JBUON 2021; 26(1): 145-151
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Efficacy of bevacizumab combined with temozolomide dose-dense regimen on recurrent glioma

Jinli Li[1]*, Weiwei Huang[2]*, Meina Piao[1], Zhengcao Liu[3], Shengjun Ji[3], Jing Xue[3], Xin Zhu[3]

[1]Department of Radiation Oncology, the Affiliated Hospital of Soochow University, Suzhou, China. [2]Department of Neurosurgery, China-Japan Union Hospital of Jilin University, Changchun, China. [3]Department of Radiation Oncology, the Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou, China.

*These authors contributed equally to this work.

Summary

Purpose: *To explore the clinical efficacy and safety of bevacizumab combined with temozolomide dose-dense regimen in the treatment of recurrent glioma.*

Methods: *The clinical data of 102 patients with recurrent glioma after surgery, radiotherapy or chemotherapy treated in our hospital from March 2016 to December 2018 were retrospectively analyzed. There were 51 patients undergoing bevacizumab combined with temozolomide treatment (Bevacizumab group), and the remaining 51 patients received temozolomide treatment alone (Control group). The clinical data of all patients were collected, the short-term efficacy, adverse reactions after treatment and quality of life score were compared between the two groups, and the levels of serum immune factors were recorded. The patients were followed up, and the overall survival (OS) rate and progression-free survival (PFS) rate were recorded.*

Results: *All patients underwent bevacizumab treatment for 2-12 cycles, with an average of 6.3 cycles. The objective response rate (ORR) was 47.1% (24/51) and 23.5% (12/51), and the clinical benefit rate (CBR) was 82.4% (42/51) and 60.8% (31/51), respectively, in the Bevacizumab group and Control group. Both ORR and CBR in the Bevacizumab group were superior to those in the Control group. After treatment, the scores of the SF-36 scale significantly rose in the two groups. After treatment, the levels of serum vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), interleukin-2 (IL-2) and IL-6 obviously declined in the two groups compared with those before treatment, while they were obviously lower in the Bevacizumab group than those in the Control group. The median OS was 9.2 months and 8.7 months, and the median PFS was 4.1 months and 3.3 months, respectively, in the Bevacizumab group and the Control group. Log-rank test revealed that the OS had no statistically significant difference between the two groups, but the PFS in the Bevacizumab group was remarkably better than that in the Control group.*

Conclusions: *Bevacizumab combined with temozolomide can significantly improve the clinical efficacy, increase the quality of life of patients, and delay the progression of recurrent glioma, with tolerable adverse reactions.*

Key words: *bevacizumab, temozolomide, dose-dense, glioma, recurrence, efficacy*

Introduction

Glioma is a common malignant intracranial tumor characterized by high malignancy and invasive growth. Surgical resection remains the preferred treatment for glioma. However, due to the invasive growth of glioma, unclear boundaries of lesions and difficulty in complete resection, the risk of tumor recurrence after operation is higher [1,2]. With the application of standard STUPP regimen (surgery combined with radiotherapy and adjuvant temozolomide chemotherapy), the median survival time of

Corresponding author: Xin Zhu, BM. Department of Radiation Oncology, the Affiliated Suzhou Hospital of Nanjing Medical University, No.33 Baita West Rd, Gusu District, Suzhou, Jiangsu, 215008, China.
Tel: +86 013862425468, Email: 59558150@qq.com
Received: 09/10/2020; Accepted: 06/11/2020

patients can reach 14 months. However, malignant glioma has strong invasiveness and difficulty in being completely resected, so it is prone to recurrence, and the median survival is only 3-9 months after recurrence. Moreover, there has been no standard systemic chemotherapy regimen yet for recurrent malignant glioma after STUPP regimen [3,4].

Bevacizumab is a monoclonal antibody targeting vascular endothelial growth factor (VEGF), which can inhibit angiogenesis and continuously control tumors, so it has been widely applied in the treatment of rectal cancer and lung cancer [5-7]. In 2012, it began to be recommended in the National Comprehensive Cancer Network (NCCN) treatment guidelines that bevacizumab alone or combined with chemotherapeutic drugs to be used for recurrent malignant glioma. However, only a few phase II studies showed that bevacizumab combined with chemotherapy can significantly improve the objective response rate (ORR) and 6-month progression-free survival (PFS) rate of patients with recurrent malignant glioma [8,9]. In this study, the clinical efficacy and safety of bevacizumab combined with temozolomide in the treatment of recurrent glioma were retrospectively analyzed, so as to provide a basis for selecting clinical therapeutic regimens for such patients.

Methods

General data

The clinical data of 102 patients with recurrent glioma after surgery, radiotherapy or chemotherapy treated in our hospital from March 2016 to December 2018 were collected. The inclusion criteria were set as follows: 1) patients aged ≥18 years old, 2) those pathologically diagnosed with malignant glioma (WHO grade III or IV), 3) those with recurrent tumor and measurable lesions confirmed by head MRI, 4) those who had recurrence for the first time, 5) those with normal hepatic, renal and coagulation functions, and 6) those with a Karnofsky performance scale score ≥60 points. The exclusion criteria involved: 1) patients who used to undergo bevacizumab treatment, 2) those with severe cardio-cerebrovascular diseases, such as heart failure, myocardial infarction, unstable angina, uncontrollable hypertension, shock, transient ischemic attacks or cerebral hemorrhage, 3) those complicated with blood diseases, endocrine system diseases, autoimmune diseases or bone marrow reserve dysfunction, 4) those with a recent history of thromboembolism, 5) those with coagulation disorders, or 6) those complicated with other primary tumors. According to different treatment methods, the patients were divided into bevacizumab + temozolomide group (Bevacizumab group, n=51) and simple temozolomide group (Control group, n=51). There were 55 males and 47 females aged 53.4±9.6 years old on average. The baseline data had

Table 1. Baseline characteristics of the studied patients

Parameters	*Bevacizumab group (n=51)* *n (%)*	*Control group (n=51)* *n (%)*	*p value*
Age (years), mean±SD	54.2±9.4	52.8±9.8	0.463
Gender (Male/ Female)	29/22	26/25	0.691
Pathological type			0.333
Glioblastoma multiforme	43 (84.3)	40 (78.4)	
Stromal astrocytoma	6 (11.8)	5 (9.8)	
Stromal oligodendroblastoma	2 (3.9)	6 (11.8)	
Tumor location			0.848
Frontal lobe	12 (23.5)	10 (19.6)	
Parietal λobe	6 (11.8)	7 (13.7)	
Temporal lobe	16 (31.4)	19 (37.3)	
Occipital lobe	6 (11.8)	5 (9.8)	
Brain stem	1 (2.0)	2 (3.9)	
Disseminated	10 (19.6)	8 (15.7)	
Pathological grading			0.424
III	31 (60.8)	27 (52.9)	
IV	20 (39.2)	24 (47.1)	
Previous surgery			0.336
Total resection	38 (74.5)	42 (82.4)	
Subtotal resection/Partial resection	13 (25.5)	9 (17.6)	
Time to recurrence (months), mean±SD	9.7±3.1	9.2±3.5	0.447
KPS score (points), mean±SD	68.71±6.79	69.90±6.94	0.384

KPS: Karnofsky performance status

no statistically significant differences between the two groups (Table 1) (p>0.05). This study was approved by the Ethics Committee of the Affiliated Hospital of Soochow University. All patients enrolled signed the informed consent in accordance with the *Declaration of Helsinki*.

Therapeutic regimens

In Control group, the patients took orally temozolomide (50 mg/m^2, trade name: Diqing, Jiangsu Tasly Diyi Pharmaceutical Co., Ltd., batch No.: 0094001, Nanjing, China) alone once a day, 2 weeks taken as 1 cycle until the progression of disease or emergence of intolerable adverse reactions.

In Bevacizumab group, bevacizumab (trade name: Avastin, Shanghai Roche Pharmaceutical Co., Ltd., S20120069, batch No.: 0907601, Shanghai, China) combined with temozolomide was adopted. Temozolomide was used in the same way as that in Control group. Bevacizumab was intravenously infused at 10 mg/kg for more than 90 min. At 30 min before administration, 10 mg of dexamethasone was intravenously injected and 20 mg diphenhydramine was intramuscularly injected to prevent allergic reactions, and electrocardiogram monitoring was performed for the blood pressure, pulse and blood oxygen saturation once every 2 weeks. If the patients had nausea, vomiting and other adverse reactions during treatment, metoclopramide, granisetron and mannitol could be administered according to the clinical symptoms to alleviate the adverse reactions. Bevacizumab was applied until the progression of tumor or emergence of intolerable toxicity, while bevacizumab combined with temozolomide chemotherapy lasted for 12 cycles at most if there was no tumor progression or until the emergence of intolerable toxicity.

Observation indexes

Head MRI (plain scan + enhancement + FLAIR imaging) was performed every 4 weeks, and the therapeutic effect was evaluated according to the Response Assessment in Neuro-Oncology Working Group (RA-NO) [10]. The therapeutic effect was classified into complete response (CR): Enhanced or non-enhanced T1 lesions completely disappear for more than 4 weeks, T2/FLAIR lesions are stable or shrink, there are no new lesions, no hormones are needed, and clinical symptoms are stable or improved. Partial response (PR): The product of the maximum diameter of enhanced T1 lesions is reduced by more than 50%, there are no new lesions, T2/FLAIR lesions are stable or shrink, the dosage of hormones is stable or reduced, and clinical symptoms are stable or improved. Stable disease (SD): The product of the maximum diameter of enhanced T1 lesions is reduced by more than 25% but less than 50%, there are no new lesions, T2/FLAIR lesions are stable or shrink, the dosage of hormones is stable or reduced, and clinical symptoms are stable or improved. Progressive disease (PD): The product of the maximum diameter of enhanced T1 lesions is increased by more than 25%, non-enhanced T2/FLAIR lesions are expanded, there are new lesions, and clinical symptoms become worsened. ORR and clinical benefit rate (CBR) were calculated: ORR = (CR + PR)/total cases × 100%, CBR = (CR + PR + PD)/total cases × 100%.

During treatment, the time and grade of adverse reactions were recorded in detail, and the adverse reactions were classified into grade 0-IV according to Common Terminology Criteria for Adverse Events v3.0. The patient quality of life at 1 month after treatment was scored using the SF-36 scale, including 8 items, and the higher the score, the better the quality of life. At 3 months after treatment, the content of VEGF, epidermal growth factor (EGF), interleukin-2 (IL-2) and IL-6 was determined via enzyme-linked immunosorbent assay (ELISA).

The patients were followed up to record the survival status. Overall survival (OS) and progression-free survival (PFS) were used as the indexes for the patient's survival. OS refers to the duration from the start of treatment to the patient's death or last follow-up, while PFS refers to the duration from the start of treatment to the disease progression or no progression but patient's death.

Statistics

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data were expressed as mean ± standard deviation, and *t*-test was performed for intergroup comparison. X^2 test or Fisher exact probability test were performed for the comparison of clinical data. The short-term efficacy and adverse reactions were compared as the one-way ordered ranked data using Mann-Whitney U test. The survival analysis was conducted using the Kaplan-Meier curves, and log-rank test was performed. P<0.05 suggested statistically significant difference.

Results

Comparison of short-term efficacy

All patients underwent bevacizumab treatment for 2-12 cycles, with an average of 6.3 cycles. In Bevacizumab group, there were 5 (9.8%) cases of CR, 19 (37.3%) cases of PR, 18 (35.3%) cases of SD and 9 (7.4%) cases of PD, and ORR and CBR were 47.1% (24/51) and 82.4% (42/51), respectively. In Control group, there were 0 cases of CR, 12 (23.5%)

Table 2. Clinical effective rates of the two studied groups

	Bevacizumab group (n=51) *n (%)*	*Control group (n=51)* *n (%)*	*p value*
CR	5 (9.8)	0 (0)	
PR	19 (37.3)	12 (23.5)	
SD	18 (35.3)	19 (37.3)	
PD	9 (7.4)	20 (39.2)	
ORR	24 (47.1)	12 (23.5)	0.013
CBR	42 (82.4)	31 (60.8)	0.016

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: objective response rate; CBR: clinical benefit rate

cases of PR, 19 (37.3%) cases of SD and 20 (39.2%) cases of PD, and ORR and CBR were 23.5% (12/51) and 60.8% (31/51), respectively. Both ORR and CBR had statistically significant differences between the two groups, and were superior in Bevacizumab group than in Control group (p=0.013, p=0.016) (Table 2).

Comparison of scores of SF-36 scale between the two groups

After treatment, Bevacizumab group had slightly better scores of physical pain, physical function, emotional function and psychological function, but slightly worse scores of vitality, general health condition, physical role and social function in SF-36 scale than Control group. There were no statistically significant differences (p>0.05) (Table 3).

Comparison of serological indexes between the two groups

Before treatment, there were no statistically significant differences in the levels of serum VEGF, EGF, IL-2 and IL-6 between the two groups (p>0.05). After treatment, the levels of serum VEGF, EGF, IL-2 and IL-6 obviously declined in the two groups compared with those before treatment, showing statistically significant differences (p<0.05), while they were obviously lower in Bevacizumab group than those in Control group (p<0.001, p=0.006, p<0.001, p=0.019) (Table 4).

Comparison of adverse reactions

The main adverse reactions included myelosuppression, nausea and vomiting, diarrhea, fatigue, fever, epistaxis and hypertension, mostly of grade I-II, and they were all alleviated after symp-

Table 3. Comparison of posttreatment SF-36 life quality scores of patients in two different groups

	Bevacizumab group (n=51) mean±SD	*Control group (n=51) mean±SD*	*p value*
Physical pain	71.27±9.48	68.06±9.11	0.084
Physical function	77.43±6.46	75.41±6.85	0.129
Vitality	74.90±6.76	75.98±6.51	0.413
General health condition	78.28±7.63	80.45±6.83	0.133
Physical role	75.24±6.34	76.88±5.79	0.176
Emotional function	69.63±7.92	67.76±8.45	0.252
Social function	76.96±7.75	78.13±7.63	0.444
Psychological function	77.85±11.35	76.11±10.69	0.427

Table 4. Comparison of pretreatment and posttreatment serum tumor markers and inflammatory factors of patients in the two studied groups

	Bevacizumab group (n=51) mean±SD	*Control group (n=51) mean±SD*	*p value*
VEGF (ng/L)			
Pretreatment	283.51±30.92	290.23±36.86	0.321
Posttreatment	179.39±21.57	202.62±30.48	0.001
EGF (ng/L)			
Pretreatment	120.71±16.85	125.56±18.46	0.169
Posttreatment	56.52±8.72	66.76±9.42	0.006
IL-2 (μg/L)			
Pretreatment	5.40±0.92	5.61±0.83	0.229
Posttreatment	2.57±0.47	2.92±0.48	0.001
IL-6 (ng/L)			
Pretreatment	351.17±44.94	346.26±46.80	0.590
Posttreatment	189.34±20.61	201.55±30.35	0.019

VEGF: vascular endothelial growth factor; EGF: epidermal growth factor; IL: interleukin

Table 5. Comparison of adverse reactions of patients in the two studied groups

Parameters	*Bevacizumab group (n=51)* *n (%)*	*Control group (n=51)* *n (%)*	*p value*
Leukopenia	17 (33.3)	15 (29.4)	0.670
Anemia	16 (31.3)	20 (39.2)	0.407
Thrombocytopenia	4 (7.8)	2 (3.9)	0.400
Nausea and vomiting	17 (33.3)	14 (27.5)	0.518
Diarrhea	13 (25.5)	10 (19.6)	0.477
Fatigue	16 (31.3)	13 (25.5)	0.510
Fever	5 (9.8)	3 (5.9)	0.461
Epistaxis	6 (11.8)	4 (7.8)	0.505
Hypertension	11 (21.6)	0 (0)	0.001

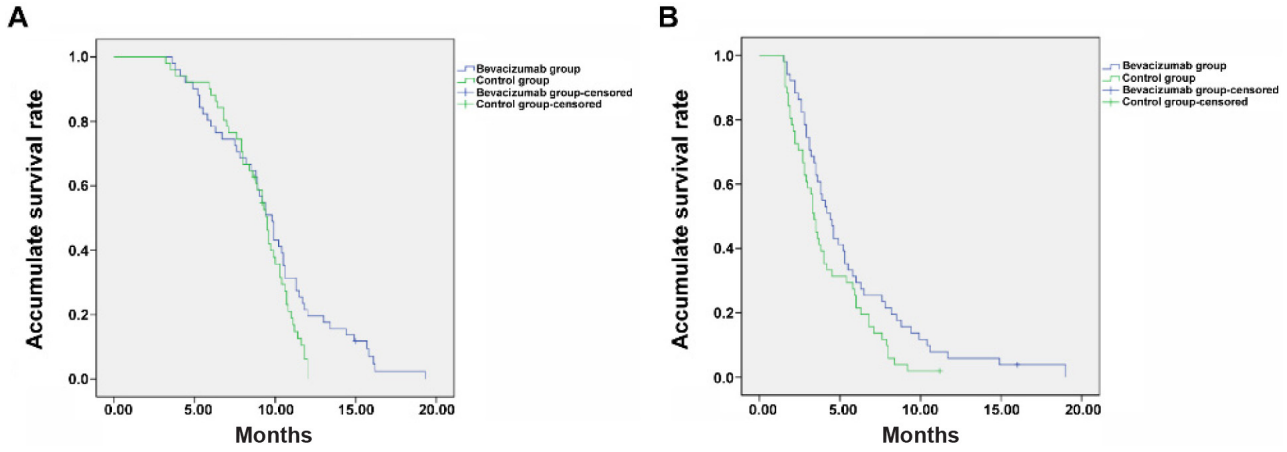

Figure 1. Kaplan-Meier survival curves of recurrent glioma patients. The difference between overall survival rate **(A)** of patients in the Bevacizumab group and Control group had no statistical significance (p=0.061). The progression-free survival rate **(B)** of patients in the Bevacizumab group were significantly higher than that of Control group (p=0.033).

tomatic treatment. Grade III-IV adverse reactions had a lower incidence rate, including 3 cases and 1 case of grade III-IV leukopenia, 2 cases and 1 case of nausea and vomiting, and 2 cases and 0 cases of anemia, respectively, in Bevacizumab group and Control group. The common adverse reaction of bevacizumab was hypertension. The incidence rate of hypertension in Bevacizumab group was markedly higher than that in Control group [11 cases (21.6%) *vs.* 0 cases, p<0.001] (Table 5).

Follow-up results of patient survival

The patients were followed up for 6-36 months. The median OS was 9.2 months and 8.7 months, and the median PFS was 4.1 months and 3.3 months, respectively, in Bevacizumab group and Control group. The 1-year OS was 19.6% (10/51) and 9.8% (5/51), and 1-year PFS was 3.9% (2/51) and 0%, respectively, in the two groups. The survival curves of patients were plotted using the Kaplan-Meier method (Figure 1). The results of log-rank test revealed that the OS had no statistically significant difference between the two groups (p=0.061), but the PFS in Bevacizumab group was remarkably better than that in Control group (p=0.033).

Discussion

Glioma is the most common primary malignant tumor in the brain. In 2005, postoperative concurrent radiochemotherapy combined with 6-cycle adjuvant temozolomide therapy was confirmed as the standard treatment for glioma in STUPP regimen. As a result, the median survival time of glioma patients reaches 14.6 months, but the therapeutic effect is still unsatisfactory. Glioma recurrence is inevitable, after which patients often die soon [11,12]. Currently, recurrent glioma can be treated with reoperation, re-radiotherapy, temozolomide dose-dense regimen, cisplatin, nimustine, *etc.*, which still benefit some patients. The treatment mainly aims to prolong the patient's PFS and OS and improve their quality of life [13,14].

In recent years, molecular targeted drug therapy targeting cell receptors, key genes and regulatory molecules has become a hot spot for cancer treatment, which is expected to improve the prognosis of glioma patients. Angiogenesis is a key driving factor for tumorigenesis, and the interaction between VEGF ligands and VEGF receptors is a key regulator of angiogenesis. High-level VEGF is associated with poor clinical prognosis. Malignant glioma is a tumor overexpressing VEGF. Bevacizumab can inhibit angiogenesis and continuously control tumors through targeting VEGF. In a phase II clinical trial on bevacizumab combined with irinotecan in the treatment of recurrent malignant glioma completed at Duke University's Brain Tumor Center in 2007, the ORR is 63%, and the median PFS and median OS are 23 weeks and 40 weeks, respectively [15]. Since then, the application of bevacizumab in glioma has been reported in a large amount of literature, including the exploration of its optimal dosage, the exploration of combined chemotherapy or other molecular targeted drugs, and the comparison of single or combined chemotherapy [16-18].

The main role of temozolomide, a second-generation alkylating agent, is to alkylate the oxygen atom on position 6 of the guanine in the DNA molecule, and exert a cytotoxic effect through the mismatch repair of the methylated adduct. The main resistance mechanism of temozolomide is that O6-methylguanine-DNA methyl transferase (MGMT) repairs methylated guanine residues. Therefore, patients with MGMT promoter methylation can better benefit from temozolomide radiochemotherapy. In the dose-dense regimen, MGMT is depleted by oral administration of higher-dose temozolomide, thereby increasing the sensitivity of tumor cells to temozolomide. The safety and effectiveness of temozolomide dose-dense regimen have been confirmed in the treatment of recurrent glioma [19,20]. Continuous administration of temozolomide can exhaust the MGMT activity in blood mononuclear cells, which provides a way to overcome temozolomide resistance and rebuild chemosensitivity, reproducing a cytotoxic effect in previously chemotherapy-resistant glioma [21]. Oral administration of low-dose temozolomide daily can inhibit the repair of endothelial cells and possesses a certain anti-angiogenic effect [22]. Moreover, there may be a synergistic effect between temozolomide and bevacizumab.

In the present study, bevacizumab combined with temozolomide dose-dense regimen was applied in the treatment of recurrent glioma, which was well tolerated. The ORR and CBR were 47.1% (24/51) and 82.4% (42/51), respectively, significantly better than those of temozolomide alone (p=0.013, p=0.016). The median OS was 9.2 months and 8.7 months, and the median PFS was 4.1 months and 3.3 months, respectively, in Bevacizumab group and Control group. It can be seen that the PFS in Bevacizumab group was remarkably better than that in Control group (p=0.033). The incidence rate of adverse reactions, except hypertension, was not significantly increased by the combination therapy. After treatment, the SF-36 scale scores of patients were all improved to varying degrees.

During the progression of glioma, highly-expressed VEGF in lesions is an important molecule causing invasive growth of tumor cells. VEGF can act on endothelial cells and promote their proliferation, thus inducing neovascularization. EGF can directly act on tumor cells and promote their proliferation, resulting in lesion growth. Moreover, IL-2 and IL-6 are cytokines able to promote tumor cell proliferation and migration and vascular endothelial cell growth [23,24]. Large amounts of IL-2, IL-6, VEGF and EGF produced locally in lesions can be released into the blood circulation. In this study, it was found that after treatment, the levels of serum VEGF, EGF, IL-2 and IL-6 obviously declined in the two groups compared with those before treatment ($p<0.05$), while they were obviously lower in Bevacizumab group than those in Control group ($p<0.001$, $p=0.006$, $p<0.001$, $p=0.019$).

As a single-center retrospective study, this study had certain limitations. For example, the sample size was not large enough, and the follow-up content was not comprehensive enough. Bevacizumab has a short effective duration and relatively high costs, so the advantageous populations benefitting from bevacizumab should be screened via gene detection in the future, and prospective clinical research should also be conducted to explore the optimal opportunity and optimal dosage of application of bevacizumab and better combined chemotherapy regimens, so as to further improve the efficacy on recurrent glioma.

Conclusions

Bevacizumab combined with temozolomide can significantly improve the clinical efficacy, improve the patient quality of life and delay the progression of recurrent glioma, with tolerable adverse reactions.

Acknowledgement

Minsheng Science and Technology Foundation of Suzhou, Grant/Award Number: SYS2019037.

Conflict of interests

The authors declare no conflict of interests.

References

1. Zhou X, Liao X, Zhang B et al. Recurrence patterns in patients with high-grade glioma following temozolomide-based chemoradiotherapy. Mol Clin Oncol 2016;5:289-94.
2. Lu J, Li D, Zeng Y et al. IDH1 mutation promotes proliferation and migration of glioma cells via EMT induction. JBUON 2019;24:2458-64.
3. Cao Y, Zhang L, Wang Y. Antitumor activity of Cedrelone in temozolomide-resistant human glioma cells is accompanied by mitochondrial mediated apoptosis, inhibition of angiogenesis, cell cycle disruption and modulation of ERK/MAPK signalling pathway. JBUON 2019;24:1204-9.
4. Qi A, Han J, Jia F, Liu C. miR-3175 and miR-134 affect proliferation, invasion and apoptosis of glioma cells through PI3K/AKT signaling pathway. JBUON 2019;24:2465-74.
5. Diaz RJ, Ali S, Qadir MG, De La Fuente MI, Ivan ME, Komotar RJ. The role of bevacizumab in the treatment of glioblastoma. J Neurooncol 2017;133:455-67.
6. Rosen LS, Jacobs IA, Burkes RL. Bevacizumab in Colorectal Cancer: Current Role in Treatment and the Potential of Biosimilars. Target Oncol 2017;12:599-610.
7. Assoun S, Brosseau S, Steinmetz C, Gounant V, Zalcman G. Bevacizumab in advanced lung cancer: state of the art. Fut Oncol 2017;13:2515-35.
8. Kreisl TN, Kim L, Moore K et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. J Clin Oncol 2009;27:740-5.
9. Friedman HS, Prados MD, Wen PY et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol 2009;27:4733-40.
10. Wen PY, Chang SM, Van den Bent MJ, Vogelbaum MA, Macdonald DR, Lee EQ. Response Assessment in Neuro-Oncology Clinical Trials. J Clin Oncol 2017;35:2439-49.
11. Tabouret E, Barrie M, Thiebaut A et al. Limited impact of prognostic factors in patients with recurrent glioblastoma multiforme treated with a bevacizumab-based regimen. J Neurooncol 2013;114:191-8.
12. Schaub C, Schafer N, Mack F et al. The earlier the better? Bevacizumab in the treatment of recurrent MGMT-non-methylated glioblastoma. J Cancer Res Clin Oncol 2016;142:1825-9.
13. Hervey-Jumper SL, Berger MS. Reoperation for recurrent high-grade glioma: a current perspective of the literature. Neurosurgery 2014;75:491-499, 498-499.
14. Dirven L, van den Bent MJ, Bottomley A et al. The impact of bevacizumab on health-related quality of life in patients treated for recurrent glioblastoma: results of the randomised controlled phase 2 BELOB trial. Eur J Cancer 2015;51:1321-30.
15. Vredenburgh JJ, Desjardins A, Herndon JN et al. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. J Clin Oncol 2007;25:4722-9.
16. Weathers SP, Han X, Liu DD et al. A randomized phase II trial of standard dose bevacizumab versus low dose bevacizumab plus lomustine (CCNU) in adults with recurrent glioblastoma. J Neurooncol 2016;129:487-94.
17. Kaloshi G, Brace G, Rroji A et al. Bevacizumab alone at 5 mg/kg in an every-3-week schedule for patients with recurrent glioblastomas: a single center experience. Tumori 2013;99:601-3.
18. Kreisl TN, Kim L, Moore K et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. J Clin Oncol 2009;27:740-5.
19. Wei W, Chen X, Ma X, Wang D, Guo Z. The efficacy and safety of various dose-dense regimens of temozolomide for recurrent high-grade glioma: a systematic review with meta-analysis. J Neurooncol 2015;125:339-49.
20. Omuro A, Chan TA, Abrey LE et al. Phase II trial of continuous low-dose temozolomide for patients with recurrent malignant glioma. Neuro Oncol 2013;15:242-50.
21. Tolcher AW, Gerson SL, Denis L et al. Marked inactivation of O6-alkylguanine-DNA alkyltransferase activity with protracted temozolomide schedules. Br J Cancer 2003;88:1004-11.
22. Neyns B, Tosoni A, Hwu WJ, Reardon DA. Dose-dense temozolomide regimens: antitumor activity, toxicity, and immunomodulatory effects. Cancer 2010;116:2868-77.
23. Wang L, Zhang L, Shen W, Liu Y, Luo Y. High expression of VEGF and PI3K in glioma stem cells provides new criteria for the grading of gliomas. Exp Ther Med 2016;11:571-6.
24. Christofides A, Kosmopoulos M, Piperi C. Pathophysiological mechanisms regulated by cytokines in gliomas. Cytokine 2015;71:377-84.