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Efficacy of *Lycium barbarum* Polysaccharide Combined with Bevacizumab in the Treatment of Recurrent High-Grade Brain Glioma and Its Effect on Immune Function

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Abstract: *Objective*: To investigate the effect of *Lycium barbarum* polysaccharide (LBP) combined with bevacizumab (BEV) in the treatment of recurrent high-grade glioma and its effect on immune function. *Methods*: A total of 103 patients with recurrent high-grade cerebral glioma admitted to Guigang People's Hospital, the Eighth Affiliated Hospital of Guangxi Medical University, from January 2020 to December 2023 were selected. According to different treatment methods, they were divided into an experimental group (n=52) and a control group (n=51). The control group was treated with BEV, and the experimental group was treated with LBP on the basis of the control group. Both groups were treated for 3 cycles. The clinical efficacy, Kelch-like epichlorohydrin-related protein-1 (Keap1)/nuclear factor E2-related factor 2 (Nrf2) signaling pathway level, immune function indexes ($CD3^+$, $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$), improvement of quality of life, and incidence of adverse reactions were compared between the two groups before and after treatment. *Results*: After 3 cycles of treatment, the objective response rate (ORR) and disease control rate (DCR) in the experimental group were significantly higher than those in the control group (P<0.05). The levels of serum Keap1 and Nrf2 in the two groups were higher than those before treatment, and those in the experimental group were higher than those in the control group (P<0.05). After treatment, except for no significant change in $CD8^+$ level, the levels of $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ in the two groups were higher than those before treatment, and those in the experimental group were higher than those in the control group (P< 0.05). The scores of psychological function, living status, physical function, and social function in the two groups were higher than those before treatment, and those in the experimental group were higher than those in the control group (P<0.05). There was no significant difference in the incidence of adverse reactions between the two groups after treatment (x^2=0.001, P=0.982). *Conclusion*: The clinical efficacy of LBP combined with BEV in the treatment of recurrent high-grade glioma is significant, which can improve immune function and improve quality of life, which may be related to the activation of the Keap1/Nrf2 pathway.

Keywords: *Lycium barbarum* polysaccharide; Bevacizumab; Recurrent high-grade brain glioma; Clinical effect; Immune function

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1. Introduction

Brain gliomas have a high incidence rate, accounting for approximately 78.3% of malignant tumors in the nervous system [1]. Among them, high-grade brain gliomas (HGG) are characterized by highly invasive growth and abnormal proliferation of vascular tissues, with a high recurrence rate and poor prognosis. However, there is currently no standard treatment protocol for recurrent high-grade brain gliomas, making it crucial to explore effective treatment options for recurrent HGG [2]. Relevant studies have indicated [3-4] that patients with brain gliomas may experience immune dysfunction during the disease process, suggesting that improving immune function could be beneficial for treating recurrent HGG (RHGG). Bevacizumab (BEV) is a broad-spectrum anti-tumor drug that has demonstrated certain efficacy in treating RHGG, and clinical recommendations suggest combining it with other treatment modalities to enhance therapeutic outcomes [5]. With the advancement of research, significant breakthroughs have been made in recent years regarding the application of traditional Chinese medicine in the field of anti-brain glioma research. Literature reports indicate that active ingredients in traditional Chinese medicine can ultimately achieve therapeutic effects on brain gliomas through mechanisms such as inducing autophagy, regulating the cell cycle, and inhibiting the activity of tumor-related factors [6]. *Lycium barbarum* polysaccharide (LBP), the primary active component of the traditional Chinese medicine *Lycium barbarum*, possesses anti-tumor, immune-regulating, and antioxidant functions [7]. Research by Li Xiaokun et al. has shown that LBP can enhance the chemotherapeutic efficacy and immune function in patients with malignant brain gliomas [8]. However, the effectiveness of combining LBP with BEV in treating recurrent high-grade brain gliomas remains unclear. Therefore, this study aimed to evaluate the efficacy and impact on immune function of LBP combined with BEV in 103 patients with recurrent high-grade brain gliomas, with the goal of providing a reference for optimizing clinical treatment protocols.

2. Materials and methods

2.1. General information

A total of 103 patients with recurrent high-grade brain gliomas admitted to the Eighth Affiliated Hospital of Guangxi Medical University, Guigang People's Hospital, from January 2020 to December 2023 were selected as the study subjects. Inclusion criteria: (1) All patients met the clinical diagnostic criteria for recurrent high-grade brain gliomas outlined in the "Brain Glioma Diagnosis and Treatment Guidelines (2022 Edition)" and were confirmed to have World Health Organization (WHO) grade III or IV brain gliomas through surgical pathology results [9–10]; (2) Karnofsky (KPS) functional status score ≥ 60; (3) Life expectancy greater than 3 months; (4) Patients and their families provided informed consent and signed the informed consent form. Exclusion criteria: (1) Patients with concurrent other malignancies or severe liver or kidney dysfunction; (2) Breastfeeding or pregnant women; (3) Patients with systemic infections; (4) Patients allergic to LBP or BEV; (5) Patients who did not complete the intervention according to the treatment protocol. Patients were divided into an experimental group (n=52) and a control group (n=51) based on different treatment modalities. The experimental group consisted of 27 males and 25 females, aged 48–65 years, with an average age of 55.79±4.56 years; 20 cases had grade III tumors, and 32 cases had grade IV tumors. The control group consisted of 26 males and 25 females, aged 47–66 years, with an average age of 56.23±4.19 years; 26 cases had grade III tumors, and 25 cases had grade IV tumors. There were no statistically significant differences in gender, age, or tumor pathological grade between the two groups (P>0.05).

2.2. Treatment methods

Control group: BEV infusion was administered every 2 weeks (10 mg/kg, produced by Roche Pharmaceuticals

Ltd., Switzerland, approval number: 20201013, specification: 400 mg/bottle), with two doses per cycle. After two consecutive cycles, a head MRI, blood routine test, and liver and kidney function tests were performed. A total of three treatment cycles were completed.

Experimental group: In addition to the control group's treatment, patients received LBP (produced by Beijing Sobola Technology Co., Ltd., batch number: 821A021, purity > 96%) at a dose of 1 tablet, three times daily. A total of three treatment cycles were completed.

2.3. Observation indicators

2.3.1. Clinical efficacy

Clinical efficacy was assessed after three treatment cycles. According to the glioma efficacy evaluation criteria, patients were classified as having a complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) [11]. The objective remission rate (ORR) = (PR + CR) / total number of cases × 100%, and the disease control rate (DCR) = (SD + PR + CR) / total number of cases × 100%.

2.3.2. Keap1/Nrf2 signaling pathway and immune function indicators

Venous blood samples (6 ml) were collected from all patients in a fasting state before and after treatment. The samples were allowed to stand at room temperature for 20-30 minutes, followed by continuous centrifugation for 5 minutes (3000 r/min). The supernatant was collected and divided into two portions. One portion was used for immune function indicator detection, with CD3+, CD4+, and CD8+ levels measured using a BD flow cytometer, and the CD4+/CD8+ ratio calculated. The other portion was used for serum Kelch-like ECH-associated protein-1 (Keap1) and nuclear factor erythroid-related factor 2 (Nrf2) detection, with serum Keap1 and Nrf2 levels measured using Keap1 and Nrf2 enzyme-linked immunosorbent assay kits produced by Jianglai Biology and Merck Biology, respectively.

2.3.3. Quality of life improvement

Before and after treatment, the Generic Quality of Life Inventory-74 (GQOLI-74) was used to evaluate the psychological function, living conditions, physical function, and social function of the two groups [12]. Each dimension was scored out of 100, with higher scores indicating better quality of life.

2.3.4. Adverse reactions

Adverse reactions in both groups, including nausea and vomiting, bone marrow suppression, and thrombocytopenia, were collected and recorded.

2.4. Statistical methods

All data were analyzed and processed using SPSS 25.0. Measurement data were expressed as mean ± standard deviation (Mean ± SD), with independent sample t-tests used for comparisons between two groups and paired t-tests used for comparisons within the same group before and after treatment. Count data were expressed as rates or percentages, with chi-square tests used for comparisons between two groups. A P-value < 0.05 indicated a statistically significant difference.

3. Results

3.1. Clinical efficacy

After three treatment cycles, the ORR and DCR in the experimental group were significantly higher than those in

the control group (P<0.05), as shown in **Table 1**.

Table 1. Clinical efficacy [n(%)]

Group	n	CR	PR	SD	PD	ORR	DCR
Experimental Group	52	2 (3.85)	35 (67.31)	12 (23.08)	3 (5.77)	37 (71.15)	49 (94.23)
Control Group	51	0 (0.00)	18 (41.18)	23 (45.10)	10 (1.37)	18 (35.29)	41 (80.39)
x^2 value						13.305	4.471
P value						0.000	0.035

3.2. Keap1/Nrf2 signaling pathway

Before treatment, there was no statistically significant difference in serum Keap1 and Nrf2 levels between the two groups ($P > 0.05$). After treatment, serum Keap1 and Nrf2 levels in both groups were higher than those before treatment, with the experimental group showing higher levels than the control group ($P < 0.05$), as shown in **Table 2**.

Table 2. keap1/nrf2 signaling pathway (Mean ± SD, μg/L)

Group	n	Keap1		Nrf2	
		Before Treatment	After Treatment	Before Treatment	After Treatment
Experimental Group	52	1.26 ± 0.29	1.60 ± 0.50*	2.08 ± 0.52	2.58 ± 0.63*
Control Group	51	1.25 ± 0.30	1.41 ± 0.41*	2.11 ± 0.50	2.34 ± 0.56*
t value		0.172	2.107	0.298	2.042
P value		0.864	0.038	0.766	0.044

Note: Compared with the same group before treatment, *$P < 0.05$

3.3. Immune indicators

Before treatment, there was no statistically significant difference in immune indicators between the two groups of patients ($P > 0.05$). After treatment, except for no significant change in CD8+ levels, the levels of CD3+, CD4+, and CD4+/CD8+ in both groups were higher than those before treatment, with the experimental group showing higher levels than the control group ($P < 0.05$). See **Table 3**.

Table 3. Comparison of immune indexes (Mean ± SD)

Group	n	CD3+ (%)		CD4+ (%)		CD8+ (%)		CD4+/CD8+ Ratio	
		Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
Experimental Group	52	55.27 ± 8.56	60.61 ± 6.07*	29.30 ± 3.65	38.63 ± 5.27*	25.05 ± 3.21	26.31 ± 3.33	1.17 ± 0.32	1.46 ± 0.35*
Control Group	51	54.18 ± 8.32	57.37 ± 7.62*	30.31 ± 3.59	34.67 ± 6.23*	26.01 ± 3.09	27.04 ± 3.62	1.17 ± 0.27	1.28 ± 0.17*
t value		0.655	2.389	1.416	3.485	1.546	1.066	0.587	3.336
P value		0.514	0.018	0.160	0.001	0.125	0.289	0.558	0.001

Note: Compared with the same group before treatment, *$P < 0.05$

3.4. Improvement in quality of life

Before treatment, there was no statistically significant difference in the scores of psychological function, living conditions, physical function, and social function between the two groups ($P > 0.05$). After treatment, the scores of psychological function, living conditions, physical function, and social function in both groups were higher than those before treatment, with the experimental group showing higher scores than the control group ($P < 0.05$), as shown in **Table 4**.

Table 4. Improvement of quality of life (Mean ± SD, point)

Group	n	Psychological Functioning		Life Status		Physical Functioning		Social Functioning	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Experimental Group	52	43.25 ± 10.37	58.71 ± 13.17*	40.24 ± 10.82	58.20 ± 15.27*	42.27 ± 13.08	58.18 ± 16.29*	45.38 ± 8.59	57.38 ± 12.60*
Control Group	51	43.31 ± 9.89	50.34 ± 12.22*	41.13 ± 10.85	50.79 ± 10.63*	43.01 ± 13.23	51.34 ± 11.05*	44.93 ± 8.61	50.73 ± 10.48*
t value		0.030	3.342	0.417	2.853	0.285	2.489	0.266	2.909
P value		0.976	0.001	0.678	0.005	0.776	0.014	0.791	0.005

Note: Compared with the same group before treatment, *$P < 0.05$

3.5. Adverse reactions

During the medication process, the experimental group experienced 2 cases of nausea and vomiting and 1 case of bone marrow suppression, with an incidence of adverse reactions of 5.77% (3/52). The control group experienced 1 case of hypertension and 1 case of bone marrow suppression, with an incidence of adverse reactions of 3.92% (2/51). There was no statistically significant difference in the incidence of adverse reactions between the two groups after treatment (x^2=0.001, P=0.982).

4. Discussion

Recurrent high-grade glioma is a common type of malignant brain tumor characterized by high mortality, strong invasiveness, and poor prognosis [13]. Currently, there is no unified treatment standard for recurrent high-grade glioma, with common treatment options including reoperation, radiotherapy, chemotherapy, and targeted therapy. However, there is still a lack of sufficient randomized trial evidence to prove that these treatments can prolong the survival of patients with recurrent high-grade glioma [14]. Therefore, finding effective treatment options is of positive significance for treating recurrent high-grade glioma. BEV, a targeted anti-angiogenic drug, has been recommended by the U.S. Food and Drug Administration as one of the recommended treatments for recurrent high-grade glioma. Previous studies have shown that BEV can effectively prolong the progression-free survival of patients with recurrent glioma by an estimated 3–4 months [15–16]. However, studies on BEV combined with chemotherapy suggest that there are still issues, such as insignificant improvement in the overall response rate (ORR) and a higher risk of adverse reactions [17]. Therefore, developing a BEV combination treatment regimen with higher safety and better efficacy is a question worthy of exploration for clinical scholars.

This study treated 103 patients with recurrent high-grade glioma with LBP combined with BEV. The results

showed that the ORR and disease control rate (DCR) in the experimental group were significantly higher than those in the control group, suggesting that LBP combined with BEV can effectively enhance the anti-tumor effect. *Lycium barbarum* polysaccharide (LBP), a medicinal and edible traditional Chinese medicine, has nutritional and health-promoting functions, including anti-tumor, immunomodulatory, free radical scavenging, and anti-radiation effects [18]. BEV, a targeted anti-angiogenic drug and a type of IgG1 monoclonal antibody, can reduce blood supply and inhibit tumor growth by inhibiting the formation of new blood vessels within the tumor [19]. However, the combined use of drugs has a more significant effect, suggesting that LBP and BEV synergistically exert anti-tumor effects, and their specific mechanisms require further study.

Immunodeficiency is prevalent in patients with recurrent high-grade glioma. T lymphocyte subsets can reflect the body's immune status, with poorer immune function leading to a higher probability of adverse prognosis, which can seriously threaten the patient's quality of life [20]. The expression of CD3+ in T lymphocyte subsets indicates the status of peripheral mature T lymphocytes and reflects cellular immune status, while CD4+ reflects the level of helper T cells. A significant decrease in the CD4+/CD8+ ratio indicates limited immune function [21]. The results of this study confirm that both BEV alone and LBP combined with BEV can improve the suppressed immune function in patients with recurrent high-grade glioma, and further demonstrate that the immunomodulatory effect of LBP combined with BEV is more pronounced. Previous studies on glioma patients have also shown that LBP can inhibit tumor proliferation, similar to the results of this study. Long-term chemotherapy not only reduces patients' immune function but also causes superoxide damage, reducing their antioxidant capacity and increasing the risk of chemotherapy-related adverse reactions to a certain extent [22]. Once activated, the Keap1/Nrf2 signaling pathway can mediate the expression of a series of antioxidant and detoxifying enzymes, protecting cells and tissues [23]. Keap1 and Nrf2, as important regulators of the antioxidant response, can further release peroxidase, glutathione synthetase, and detoxifying enzymes to jointly resist oxidative stress in the body and restore cellular homeostasis [24]. In this study, the levels of Keap1 and Nrf2 in both groups increased after treatment compared to before treatment, and the serum levels of Keap1 and Nrf2 in the experimental group were significantly upregulated, suggesting that the LBP combined with the BEV treatment regimen may exert antioxidant effects by activating the Keap1/Nrf2 signaling pathway and enhancing clinical efficacy. The results of this study also show that LBP combined with BEV treatment can improve the quality of life of patients with recurrent high-grade glioma, and no serious adverse reactions were observed during treatment, suggesting that it can be further promoted clinically with good safety.

5. Conclusion

In summary, LBP combined with BEV has significant clinical efficacy in treating recurrent high-grade glioma, can improve immune function, and enhance quality of life, possibly related to the activation of the Keap1/Nrf2 pathway. However, due to the retrospective nature of this study, the small number of subjects included, and the short observation period, the effects of LBP combined with BEV on recurrent high-grade glioma still require further validation by expanding the sample size and extending the observation period in subsequent studies.

Disclosure statement

The authors declare no conflict of interest.

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