statistically significant.

Results

Univariate and Multivariate Regression Analysis

In this study, 17 potential factors associated with PFS and OS were analyzed. A univariate Cox regression analysis was conducted on these factors, revealing that 8 significantly influenced PFS ($P < 0.05$), including BEV usage, BEV cycles, and reoperation, among others. These 8 factors were then incorporated into a multivariate mixed-effects regression model, which identified BEV usage, BEV cycles, TMZ cycles, reoperation, and pathological grade as independent risk factors for PFS ($P < 0.05$). For OS, 7 factors that showed statistical significance in the univariate analysis were selected for inclusion in the multivariate model. The analysis indicated that only TMZ cycles and reoperation were independent risk factors for OS ($P < 0.001$). The results of the univariate and multivariate regression analyses are summarized in Table 2.

Therapeutic Effect

The median PFS was 5 months in the non-BEV group and 7 months in BEV groups ($P < 0.05$). OS was 9.5 months in the non-BEV group compared with 13 months in the BEV group ($P > 0.05$). There was no difference in PFS and OS between low-dose BEV group and high-dose BEV group ($P > 0.05$). The PFS and OS of 39 patients who did not undergo reoperation were 3 months and 5 months, respectively. For patients who underwent reoperation, PFS was 7 months and OS was 13 months ($P < 0.05$). The median PFS for all patients was 7 months. Of the 112 patients with PFS≤7 months, 61 (54.5%) received BEV and 51 (45.5%) did not ($P > 0.05$). Of the 70 patients with PFS > 7 months, 49 patients (70.0%) received BEV and 21 (30.0%) did not ($P < 0.05$). The median OS of enrolled patients was 11 months. Of the 92 patients with OS≤11 months, 49 (53.3%) received BEV and 43 (46.7%) did not ($P > 0.05$). Of the 90 patients with OS > 11 months, 61 (67.8%) received BEV and 29 (32.2%) did not ($P < 0.05$). Regarding overall response rates, the response rates at 3, 6, 12, and 24 months were 75.3%, 59.9%, 34.1%, and 8.2%, respectively. Figure 1 shows the survival curves of PFS and OS for the three groups.

Clinical Manifestation

There were no significant differences in baseline levels of brain edema, steroid dose, and KPS among the three groups. Table 3 presents a summary of the changes in brain edema, KPS, and steroid dose during treatment for all patients. After

Table 2 Univariate and Multivariate Regression Analysis

Parameter	UV HR (95% CI)	UV p	MV HR (95% CI)	MV p*
Progression-free survival				
BEV usage	0.676 (0.496–0.921)	0.013	0.789 (0.653–0.954)	0.014*
BEV cycles	0.934 (0.910–0.958)	<0.001	1.534 (1.045–2.253)	0.029*
TMZ cycles	0.816 (0.785–0.848)	<0.001	0.840 (0.803–0.879)	<0.001*
IDH	1.414 (1.018–1.965)	0.039		
MGMT	1.928 (1.362–2.729)	<0.001		
Reoperation	3.524 (2.359–5.263)	<0.001	2.123 (1.427–3.160)	<0.001*
Pathological grade	1.662 (1.196–2.309)	0.002	1.579 (1.103–2.259)	0.013*
Reoperation to BEV	0.872 (0.769–0.988)	0.032		
Overall survival				
BEV cycles	0.942 (0.920–0.965)	<0.001		
TMZ cycles	0.722 (0.691–0.756)	<0.001	0.729 (0.693–0.767)	<0.001*
IDH	1.582 (1.133–2.208)	0.007		
MGMT	1.891 (1.328–2.691)	<0.001		
Reoperation	3.789 (2.536–5.661)	<0.001	2.325 (1.544–3.501)	<0.001*
Pathological grade	1.665 (1.195–2.321)	0.003		
KPS	0.988 (0.978–0.998)	0.023		

Notes: * indicates p-value < 0.05.
Abbreviations: UV, univariable; MV, multivariable; CI, confidence interval; HR, hazard ratio; BEV, bevacizumab; TMZ, Temozolomide; KPS, karnofsky performance score.

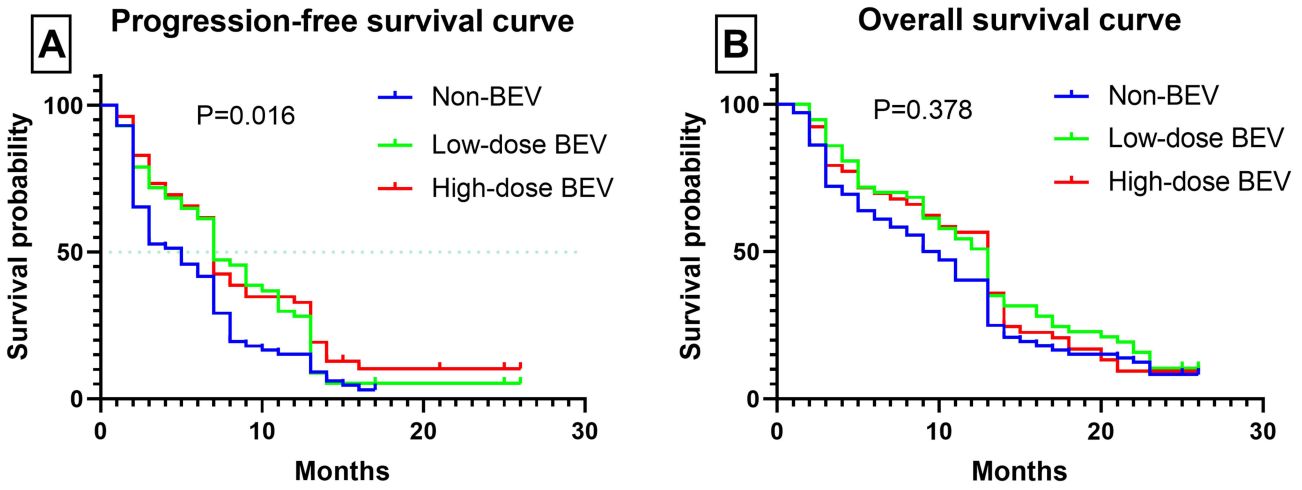

Figure 1 The survival curves of progression-free survival (PFS) and overall survival (OS) were plotted by Kaplan-Meier method. (Panel **A**): Survival curves of PFS in the three groups. (Panel **B**): Survival curves of OS in the three groups.

3 months of treatment, KPS was lower in the non-BEV group than in the BEV group, with a median difference of 20 points (P<0.05). At 6 and 12 months, the difference in KPS between the non-BEV and BEV groups was smaller, with a median difference of 10 points (P<0.05). Steroid doses were higher in the non-BEV group than in the BEV group from 3 to 12 months (P<0.05). Meanwhile, a significant difference in brain edema was observed between the non-BEV and BEV groups (P<0.05). At 24 months after treatment, there were no differences in KPS, steroid dose, and brain edema among the non-BEV, low-dose BEV, and high-dose BEV groups (P>0.05). Throughout the course of treatment, there was no difference in KPS, steroid dose, and brain edema between the low-dose and high-dose BEV groups (P>0.05).

Adverse Drug Events

BEV-associated adverse effects included various types of bleeding, headaches, hypertension, blood toxicity, thrombosis, proteinuria, gastrointestinal perforation, delayed wound healing, congestive heart failure, sepsis, and nephrotic

Table 3 Changes in KPS, Steroids, and Brain Edema in the Three Groups During Treatment

Parameter	Non-BEV (n=72)	Low-Dose BEV (n=57)	High-Dose BEV (n=53)	P-value
KPS				
3 months	50±12.84	70±10.25	70±14.97	<0.001*
6 months	50±12.72	60±11.50	60±11.27	<0.001*
12 months	50±12.24	60±11.23	60±9.80	0.042*
24 months	45±10.49	55±5.48	60±11.40	0.122
Steroid (mg)				
3 months	40±19.72	20±13.25	20±20.02	<0.001*
6 months	40±17.16	20±16.32	20±21.05	<0.001*
12 months	40±18.34	20±21.99	20±20.30	0.007*
24 months	40±24.50	20±24.50	20±26.83	0.108
Brain edema (ccm)				
3 months	21±11.02	15±7.13	14.50±7.25	0.017*
6 months	24±7.60	16±5.74	12±6.51	<0.001*
12 months	30±5.96	26±5.93	24±7.38	0.003*
24 months	29±14.42	32.50±17.07	27±5.54	0.934

Notes: * indicates p-value < 0.05.
Abbreviations: BEV, bevacizumab; KPS, karnofsky performance score.

syndrome.[18–20] The incidence of BEV-related adverse events may be dose-dependent.[21] Thirty-seven patients in the three groups had nausea, 23 had thrombocytopenia, which may be related to TMZ. Among the patients treated with BEV in the two groups, 47 were considered to have new-onset hypertension, and 32 were considered to be fatigued. Both hypertension and fatigue were considered to be related to BEV. There was no difference in adverse reactions between different dose groups. No serious adverse reactions, such as gastrointestinal perforation, cerebral hemorrhage, or pulmonary embolism, were observed in this study, which may be related to the low dose of BEV.

Discussion

VEGF serves as a potent mediator of angiogenesis, vascular permeability, and glioma growth in brain tumors.[22] Increasing evidence indicates that VEGF not only promotes angiogenesis but also plays a crucial role in immune suppression within the tumor microenvironment.[23] It has been demonstrated to inhibit dendritic cell maturation, reduce T cell tumor infiltration, and promote the accumulation of suppressive cell types, contributing to the formation of an immunosuppressive environment associated with poorer outcomes in cancer patients.[8] Targeting VEGF with BEV may not only exert anti-angiogenic effects but also potentially reverse VEGF-mediated immune suppression. By modulating the VEGF signaling pathway, BEV could activate immune cell activity, enhance immune responses against tumors, and provide a dual mechanism of inhibiting tumor neovascularization while promoting immune surveillance within brain tumors.[24]

While large-scale studies have failed to demonstrate improved OS with BEV in GBM patients, its use in treating rHGG has gained widespread acceptance. However, it is crucial to acknowledge the limited penetration of antibodies, including BEV, through the blood-brain barrier (BBB), significantly limiting their effectiveness in brain tissue. Furthermore, BEV tightens the BBB, potentially offsetting its beneficial effects on immune cells and potential angiogenesis. Despite reports of VEGF concentrations in the cyst fluid of GBM patients being 200 to 300 times higher than in serum, VEGF remains undetectable in peripheral blood using enzyme-linked immunosorbent assay (ELISA). In contrast, other cancer types may exhibit lower VEGF levels in tumors but detectable concentrations in peripheral blood.[25] This observation highlights the BBB's ability to prevent peripheral VEGF leakage and neutralization, leading to significantly elevated VEGF concentrations within brain cancer tissue. Such high levels of VEGF markedly suppress immune cell activity.[22] Under these conditions, traditional intravenous administration of BEV may be inefficient due to limited BBB penetration.

In addition to traditional intravenous administration, several advanced methods for drug delivery to the brain have been developed, including stereotactic convection-enhanced delivery,[26] slow-release polymers,[27] polymeric micelles,[28] focused ultrasound,[29] and intraarterial administration.[30] Recent studies have shown that intra-arterial administration of BEV significantly improves OS in newly diagnosed GBM patients following surgical resection compared to historical data.[31–33] Using radiolabeling techniques in animal models, permeability of the BBB through osmotic BBB opening (OBBBO) dramatically increases BEV penetration into brain tissue, enabling its action within brain cancer tissue instead of acting merely peripherally.[34] This suggests that combining intra-arterial administration with OBBBO may offer a new therapeutic approach by facilitating direct drug delivery to brain cancer tissue.[35] This enhanced delivery not only strengthens BEV's anti-angiogenic effects within brain cancer tissue but also allows it to counteract VEGF-mediated immune suppression, potentially improving patient outcomes. Thus, the pivotal therapeutic action of BEV may lie in its enhancement of the immune system rather than its anti-angiogenic activity. Future research and clinical trials should further explore methods such as OBBBO to enhance BEV delivery to brain cancer tissue, optimizing its therapeutic efficacy and improving patient prognosis.

Additionally, BEV exhibits steroid-sparing effects and enhances the quality of life for patients with rHGG.[36] BEV has been utilized in the treatment of HGG for over 10 years, yet the determination of an optimal dosage remains controversial.[37] High-dose BEV can rapidly alleviate brain edema, but simultaneously promotes tumor hypoxia and accelerates tumor resistance, posing challenges in balancing its therapeutic benefits and potential drawbacks.[38] Chronic exposure to high-dose BEV can lead to tumor resistance and promote a more aggressive tumor phenotype.[39,40] When treating rHGG with standard doses of BEV (10mg/kg), it leads to reduced vascular permeability, thereby limiting the effectiveness of chemotherapy.[41] In contrast, low-dose BEV has demonstrated efficacy in alleviating cerebral edema and

treating radiation necrosis.[42,43] Therefore, the exploration of low-dose BEV strategies to improve survival outcomes appears feasible.

In this study, PFS in the non-BEV group was shorter than in the BEV groups, indicating that BEV can prolong PFS in rHGG patients. While the OS was longer in the BEV group compared to the non-BEV group, the observed difference did not reach statistical significance, indicating a limited impact of BEV on OS. The results of both univariate and multivariate regression analyses further confirmed this point. Interestingly, our analysis revealed that approximately 70% of patients with both longer PFS and OS belonged to the BEV group. These findings suggest a potential positive impact of BEV on the OS of rHGG patients. However, the limited impact of BEV on OS may also be influenced by the effects of prior radiotherapy. Evidence from a primate study demonstrated that 82% of healthy rhesus monkeys developed de novo GBM within 2.5 to 8 years following fractionated whole-brain radiation therapy (WBRT), suggesting a high rate of radiation-induced gliomagenesis.[44] This phenomenon implies that radiotherapy may contribute to the emergence of new brain tumors or exacerbate tumor progression, potentially offsetting the benefits of subsequent therapies such as BEV over the long term. This aspect could help explain why BEV's effect on extending OS has been less pronounced, as long-term post-radiation changes in the tumor microenvironment may present additional therapeutic challenges.

Our study found no significant differences in PFS and OS between the low-dose BEV group and the high-dose BEV group. However, it is important to note that these findings may be under-powered due to the small sample size in each group, which could limit our ability to detect equivalence between the two dosages. These findings suggest the feasibility of utilizing low-dose BEV in the management of rHGG patients, pending further studies with larger cohorts to confirm these results. Previous studies have demonstrated a slight superiority in PFS when low-dose BEV is administered, further supporting its potential as a treatment strategy for rHGG patients.[45,46]

The PFS and OS of the reoperation group were longer than those of the non-reoperation group, suggesting that surgery is an effective means to improve the prognosis of rHGG. This is consistent with previous reports, and the results of the multivariate mixed model in this study also support this conclusion.[47] The KPS in the non-BEV group was consistently lower than that in the BEV group, indicating that BEV can improve the clinical symptoms of HGG patients. At the same time, the lower dose of steroids in the BEV group compared to the non-BEV group indicates that BEV can reduce steroid use. From 3 months to 12 months, brain edema was more severe in the non-BEV group compared to the BEV group, suggesting that BEV can effectively alleviate brain edema. However, at 24 months after treatment, there was no significant difference in brain edema among the three treatment groups (BEV low-dose, BEV high-dose, and non-BEV). These findings suggest that BEV's efficacy in treating brain edema caused by tumor recurrence is limited.

The relationship between BEV dose and the incidence of adverse events is unknown.[21] A lower dose may reduce the incidence of adverse events.[48] In this study, there was no significant difference in the incidence of adverse events between the low-dose and high-dose groups. This may be attributed to the fact that the drug dose used in the study was lower than the standard level. Additionally, a separate study involving 49 patients demonstrated that by lowering the BEV dose, it was estimated to achieve cost savings of $1,439,726.08. This suggests that using a lower dose not only maintains efficacy but also has the potential to significantly reduce treatment costs.[49] In this study, the median treatment duration was 5 months in the high-dose group and 7 months in the low-dose group. The total amount of drug used in the high-dose group was 3.26 times that in the low-dose group. While lowering the dose may prolong the treatment period, it will reduce the financial burden on patients.

However, several limitations of this study should be acknowledged. Firstly, as a single-center study, the results may not be fully representative and could benefit from replication in multicenter studies. Secondly, due to its retrospective nature, our study was limited in terms of the evidence it could gather. Therefore, there is a need for more prospective studies to be conducted to comprehensively evaluate the efficacy of BEV in patients with rHGG.

Conclusion

This study aimed to investigate the impact of the absence of BEV and varying dosages of BEV on PFS and OS among patients with rHGG. The findings indicate that BEV administration can prolong PFS in rHGG patients and potentially confer benefits for long-term OS. Notably, the efficacy of low-dose BEV was comparable to that of high-dose BEV. In

conclusion, long-term low-dose BEV administration may serve as a viable therapeutic alternative for the treatment of rHGG.

Data Sharing Statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Consent to Participate

Written informed consent was obtained from all individual participants included in the study.

Consent to Publish

We confirm that the manuscript submitted for publication does not contain any personal data or sensitive information that could identify individual patients or research participants. All authors have provided their consent for the publication of this manuscript.

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Disclosure

The authors have no relevant financial or non-financial interests to disclose.

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