ORIGINAL RESEARCH

Clinical Efficacy of Bevacizumab Combined with Temozolomide in Treating Gliomas

Puxian Li, MD; Aihong Qi, MM; Qiang Li, MM

ABSTRACT

Objective • To examine the clinical efficacy of bevacizumab (BEV) combined with temozolomide (TMZ) as a treatment for patients with recurrent malignant gliomas.

Methods • 50 patients with recurrent malignant gliomas treated at our hospital between January 2019 and January 2022 were enrolled and randomized to the control group and combine group using a random table method, with 25 cases in each group. The control group received TMZ and the combine group received BEV plus TMZ. The disease control rate (DCR), the quality-of-life score before and after treatment, and the median 6-month progression-free survival (PFS) rate as well as adverse reactions were recorded and compared.

Results • There was a significant difference in DCR between the combine group (80%) and the control group (52%) (χ^2 = 5.556, P = .018). In each of the quality-of-life scales, the scores of the combine group were significantly greater than those of the control group after treatment, and the difference was statistically significant (P < .05). In the control group, the median PFS was 16.2 weeks, and the six-month PFS was 19.8%. However, in the combine group, the median PFS was 21.9 weeks, and the six-month PFS was 43.1% (P < .05). Comparing the two groups, the rate of adverse reactions in the control group was significantly higher (44.0% vs 12.0%) (χ^2 = 6.349, P = .012).

Conclusion • BEV plus TMZ is remarkable in the treatment of patients with recurrent malignant gliomas. The combination treatment improves the DCR and PFS of patients and their quality of life, and does not increase adverse reactions, making it a promising approach that deserves widespread promotion and clinical application. (*Altern Ther Health Med.* [E-pub ahead of print.])

Puxian Li, MD, Department of Neurosurgery; Affiliated Hospital of Qingdao Binhai University; Qingdao; China. Qingdao Binhai University; Medical College; Qingdao; China. Department of Neurosurgery; Jinan City People's Hospital; Jinan; China**. Aihong Qi**, MM, Nursing Department; Affiliated Hospital of Qingdao Binhai University; Qingdao; China. **Qiang Li**, MM, Department of Neurosurgery; Jinan City People's Hospital; Jinan; China.

Corresponding author: Aihong Qi, MM
E-mail: shihuan78820051@163.com

INTRODUCTION

Glioma, a type of tumor occurring in the brain and spinal cord, originates from glial cells that support and assist nerve cells.[1,2] Gliomas account for over 40% of all intracranial tumors, with glioblastoma representing approximately 77.5% of gliomas.[3] The incidence of gliomas is highest after the age of 40, and with the aging population, it is gradually increasing among individuals over 60 years. Clinical manifestations of glioma commonly include headaches, nausea and vomiting, seizures, and blurred vision.[4,5] The symptoms may vary depending on the degree of malignancy, with severe cases presenting visual impairment and motor and sensory dysfunction.

Currently, surgical resection is the primary treatment approach for gliomas. However, due to the infiltrative growth, strong invasiveness, unclear tumor boundaries with surrounding normal tissues, and rapid cell division and renewal characteristic of malignant gliomas, complete removal of the lesions through surgery is often challenging. Consequently, residual tumor cells may persist in normal tissues, leading to a poor prognosis and a high risk of recurrence.[6,7]

Traditional Chinese medicine (TCM) has played a significant role in glioma treatment, advocating for the use of methods that warm Yang, activate blood circulation, and replenish Qi to improve the postoperative blood stasis state in patients with malignant glioma. This approach aims to enhance the body's resistance, promote a balanced state of Yin and Yang, and improve overall survival and prognosis. However, due to individual variations in the characteristics and manifestation of the disease, the widespread application of TCM in this context remains challenging.[8]

The studies in this field face several challenges, namely, 1) limited treatment options: gliomas are complex tumors with diverse molecular characteristics and clinical behaviors. The

available treatment options, including surgery and chemotherapy, have limitations in achieving complete tumor eradication and preventing recurrence. This necessitates the exploration of novel treatment approaches. 2) Heterogeneity of gliomas: gliomas exhibit significant heterogeneity at the molecular level, making it challenging to develop standardized treatment strategies. The varying genetic and molecular profiles of gliomas contribute to differences in treatment response and outcomes. Thus, personalized treatment approaches are needed. 3) Blood-brain barrier: the blood-brain barrier presents a significant challenge in treating gliomas. It restricts the penetration of systemic chemotherapy agents into the brain, thus reducing their effectiveness. Overcoming this barrier and improving drug delivery to the tumor site are areas of active research. 4) Integration of traditional medicine: traditional medicine, such as TCM, has been used in glioma treatment. However, integrating TCM into mainstream medicine poses challenges due to the lack of standardized protocols, limited scientific evidence, and potential herb-drug interactions. Exploring the integration of TCM with conventional treatments requires rigorous research. 5) Clinical trial logistics: conducting clinical trials for gliomas is logistically demanding. Glioma patients often require long-term follow-up, specialized imaging assessments, and multidisciplinary management. Recruiting an adequate number of eligible patients and ensuring compliance with treatment protocols over the long term can be challenging. Ethical considerations related to placebo control and potential risks must also be addressed.

Considering these challenges, this study aims to address the gaps in knowledge regarding the combination of bevacizumab (BEV) and temozolomide (TMZ) in glioma treatment. By investigating the clinical effectiveness, quality of life, progression-free survival, and adverse reactions associated with this combination therapy, the study aims to provide valuable insights for improving treatment outcomes and guiding future research in glioma management. Therefore, the present study endeavors to establish an effective treatment modality for recurrent malignant glioma. One potential approach involves the use of BEV, a monoclonal antibody that targets vascular endothelial growth factor and is commonly employed in the treatment of rectal and lung cancers.[9] Another drug, TMZ, is widely used in clinical practice for brain tumor treatment due to its high bioavailability. However, studies have shown that using TMZ alone for the treatment of recurrent malignant gliomas yields unsatisfactory overall response rates.[10] Consequently, there is a lack of comprehensive research on the combination of BEV and TMZ in glioma treatment. Therefore, this study aims to explore the potential benefits of combining these two drugs as a treatment approach for glioma, providing valuable insights for future clinical medication strategies.

DATA AND METHODS

Study design

This study was a prospective randomized controlled trial, with DCR as the main index. After a review of previous literature, the disease control rate (DCR) of BEV treatment was found to be 50%, while the DCR of the combined group was expected to be 85%, and a statistical efficacy (1-β) of 0.8. Single-tail test was adopted, and the minimum sample size was calculated to be 20 cases in each group. A total of 50 patients were enrolled with recurrent malignant gliomas treated at our hospital between January 2019 and January 2022, and randomized to the control group and combine group by random table method, with 25 cases in each group. The control group received only BEV, while TMZ combined with BEV was administered to the combine group. The medical staff informed all patients and their families about the experiment, as well as the procedures and results of the experiment. The study was approved by the Jinan City People's Hospital Ethics Committee (No. 2019-CL2252) after informed consent was signed by the patients.

Inclusion criteria: (1) Patients who were diagnosed with malignant glioma by histopathological examination. (2) Patients with the first recurrence after standard treatment and the presence of intracranial tumor recurrence and measurable lesions were confirmed by magnetic resonance imaging (MRI). (3) Patients who had radiotherapy more than two months before the study. (4) Patients who did not use other targeted drug therapy before treatment. (5) Patients who did not have other underlying diseases.

Exclusion criteria: (1) Patients who were previously treated with BEV or TMZ. (2) Patients with severe intracranial infections. (3) Patients with severe cardiovascular and cerebrovascular diseases.

Methods

The control group received treatment with TMZ (Manufacturer: Orion Corporation, Registered number of approval: H20171091, 100 mg × 5 s), administered at a dose of 200 mg/(m2·times), once a day, for a minimum of one to five days, with a treatment cycle of twenty-eight days, lasting for a total of six months. In the event of adverse reactions, the administration of the drug was immediately discontinued, and the patient was withdrawn from the study.

The combine group, based on the control group received treatment with TMZ. It also received treatment with BEV (Manufacturer: Roche Diagnostics GmbH, Registered number of approval: S20120069, 400 mg). The dose administered was 10 mg/kg via intravenous infusion, with an infusion time of at least 90 minutes, once every fourteen days, for a total of six months. In case of mild adverse reactions such as vomiting, appropriate medications were administered to alleviate the symptoms. If more severe adverse reactions occurred, the administration of the drugs was promptly discontinued, and the patients received appropriate treatment accordingly.

Observation indicators

Clinical effectiveness. The clinical effectiveness of the treatment was evaluated using the Response Evaluation Criteria In Solid Tumours (RECIST).[11] Complete remission (CR) was defined as the complete resolution of intracranial

lesions, confirmed by MRI with no appearance of new lesions for four consecutive weeks. Partial response (PR) was defined as a reduction in the volume of intracranial lesions by more than 50% without the appearance of new lesions for four consecutive weeks. Stable disease (SD) was defined as a decrease in the volume of intracranial lesions by less than 50% without the presence of non-enhancing lesions in the brain for four consecutive weeks. Disease progression (DP) was defined as a significant increase in the volume of unmeasurable intracranial lesions after MRI examination. The disease control rate (DCR) was calculated as the percentage of patients with CR, PR, and SD out of the total number of cases [(CR+PR+SD)/ total number of cases × 100%].

Quality of life. The quality of life of the patients was evaluated using the SF-36 Quality of Life Scale,[12] provided by the National Institutes of Health (NIH). The scale assessed five aspects of quality of life, including physical pain, physiological function, emotional function, mental state, and social function. A higher score on the scale indicated an improved quality of life.

Progression-free survival (PFS). PFS was defined as the duration from the start of treatment until disease progression or death from any cause. The PFS rates were compared between the two groups of patients after six months.

Statistical analysis

Statistical analysis was performed using SPSS 22.0 software. Measurement data were expressed as mean ± standard deviation, and a *t* test was conducted. Count data were presented as percentages, and a chi-square test was performed. The significance level was set at $P < .05$.

RESULTS

Comparison of general information

The control group consisted of 14 males and 11 females, ages ranging from 25 to 76 years, with an average age of (48.31 ± 6.12) years; the mean time from surgery to recurrence was (15.32 ± 4.17) months. In all, there were 10 cases of prefrontal lobe tumors, 10 instances of temporal lobe tumors, two occipital lobe tumors, and three instances of midline tumors. The combine group consisted of 16 males and 9 females, with ages ranging from 23 to 76, and an average age of (47.24 ± 6.08) years; the mean time from surgery to recurrence was (15.47 ± 4.50) months. The location of the tumors is as follows: 10 cases were in the prefrontal cortex, 8 in the temporal cortex, 3 in the occipital cortex, and 4 in the midline. The general data did not differ significantly between the two groups ($P > .05$), as shown in Table 1.

Comparison of clinical treatment effectiveness

In the control group, there were 5 cases of PR, 8 cases of SD, and 12 cases of DP, with a DCR of 52% (13/25). In the combine group, there was 1 case of CR, 13 cases of PR, 6 cases of SD, and 5 cases of DP, with a DCR of 80% (20/25), which was significantly higher than that in the control group (52%) ($\chi^2 = 5.556$, $P = .018$), as shown in Table 2.

Table 1. Comparison of General Information

	Control group	Combine group	χ^2/t	*P* value
Gender (Male/female)	14/11	16/9	0.333	.564
Age (years)	48.31 ± 6.12	47.24 ± 6.08	0.555	.585
surgery to recurrence time (months)	15.32 ± 4.17	15.47 ± 4.50	0.109	.914
Location			0.565	.904
Prefrontal lobe	10	10		
Temporal lobe	10	8		
Occipital lobe	2	3		
Midline	3	4		

Table 2. Comparison of Clinical Treatment Effectiveness Between the Two Groups

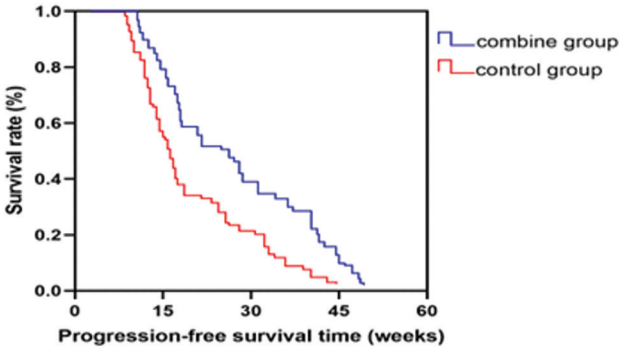
Group	n	CR	PR	SD	DP	Effectiveness rate (%)
Control group	25	0	5	8	12	13 (52%)
Combine group	25	1	13	6	5	20 (80%)
χ^2						5.556
P value						.018

Table 3. Comparison of Quality-of-Life Scores

Groups	n	Body pain		Physiological function,	
		Before	After	Before	After
Control group	25	46.92 ± 6.24	60.88 ± 9.04	44.33 ± 6.15	61.93 ± 7.12
Combine group	25	47.32 ± 6.17	68.91 ± 9.37	45.19 ± 6.22	69.36 ± 9.48
t		0.276	3.791	0.653	4.117
P value		.783	<.001	.561	<.001

Groups	Emotional function		Mental state		Social function	
	Before	After	Before	After	Before	After
Control group	45.17 ± 7.28	63.18 ± 9.76	47.98 ± 6.75	64.41 ± 8.72	47.31 ± 7.36	63.62 ± 8.52
Combine group	46.13 ± 7.54	70.58 ± 10.42	48.24 ± 6.40	71.93 ± 10.67	46.62 ± 7.13	70.57 ± 9.46
t	0.448	3.721	0.362	3.479	0.173	3.657
P value	.472	<.001	.728	<.001	.874	<.001

Figure 1. Comparison of Six-Month PFS Between the Two Groups of Patients



Comparison of quality-of-life scores

In the five scales of body pain, physiological function, emotional function, mental state, and social function, there were no apparent differences between the two groups before treatment. However, after treatment was completed, the scores of each scale of quality of life in the combine group were substantially higher than in the control group ($P < .05$), see Table 3.

Comparison of six-month PFS

In the control group, the median PFS was 16.2 weeks, and the six-month PFS rate was 19.8%. Among the combine group, the median PFS was 21.9 weeks, and the six-month PFS rate was 43.1%. The six-month PFS rate of the combine group was higher than the control group ($P < .05$), as shown in Figure 1.

Table 4. Comparison of Adverse Reactions

Groups	n	Neutropenia	Nausea and vomiting	Hypertension	Overall adverse reactions rate (%)
Control group	25	6	3	2	11 (44.0%)
Combine group	25	1	2	0	3 (12.0%)
χ^2					6.349
P value					.012

Comparison of adverse reactions

In the combine group, there was 1 case of neutropenia and 2 cases of nausea and vomiting, with an overall adverse reactions rate of 12.00% (3/25). While, in the control group, there were 6 cases of neutropenia, 3 cases of nausea and vomiting, and 2 cases of hypertension, with an overall adverse reactions rate of 44.00% (11/25), which was substantially higher than that in the combine group (χ^2 = 6.349, P = .001), see Table 4.

DISCUSSION

Primary central nervous system cancers account for 1.6% of cancers diagnosed annually worldwide, with glioma being the most common histological type. High-grade glioma accounts for 35-45% of primary brain tumors and includes glioblastoma, anaplastic astrocytoma, and anaplastic oligodendroglioma. Due to its aggressive and diffuse invasive nature, recurrence is common and usually causes the tumor to spread rapidly to other brain regions.[12] Currently, there is no effective clinical treatment for recurrent malignant glioma, and re-operation and re-radiotherapy are mainly used. However, unfortunately, this method fails to improve the survival time of patients significantly.[13,14] It is therefore imperative for clinicians to seek out a treatment plan that can improve the lives of patients with recurrent malignant gliomas.

The findings of the present study have important implications for the treatment of recurrent malignant gliomas. The results demonstrate that the combination of BEV and TMZ significantly improves DCR and PFS compared to TMZ alone. Additionally, patients receiving BEV plus TMZ exhibited better quality of life scores after treatment, indicating a positive impact on their overall well-being.

The observed higher DCR in the combine group suggests that the addition of BEV to TMZ may enhance the tumor response and control, potentially leading to improved patient outcomes. This finding is consistent with previous studies that have highlighted the anti-angiogenic properties of BEV, which can inhibit the formation of new blood vessels necessary for tumor growth and progression. By targeting the tumor microenvironment, BEV may contribute to reducing tumor size and improving disease control.

Furthermore, the longer median PFS and higher six-month PFS rate in the combine group indicate that the addition of BEV to TMZ treatment may prolong the time until disease progression, providing patients with a longer period of stable disease. This finding is particularly significant as recurrent malignant gliomas often have a poor prognosis and limited treatment options. The improved PFS observed in the combine group suggests that BEV plus TMZ may offer a promising therapeutic approach for these patients.

Importantly, the combination therapy did not result in an increase in adverse reactions compared to TMZ alone. This suggests that the addition of BEV to the treatment regimen does not compromise patient safety and tolerability. The lower rate of adverse reactions in the combine group may be attributed to the enhanced effectiveness of the treatment, leading to better disease control, and potentially reducing the need for additional interventions or treatments that may carry their risks.

TMZ is a second-generation alkylating agent with broad-spectrum anti-tumor effects and many uses. They are mainly stored in brain tumor tissue and act on different stages of tumor cell division, resulting in the alkylation of tumor cell DNA, which in turn affects tumor growth. Although treatment options for glioblastoma have expanded in the decade since TMZ was approved, long-term survival remains dismal.[15]

Anti-tumor vascular drugs have shown good efficacy in treating other tumors and thus the use of targeted anti-vascular therapies to treat recurrent malignant gliomas may provide a new direction for treating this disease.[16] Humanized vascular endothelial growth factor receptor (VEGFR) monoclonal antibodies bind specifically to vascular endothelial growth factor (VEGF) receptors, inhibit endothelial cell division, enable tumor vascular degeneration, inhibit angiogenesis, and ultimately halt tumor growth.[17] In recent years, many studies have shown that glioma patients are associated with upregulation of VEGF expression.[18] Based on this theory, BEV can be used to treat glioma. BEV is a targeted therapeutic antibody that binds and inhibits VEGF protein in tumor cells.[19] Glioblastoma is characterized by the formation of strong new blood vessels, possibly due to overexpression of VEGF and other pro-angiogenic factors. BEV is typically used to inhibit VEGF and to block tumor angiogenesis, which reduces a tumor's vasculature and blood supply, slowing the growth and spread of tumor cells.[20] Many cytotoxic agents in combination with BEV have shown benefit in clinical trials of recurrent malignant glioma but their efficacy has not been agreed upon. Some studies have pointed out that BEV combined with TMZ can improve and prolong the life of patients.[21]

Despite the preliminary exploration of the clinical efficacy of BEV combined with TMZ in treating recurrent malignant gliomas, the study should acknowledge the limitations. (1) Single-center study: The research was conducted in a single hospital, thus lacking data from multiple centers or regions. This limits the generalizability of the study results, as they may be influenced by regional and ethnic variations. (2) Lack of comparison group selection: The control group received only TMZ treatment, without a comparison group receiving alternative treatment methods. Without comparisons to other treatment regimens, it is challenging to determine the relative superiority and independent effects of BEV combined with TMZ. (3) Short study duration: The observation period of this study was 6 months, which is insufficient to evaluate long-term treatment effects and patient survival rates. The lack of long-term

follow-up data restricts a comprehensive assessment of the long-term efficacy and safety of this treatment approach. (4) Absence of a placebo control group: The study only established a BEV plus TMZ treatment group and a TMZ treatment group, without a placebo control group. Therefore, it is not possible to exclude the influence of natural recovery or psychological factors on treatment outcomes, potentially introducing a placebo effect.

Future research directions in this field can focus on addressing the limitations of the current study and further advancing the understanding of the clinical efficacy of BEV combined with TMZ in treating recurrent malignant gliomas. Some potential future research directions include: A) Large-scale multicenter studies: Conducting studies with a larger sample size and involving multiple centers can enhance the generalizability of the findings and provide a more robust assessment of the treatment's effectiveness. B) Long-term follow-up: Extending the follow-up period beyond 6 months to evaluate the long-term outcomes, including overall survival, progression-free survival, and quality of life, can provide a more comprehensive understanding of the treatment's durability and impact on patient outcomes. C) Comparative effectiveness studies: Comparing the efficacy and safety of BEV plus TMZ with other treatment modalities, such as different chemotherapy regimens or targeted therapies, can help determine the optimal treatment approach for recurrent malignant gliomas. D) Placebo-controlled trials: Conducting randomized controlled trials with placebo control groups can better evaluate the specific effects of BEV plus TMZ while accounting for potential placebo effects and psychological factors.

CONCLUSION

In conclusion, the findings of this study suggest that BEV plus TMZ is a remarkable treatment option for patients with recurrent malignant gliomas. The combination therapy improves disease control, prolongs progression-free survival, enhances quality of life, and does not increase the incidence of adverse reactions. These results support the potential of BEV plus TMZ as a promising therapeutic strategy that warrants further investigation and widespread clinical application.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article.

AUTHOR DISCLOSURE STATEMENT

The authors declare that they have no conflict of interest.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ACKNOWLEDGEMENT

We thank all members involved in this study.

REFERENCES

1. Chua J, Nafziger E, Leung D. Evidence-Based Practice: Temozolomide Beyond Glioblastoma. *Curr Oncol Rep*. 2019;21(4):30. doi:10.1007/s11912-019-0783-5
2. Crotty EE, Leary SES, Geyer JR, et al. Children with DIPG and high-grade glioma treated with temozolomide, irinotecan, and bevacizumab: the Seattle Children's Hospital experience. *J Neurooncol*. 2020;148(3):607-617. doi:10.1007/s11060-020-03558-w
3. Dixit KS, Sachdev S, Amidei C, et al. A multi-center prospective study of re-irradiation with bevacizumab and temozolomide in patients with bevacizumab refractory recurrent high-grade gliomas. *J Neurooncol*. 2021;155(3):297-306. doi:10.1007/s11060-021-03875-8
4. Fisher JP, Adamson DC. Current FDA-Approved Therapies for High-Grade Malignant Gliomas. *Biomedicines*. 2021;9(3):324. doi:10.3390/biomedicines9030324
5. Gerstner ER, Emblem KE, Chang K, et al. Bevacizumab Reduces Permeability and Concurrent Temozolomide Delivery in a Subset of Patients with Recurrent Glioblastoma. *Clin Cancer Res*. 2020;26(1):206-212. doi:10.1158/1078-0432.CCR-19-1739
6. Griveau A, Seano G, Shelton SJ, et al. A Glial Signature and Wnt7 Signaling Regulate Glioma-Vascular Interactions and Tumor Microenvironment. *Cancer Cell*. 2018;33(5):874-889.e7. doi:10.1016/j.ccell.2018.03.020
7. Le Rhun E, Preusser M, Roth P, et al. Molecular targeted therapy of glioblastoma. *Cancer Treat Rev*. 2019;80:101896. doi:10.1016/j.ctrv.2019.101896
8. Wang J, Qi F, Wang Z, et al. A review of traditional Chinese medicine for treatment of glioblastoma. *Biosci Trends*. 2020;13(6):476-487. doi:10.5582/bst.2019.01323
9. Li J, Huang W, Piao M, et al. Efficacy of bevacizumab combined with temozolomide dose-dense regimen on recurrent glioma. *JBUON*. 2021;26(1):145-151.
10. van den Bent MJ, Tesileanu CMS, Wick W, et al. Adjuvant and concurrent temozolomide for 1p/19q non-co-deleted anaplastic glioma (CATNON; EORTC study 26053-22054): second interim analysis of a randomised, open-label, phase 3 study. *Lancet Oncol*. 2021;22(6):813-823. doi:10.1016/S1470-2045(21)00090-5
11. Seymour L, Bogaerts J, Perrone A, et al; RECIST working group. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. [published correction appears in Lancet Oncol. 2019 May;20(5):e242]. *Lancet Oncol*. 2017;18(3):e143-e152. doi:10.1016/S1470-2045(17)30074-8
12. Khatri D, Jaiswal A, Das KK, Pandey S, Bhaisora K, Kumar R. Health-related quality of life after surgery in supratentorial gliomas. *Neurol India*. 2019;67(2):467-475. doi:10.4103/0028-3886.257998
13. McDuff SGR, Dietrich J, Atkins KM, Oh KS, Loeffler JS, Shih HA. Radiation and chemotherapy for high-risk lower grade gliomas: choosing between temozolomide and PCV. *Cancer Med*. 2020;9(1):3-11. doi:10.1002/cam4.2686
14. Tan AC, Ashley DM, López GY, Malinzak M, Friedman HS, Khasraw M. Management of glioblastoma: state of the art and future directions. *CA Cancer J Clin*. 2020;70(4):299-312. doi:10.3322/caac.21613
15. Tanaka S. [Glioblastoma]. *No Shinkei Geka*. 2021;49(3):623-631. doi:10.11477/mf.1436204436
16. van den Bent MJ, Chang SM. Grade II and III Oligodendroglioma and Astrocytoma. *Neurol Clin*. 2018;36(3):467-484. doi:10.1016/j.ncl.2018.04.005
17. van den Bent MJ, Klein M, Smits M, et al. Bevacizumab and temozolomide in patients with first recurrence of WHO grade II and III glioma, without 1p/19q co-deletion (TAVAREC): a randomised controlled phase 2 EORTC trial. *Lancet Oncol*. 2018;19(9):1170-1179. doi:10.1016/S1470-2045(18)30362-0
18. Wang X, Chen D, Qiu J, Li S, Zheng X. The relationship between the degree of brain edema regression and changes in cognitive function in patients with recurrent glioma treated with bevacizumab and temozolomide. *Quant Imaging Med Surg*. 2021;11(11):4556-4568. doi:10.21037/qims-20-1084
19. Weller M, Le Rhun E. How did lomustine become standard of care in recurrent glioblastoma? *Cancer Treat Rev*. 2020;87:102029. doi:10.1016/j.ctrv.2020.102029
20. Tomar MS, Kumar A, Srivastava C, Shrivastava A. Elucidating the mechanisms of Temozolomide resistance in gliomas and the strategies to overcome the resistance. *Biochim Biophys Acta Rev Cancer*. 2021;1876(2):188616. doi:10.1016/j.bbcan.2021.188616
21. Yu Y, Villanueva-Meyer J, Grimmer MR, et al. Temozolomide-induced hypermutation is associated with distant recurrence and reduced survival after high-grade transformation of low-grade IDH-mutant gliomas. *Neuro-oncol*. 2021;23(11):1872-1884. doi:10.1093/neuonc/noab081