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Original Research

Effect of low-dose bevacizumab on health-related quality of life in patients with recurrent high-grade glioma: A retrospective clinical study

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ABSTRACT

Background: We retrospectively analyzed the effects of low-dose bevacizumab (BEV) combined with temozolomide (TMZ) on health-related quality of life (HRQL) in patients with recurrent high-grade glioma (rHGG).
Methods: A total of 129 patients with rHGG were included in this study. Patients were divided into a combination group and TMZ group based on the treatment they received. The Quality of Life Questionnaire Core 30 (QLQ-C30) and EORTC Brain Cancer Module (QLQ-BN20) were used to evaluate HRQL in all patients before and after treatment. Categorical variables were compared using the chi-squared test. The data for all continuous variables were first tested for a normal distribution. If the data conformed to a normal distribution, a T test was used for comparison. If the data did not conform to a normal distribution, the rank-sum test was used.
Results: There were differences in PFS and PFS-6 between the BEV + TMZ and TMZ groups ($P < 0.05$). However, there was no difference in the OS between the two groups ($P > 0.05$). The BEV + TMZ group performed better than the TMZ group in both the QLQ-C30 and QLQ-BN20. In addition, the KPS score was higher in the BEV + TMZ group than in the TMZ group. Steroid doses given were lower in the BEV + TMZ group than in the TMZ group ($P < 0.05$).
Conclusions: Low-dose BEV + TMZ can relieve the clinical symptoms of rHGG patients, reduce their steroid dose, improve HRQL, and prolong PFS, but does not bear any benefit on OS.

1. Introduction

Gliomas are the most common primary craniocerebral tumors and they can be classified into a scale of Grade I-IV according to the World Health Organization (WHO) [1]. Grades III and IV are classified as high-grade gliomas (HGGs). For newly diagnosed HGG, the pursuit of surgical resection with a maximum safe margin is the most critical prognostic factor [2]. At the same time, fractionated radiotherapy and temozolomide (TMZ) therapy post-surgery also play an equally significant role [3]. Unfortunately, nearly all HGG patients have a relapse after standard treatment, and the prognosis is usually extremely poor [4]. For recurrent HGG (rHGG) patients, no standard treatment regimen has been established yet.

Daily low-dose TMZ has been proven to be a safe and effective treatment for rHGG [5–7]. In recent years, research has shown that anti-angiogenesis drugs may play a clinically significant role in the treatment of rHGG [8–10]. Bevacizumab (BEV) is an anti-angiogenic drug that was first used to treat recurrent glioblastoma in 2009 [11]. The commonly recommended dose of BEV is 5 to 15 mg/kg [12,13]. Most studies have focused on the survival time of patients with rHGG, with little attention paid to their health-related quality of life (HRQL). Considering the limited survival of rHGG patients, it becomes crucial to improve their HRQL [14]. Studies have shown that BEV treatment can delay the deterioration of HRQL [15]. BEV was found to fail to improve HRQL in patients with recurrent glioblastoma as a single agent or as part of combination therapy [16]. Two large phase III studies of patients with newly diagnosed glioblastoma showed conflicting HRQL outcomes in patients who received BEV [17,18]. Therefore, the efficacy of BEV on HRQL in patients with rHGG is controversial. We retrospectively analyzed the clinical data of 129 patients to explore whether low-dose BEV (3 mg/kg) combined with TMZ can prolong their survival and improve their HRQL.

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2. Material and Methods

2.1. Patients

The inclusion criteria were as follows: (1) patient was diagnosed with grade III or IV glioma based on histology; (2) tumor recurrence confirmed via histological examination or imaging; (3) patient received standard treatment, including surgery, radiotherapy, and chemotherapy, but not BEV; (4) recurrent lesions were measurable through magnetic resonance imaging (MRI); (5) patient had no history of abnormal bleeding and had normal liver and kidney functions; (6) complete clinical data was available. The exclusion criteria were as follows: (1) patient was newly diagnosed with HGG; (2) patient had a recent history of active bleeding or stroke. Imaging examinations were completed within 3 days after surgery. A complete resection was considered when no enhanced tumor signal was found on postoperative imaging. A subtotal resection was considered when the residual enhancement signal did not exceed 5 % of the preoperative signal on postoperative imaging. A partial resection was considered when the residual enhancement was more than 5 % of the preoperative volume on postoperative imaging. A total of 129 patients (71 men and 58 women; median age 61 ± 10.58 years) were enrolled in the study; of which, 114 patients underwent reoperation for histologically confirmed tumor recurrence. Fifteens patients refused or were unable to undergo reoperation for various reasons. Imaging assessments were performed by two experienced neurosurgeons to rule out pseudoprogression. The detailed demographic characteristics of the patients are presented on Table 1. The hospital's academic ethics committee approved this study. This research follows the Declaration of Helsinki.

2.2. Treatments

Sixty-seven patients were treated with a daily low dose of TMZ (50 mg/m^2) plus intravenous BEV (3 mg/kg) every two weeks, which was defined as a cycle. The other 62 patients could not receive BEV treatment due to underlying diseases, such as gastric ulcer and thrombosis. Therefore, these patients were assigned to the TMZ group, who received a low dose of TMZ (50 mg/m^2) daily. Each course of TMZ was administered for 28 days. This drug can be used for a long time until serious toxic effects occur. The maximum duration of TMZ use in this study was 14 cycles. Hematological examination was performed before each treatment cycle. Patients in the BEV + TMZ group completed at least two BEV cycles.

2.3. Evaluation of efficacy

MRI was performed before treatment and after two BEV cycles [19,20]. Tumor volume was measured using T1-weighted enhanced and T2/FLAIR sequences, and edema volume was measured using unenhanced T2/FLAIR sequences. Accurate tumor and edema volumes were obtained by accumulating the volumes on each axial image [21]. The therapeutic response was evaluated by the Response Assessment in Neuro-Oncology (RANO) criteria [22]. Complete response (CR) was defined as the disappearance of tumor signal. Partial response (PR) was defined as $\geq$ 50 % reduction of tumor area in 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 $\geq$ 25 %. The overall response rate (OR) included CR and PR. Edema volume was defined as a minimum of 10 % reduction in V_E after treatment. An increase in the edema volume was defined as uncontrolled edema. In addition, a $\leq$ 10 % change in V_E was also considered to be uncontrolled edema [23]. Progression-free survival (PFS) and overall survival (OS) were calculated from the start of BEV + TMZ daily dose cycle. PFS-6 was defined as the percentage of patients who survived without tumor progression six months after treatment.

Table 1
Baseline characteristics of all patients.

Parameter	BEV + TMZ (n = 67)	TMZ (n = 62)	95 % CI	P
Age(mean), years	55.97 ± 11.19	58.85 ± 9.74	−6.533–0.764	0.115
Sex (N, %)				0.452
Male	39	32		
Female	28	30		
Pathological grade (N, %)				0.967
WHO III	16	15		
WHO IV	51	47		
Extent of resection (N, %)				0.939
Complete resection	49	47		
Subtotal resection	11	9		
Partial resection	7	6		
Tumor location				0.918
Frontal lobe	21	23		
Temporal lobe	22	16		
Parietal lobe	7	8		
Frontotemporal lobe	9	7		
Parietooccipital lobe	5	6		
Brainstem	3	2		
IDH status				0.503
Mutation	22	17		
Wild type	45	45		
Promoter of MGMT				0.366
Methylated	21	15		
Unmethylated	46	47		
Last TMZ to recurrence (months)	2.36 ± 1.16	2.27 ± 1.01	−0.295–0.463	0.815
Operation to first BEV (months)	3.52 ± 0.96	3.63 ± 0.91	−0.432–0.219	0.466
Karnofsky score	57.61 ± 11.69	60.65 ± 11.00	−6.985–0.919	0.142
Steroids dosage	40 mg/d	40 mg/d		
Course of steroids (day)	5.15 ± 0.84	4.94 ± 1.01	−0.111–0.538	0.110
Reoperation	60	54		0.465
Volume of edema (ccm)	54.58 ± 15.43	53.56 ± 18.58	−4.962–6.998	0.111
Volume of tumor (ccm)	40.21 ± 13.33	33.95 ± 12.57	1.746–10.768	0.063

Abbreviations: BEV, bevacizumab; TMZ, temozolomide; CI, confidence interval; WHO, World Health Organization.

2.4. Assessment of KPS and steroids

The KPS has been commonly used for the general assessment of patients with tumor since its development in 1948 [24]. The KPS assessment was performed independently by two experienced neurosurgeons and the assessment agreement was 97.67 %. The three inconsistent patients were finally evaluated by these two neurosurgeons after discussion. Previous studies have shown that BEV can reduce steroid dependence in patients with HGGs [25,26]. High BEV doses (5–15 mg/kg) were reported in these studies. Here, however, we investigated the effect of low-dose BEV on steroid dependence in rHGG patients.

2.5. Assessment of health-related quality of life

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and European Organization for Research and Treatment of Cancer Module (QLQ-BN20) are commonly used questionnaires to evaluate HRQL in cancer patients. The accuracy and effectiveness of these two scales in evaluating HRQL in cancer patients have been confirmed in many studies [27–30]. The QLQ-C30 consists of 30 items in 15 different domains. All 15 domains are relevant to the patients' HRQL. The functional domains include physical, role, cognitive, emotional, and social functions. The symptom domains include fatigue, pain, and vomiting. The following

factors are also assessed: Global health status, dyspnea, insomnia, anorexia, constipation, diarrhea and financial impact [31]. As a supplement to QLQ-C30, QLQ-BN20 is mainly used for the evaluation of HRQL in patients with craniocerebral diseases. It is composed of 11 domains with 20 items in total. The 11 domains include future uncertainty, visual impairment, motor dysfunction, communication impairment, headache, seizures, drowsiness, hair loss, itching, leg weakness, and bladder control difficulties.

The total score for each domain is 100. The scores of different domains represented different HRQL levels [32,33]. In the QLQ-C30, higher scores in the functional and global health status domains indicate a higher HRQL in the patient. In contrast, higher scores on other aspects represent a lower HRQL. In the QLQ-BN20, the higher the score, the lower the patient's HRQL. Differences in the mean of HRQL parameters $\geq$ 10 points are classified as being clinically significant, whereas changes of $>$ 20 points represent a very large effect [32]. In this study, patients answered QLQ-C30 and QLQ-BN20 every one month after treatment. Five patients who were unable to complete the questionnaire were assessed by agents based on their performance (three in the BEV + TMZ group and two in the TMZ group). The clinical symptoms of these patients improved after treatment. In order to reduce errors, the agent still fills out the questionnaire based on the patient's performance after treatment.

2.6. Statistical analysis

Continuous variables are presented as mean ± standard deviation (mean ± SD). All categorical variables were described as the number of patients or percentage (%). The data for all continuous variables were first tested for a normal distribution. If the data conformed to a normal distribution, the *t*-test was used for comparison. If the data did not conform to a normal distribution, the rank sum test was used for comparison. Categorical variables were compared using the chi-squared test. All data in this study were analyzed using SPSS (version 26.0, IBM). $P < 0.05$ was defined as statistically significant.

3. Results

3.1. Univariate and multivariate cox regression analysis

Sixty-two patients were unable to receive BEV because of gastric ulcers, thrombosis, heart failure, or poor hypertension control. Univariate COX regression analysis showed that thrombosis (hazard ratio [HR] = 1.895, 95 % confidence interval [CI] = 1.074–3.344) and heart failure (HR = 2.214, 95 % CI = 1.044–4.695) were risk factors for PFS in patients with rHGG. Meanwhile, poorly controlled hypertension, thrombosis and heart failure were risk factors for OS. However, the multivariate analysis showed that these variables were not associated with PFS or OS ($P > 0.05$). (Table 2).

3.2. Assessment of efficacy

The mean of PFS in the BEV + TMZ group was 4.57 ± 2.27 months, compared with 3.45 ± 1.95 months in the TMZ group, which was statistically different ($P = 0.003$). The OS was 6.69 ± 2.85 months for the BEV + TMZ group and 5.81 ± 2.33 months for the TMZ group ($P = 0.060$). PFS-6 was 34.3 % in the BEV + TMZ group and 17.7 % in the TMZ group ($P = 0.033$). Regarding response rates, 4.5 % and 80.6 % of patients in the BEV + TMZ group achieved CR and PR, respectively. PD was observed in one patient and SD in the remaining patients. In the TMZ group, PR occurred in 45.2 % of patients, SD was observed in 30.6 %, and PD occurred in 24.2 %. PFS was 4.20 ± 2.24 in the reoperation group and 2.73 ± 1.16 in the non-reoperation group ($P = 0.016$). The OS was 6.60 ± 2.57 in the reoperation group and 3.73 ± 1.71 in the non-reoperation group ($P = 0.001$). After two cycles of BEV treatment, the volume of cerebral edema decreased from 54.58 ± 15.43 to 34.72 ±

Table 2
Univariate and multivariate cox regression analysis.

Parameter	UV HR (95 % CI)	UV p	MV HR (95 % CI)	MV p*
Progression-free survival				
uncontrolled hypertension	1.618 (0.918–2.853)	0.096		
thrombosis	1.895 (1.074–3.344)	0.027	1.761 (0.987–3.141)	0.055
gastric ulcer	1.720 (0.804–3.679)	0.162		
operation within 4 weeks	1.127 (0.530–2.400)	0.756		
congestive heart failure	2.214 (1.044–4.695)	0.038	1.944 (0.905–4.173)	0.088
Overall survival				
uncontrolled hypertension	2.294 (1.180–4.459)	0.014	1.874 (0.933–3.766)	0.078
thrombosis	2.340 (1.161–4.717)	0.017	1.817 (0.864–3.818)	0.115
gastric ulcer	1.915 (0.830–4.418)	0.128		
operation within 4 weeks	1.793 (0.811–3.963)	0.149		
congestive heart failure	2.611 (1.163–5.862)	0.020	2.258 (0.989–5.156)	0.053

Notes: *Those variables found significant at $p < 0.05$ in univariable analyses were entered into multivariable cox-regression analyses.
Abbreviations: UV, univariable; MV, multivariable; CI, confidence interval; HR, hazard ratio.

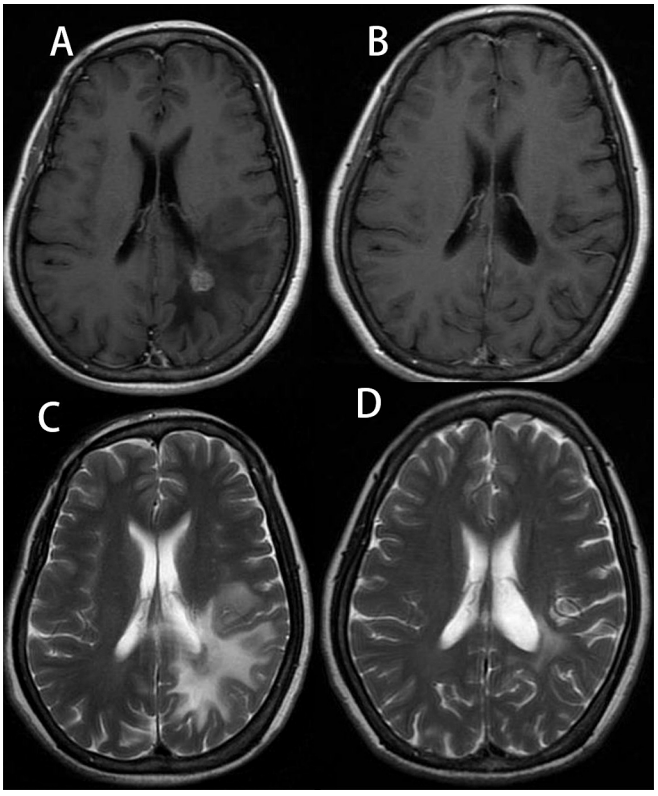

Fig. 1. Imaging changes before and after treatment in a patient with rHGG in the BEV + TMZ group. A: Imaging findings of the tumor on T1-enhanced sequence before treatment. B: Tumor enhancement signal on T1-enhanced sequence disappeared after 2 cycles of BEV. C: Imaging findings of brain edema on T2-weighted sequence before treatment. D: Significant decrease in brain edema volume on T2-weighted sequences after 2 cycles of BEV treatment.

11.32 ccm in the BEV + TMZ group, while there was no significant change in the TMZ group (P < 0.001). The tumor volume before and after treatment showed no obvious changes (P = 0.064). Fig. 1 shows the imaging changes of the tumor and brain edema in a patient with rHGG in the BEV + TMZ group before and after two cycles of BEV treatment.

3.3. KPS and steroids

Before treatment, the KPS of the BEV + TMZ group was 57.61 ± 11.69, while that of the TMZ group was 60.65 ± 11.00 (P = 0.142). After treatment, the KPS level of the BEV + TMZ group increased to 64.33 ± 11.18, while that of the TMZ group decreased to 59.52 ± 11.37. Although there was no significant change in KPS values, the comparison between the two groups was statistically different (P = 0.029).

Steroids are routinely used to treat cerebral edema. All patients received methylprednisolone(40 mg) prior to inclusion in the study. The BEV + TMZ group received 5.15 days of methylprednisolone treatment compared with 4.94 days in the TMZ group. After treatment, the methylprednisolone dose of the combined group was 21.04 ± 9.87 mg, while that of the TMZ group was 26.45 ± 10.88 mg (P = 0.003). Patients who did not undergo surgery had worse KPS scores and higher steroid doses than those who underwent reoperation. The post-treatment KPS was 63.33 ± 10.45 in the patients who underwent reoperation and 52.00 ± 14.24 in these 15 patients (P = 0.002). The methylprednisolone dose was 22.63 ± 10.22 mg in patients who underwent reoperation and 31.33 ± 11.26 mg in patients who did not undergo reoperation (P = 0.005).

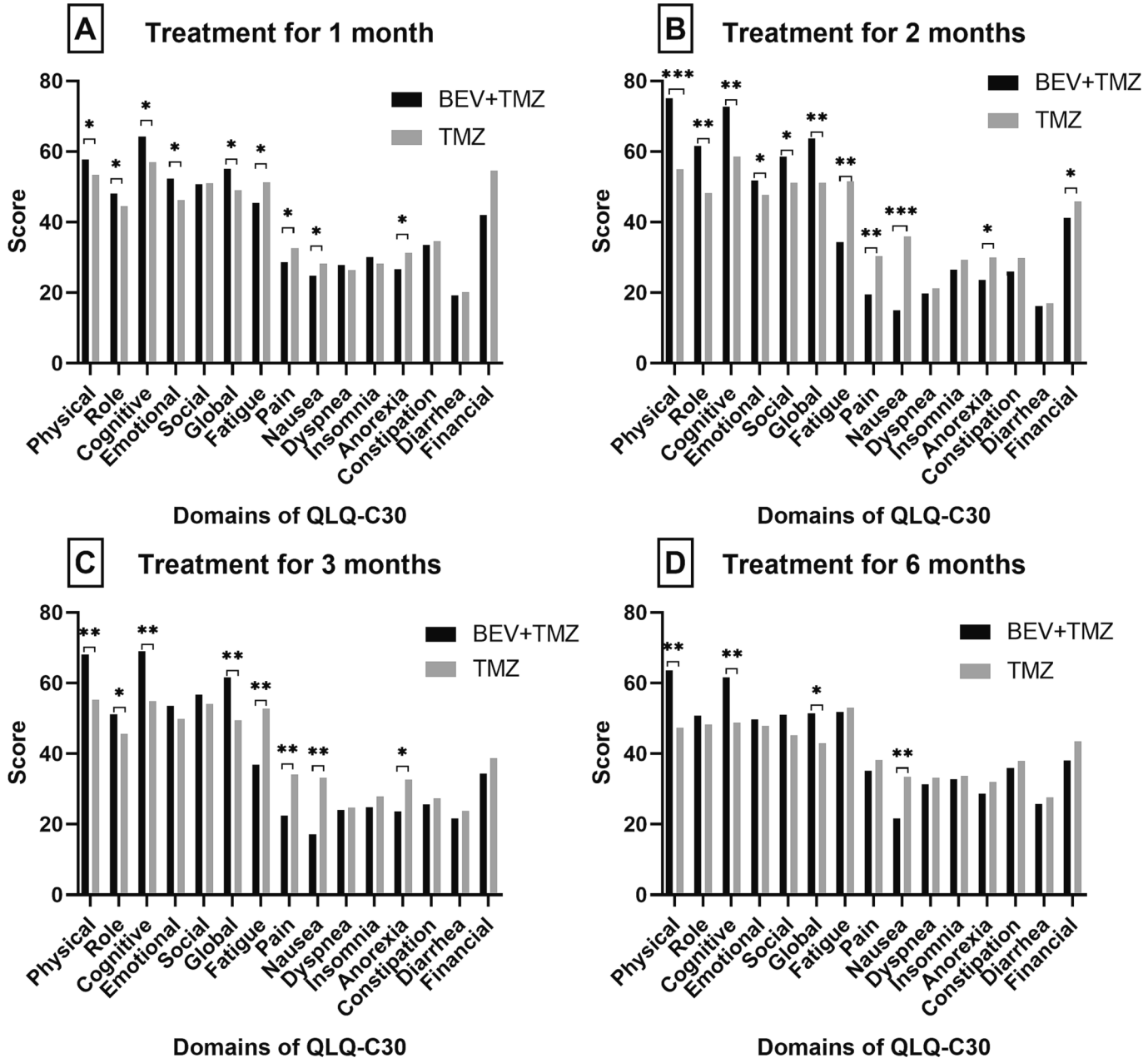

Fig. 2. Changes in QLQ-C30 during treatment in the BEV + TMZ and TMZ groups. A: Performance of QLQ-C30 in the two groups after one month of treatment. B: Performance of QLQ-C30 in the two groups after two months of treatment. C: Performance of QLQ-C30 in the two groups after three months of treatment. D: Performance of QLQ-C30 in the two groups after six months of treatment. (* represents statistical differences; ** represents statistical differences and the difference in mean ≥ 10 points; *** represents statistical differences and the difference in mean ≥ 20 points.).

3.4. Health-related quality of life

There was no difference in the performance of each domain of QLQ-C30 between the BEV + TMZ and TMZ groups before treatment (P > 0.05). After one month of treatment, there were differences between the two groups in 9 domains, including functional domains, global health status, symptom domains, and anorexia (P < 0.05). However, the differences in these 9 domains were not clinically significant (Mean differences < 10 points). After two months of treatment, the BEV + TMZ group was different from the TMZ group in 11 domains of functional domains, global health status, symptom domains, anorexia and financial impact (P < 0.05). Meanwhile, the differences between the two groups in 7 domains of physical function, role function, cognitive function, global health status and symptoms have clinical significance. The mean of physical function was 75.18 ± 5.68 in the BEV + TMZ group and 55.05 ± 9.18 in the TMZ group, with a difference of more than 20 points. In addition, nausea scores were 14.96 ± 3.34 in the BEV + TMZ group and 35.88 ± 11.46 in the TMZ group, a difference of more than 20 points in the mean. After three months, there were differences between the two groups in 8 domains: physical function, role function, cognitive function, global health status, symptom scales and anorexia (P < 0.05). At this point, the differences between the two groups in the following 6 domains have clinical significance: physical function, cognitive function, global health status, and symptom scales. After six months of treatment, there were differences between the two groups in physical function, cognitive function, global health status and nausea (P < 0.05). Apart from global health status, the differences in the other three areas have clinical significance. Fig. 2 details the changes in QLQ-C30 over the course of treatment. (Fig. 2).

There was no difference in the performance of each domain of QLQ-BN20 between the BEV + TMZ and TMZ groups before treatment (P > 0.05). After one month of treatment, there were differences in motor dysfunction, headache, and leg weakness between the two groups, but no clinical significance. After two months of treatment, the two groups showed differences in six domains: visual impairment, motor dysfunction, communication impairment, headache, drowsiness, and leg weakness (P < 0.05). Among them, the differences in motor dysfunction, communication impairment, headache and leg weakness had clinical

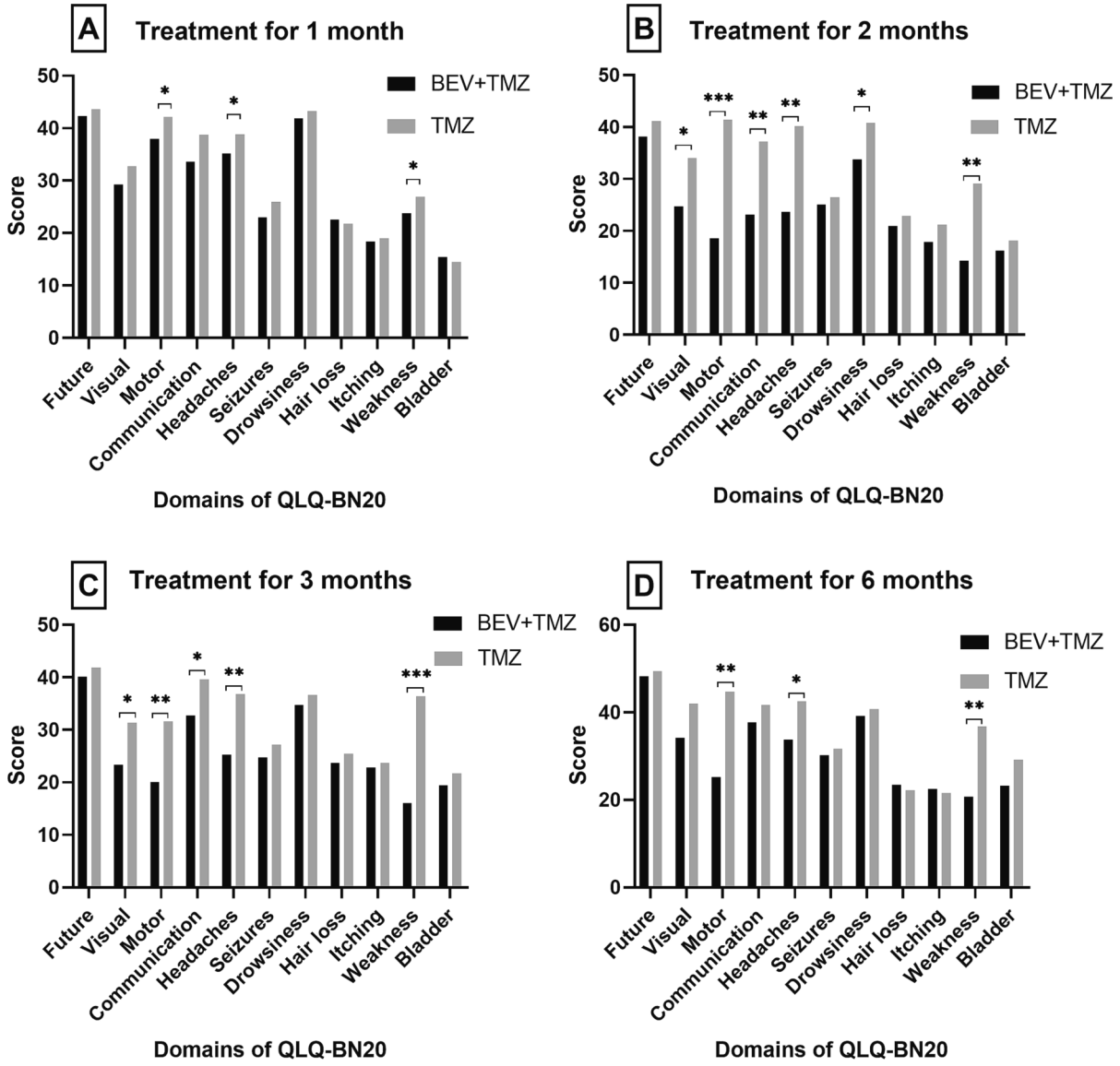

Fig. 3. Changes in QLQ-BN20 during treatment in the BEV + TMZ and TMZ groups. A: Performance of QLQ- BN20 in the two groups after one month of treatment. B: Performance of QLQ- BN20 in the two groups after two months of treatment. C: Performance of QLQ- BN20 in the two groups after three months of treatment. D: Performance of QLQ- BN20 in the two groups after six months of treatment. (* represents statistical differences; ** represents statistical differences and the difference in mean ≥ 10 points; *** represents statistical differences and the difference in mean ≥ 20 points.).

significance. The difference in the mean of the motor dysfunction between the two groups was greater than 20 points (18.61 ± 5.06 VS 41.42 ± 10.28). After three months of treatment, there were differences between the two groups in five domains: visual impairment, motor dysfunction, communication impairment, headache, and leg weakness ($P < 0.05$). The differences in the three domains of motor dysfunction, headache and leg weakness have clinical significance. At this time, the difference between the mean of the two groups in the field of leg weakness was greater than 20 points (16.08 ± 3.54 VS 36.39 ± 8.82). At six months, there were differences between the two groups in the domains of motor dysfunction, headache, and leg weakness, with clinical significance observed in the domains of motor dysfunction and leg weakness. Fig. 3 details the changes in QLQ-BN20 over the course of treatment. (Fig. 3).

3.5. Adverse events

The reported adverse effects associated with BEV include: various types of bleeding, headaches, hypertension, blood toxicity, thrombosis, proteinuria, gastrointestinal perforation, delayed wound healing, congestive heart failure, sepsis, and nephrotic syndrome [34–38]. It has been reported that lower BEV doses may be associated with fewer adverse effects [39]. In our study, hypertension was the most common adverse event and was observed in 27 cases. Seven patients had thrombocytopenia and five had nausea and vomiting. Both groups had thrombocytopenia, nausea, and vomiting. These adverse effects may be related to TMZ. No serious adverse effects, such as gastrointestinal perforation, cerebral hemorrhage, or pulmonary embolism, were observed in this study, which may be related to the smaller dose and shorter duration of BEV we used.

4. Discussion

Despite aggressive treatment, recurrence remains an inevitable problem in HGG treatment. There is no established standard treatment regimen for dealing with disease recurrence [40]. Treatment at the time of recurrence must be individualized depending on the patient's age, clinical condition, performance status, tumor volume, and location. It has been widely accepted that reoperation can prolong the survival of patients with rHGG [41–43]. In this study, patients who did not undergo reoperation had worse OS. Steroids are commonly used in the treatment of brain edema, and BEV can relieve the clinical symptoms of steroid-refractory brain edema [44]. Steroid doses were adjusted according to the patient's clinical performance. The steroid dose was significantly lower in the combination group than in the TMZ group before treatment. After treatment, KPS increased in the BEV + TMZ group and decreased in the TMZ group. In our study, 15 patients refused or were unable to undergo surgery for various reasons. These 15 patients had lower KPS scores and required larger steroid doses to control their clinical symptoms when compared to patients undergoing reoperation.

A previous study confirmed that the antitumor effect of BEV was dose-dependent [45]. Studies have demonstrated that BEV (10 mg/kg) can prolong PFS and OS in rHGG [9]. Another study demonstrated that BEV (10 mg/kg) combined with TMZ did not improve OS or PFS at 12 months in rHGG patients without a 1p/19q deletion [46]. In addition, Norden reported that antiangiogenic therapy may fail to prolong OS in patients with rHGG [47]. The mean PFS was longer in the BEV + TMZ group than in the TMZ group in this study. In addition, PFS-6 levels were greater in the BEV + TMZ group than in the TMZ group. This indicates that low-dose BEV can prolong the PFS in patients with rHGG. However, we observed no statistical difference in OS between the two groups; therefore, we believe that low-dose BEV has no benefit on the OS of rHGG patients. Sixty-two patients did not receive BEV due to contraindications. Multivariate COX regression analysis showed that these contraindications were not associated with PFS or OS in patients with rHGG.

BEV inhibits tumor progression by inhibiting tumor neovascularization. In addition, BEV can reduce the permeability of tumor blood vessels, thereby reducing the generation of peritumoral edema [48,49]. Clinical symptoms and cognitive impairment may be caused by tumor-related factors and treatment-related adverse reactions. With the control of peritumor edema, patients' cognitive status and quality of life improve rapidly, regardless of the degree of tumor regression [50]. Studies have shown that BEV can alleviate refractory brain edema and improve neurological function [51]. Low-dose BEV has also been shown to alleviate brain edema [52]. Another study demonstrated that ultra-low dose BEV (1 mg/kg) was effective in treating radiation necrosis [53]. In this study, it was found that the edema volume decreased in the BEV + TMZ group, while no significant change was observed in the TMZ group. It was further confirmed that low-dose BEV effectively alleviated brain edema. Therefore, we believe that low-dose BEV can act on tumor neovascularization, inhibit peritumoral edema, and exert anti-tumor effects, thereby relieving clinical symptoms, improving HRQL, and prolonging PFS in patients with rHGG.

Given the limited survival of patients with rHGG, the importance of HRQL has received increasing attention. Compared with the TMZ group, the BEV + TMZ group showed the most significant improvement in HRQL two months after treatment, which indicates that low-dose BEV may improve HRQL levels in rHGG patients to some extent, but the process is relatively slow. At six months, the HRQL level of patients in both groups decreased, which we thought was related to tumor progression. However, the performance of the BEV + TMZ group is still better than that of the TMZ group, indicating that low-dose BEV can alleviate the deterioration of HRQL caused by tumor progression to some extent. Throughout the treatment, the differences in HRQL between the two groups were mainly in the domains of physical function, cognitive function, and symptoms such as motor dysfunction, nausea, and leg weakness. These symptoms are related to intracranial hypertension, so we believe that the improvement of HRQL level by low-dose BEV in rHGG patients is related to its effect on alleviating brain edema.

Despite these findings, our study had several limitations. First, this was a single-center study, and the results would be more representative if we could conduct further multicenter studies. Second, our study was retrospective in nature and the evidence we gathered was limited. In addition, the HRQL questionnaire was completed by agents in five patients, which may also lead to bias. Finally, for future studies, increasing the duration of follow-up and BEV cycles would allow a more accurate assessment of the effects of BEV.

5. Conclusions

Previous studies have focused on PFS and OS in patients with rHGG, whereas less attention has been paid to their HRQL. To the best of our knowledge, our study is the first to demonstrate that low-dose BEV + TMZ may improve HRQL to some extent and reduce steroid doses in rHGG patients. In addition, low-dose BEV + TMZ can prolong PFS in patients with rHGG, however it has no benefit in OS.

6. Ethical standards

All persons gave their informed consent prior to their inclusion in the study. This study was performed in line with the principles of the Declaration of Helsinki. The academic and ethical committee of our hospital approved the study.

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8. Authors' contributions

Yiyao Cao and Maoying Zhang participated in the design of this study

and collected important background information. Yonghong Liao and Xuexue Bai completed related literature retrieval, data acquisition and data analysis. Yonghong Liao and Xuexue Bai drafted the manuscript, Yiyao Cao and Maoying Zhang completed the revision of the manuscript. All the authors read and approved the final manuscript. Yiyao Cao and Maoying Zhang are responsible for the final manuscript. The authors declare that there are no conflicts of interest.

CRediT authorship contribution statement

Yonghong Liao: Data curation, Investigation, Methodology, Writing – original draft. **Xuexue Bai:** Data curation, Formal analysis, Investigation, Writing – original draft. **Yiyao Cao:** Conceptualization, Methodology, Resources, Supervision, Writing – review & editing. **Maoying Zhang:** Conceptualization, Data curation, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability statement:

The authors declare that relevant raw data can be provided.

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