Anlotinib as Monotherapy or Combination Therapy for Recurrent High-Grade Glioma: A Retrospective Study

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ABSTRACT

BACKGROUND: Anlotinib is a multi-target anti-angiogenic agent. The retrospective study was conducted to evaluate the safety and effectiveness of anlotinib as monotherapy or combination therapy for the treatment of recurrent high-grade gliomas.

METHODS: In this retrospective study, patients with recurrent high-grade glioma (according to the 2021 World Health Organization classification as levels III-IV) at Sichuan Cancer Hospital from June 2019 to June 2022 were included. The patients were divided into an anlotinib-monotherapy group and an anlotinib-combination group, and received oral anlotinib 8 to 12 mg once a day, with 2 weeks on/1 week off. The primary endpoint was progression-free survival (PFS). The Secondary endpoints included overall survival (OS), 6-month PFS rate, objective response rate (ORR), and disease control rate (DCR). Also, adverse events were evaluated using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE version 5.0).

RESULTS: A total of 29 patients (including 20 glioblastomas, 1 diffuse midline glioma, 5 anaplastic astrocytoma, and 3 anaplastic oligodendroglioma) were included in this study. Of these, 34.48% of the patients were treated with anlotinib alone and 65.52% with anlotinib combination therapy. The median follow-up time was 11.6 months (95% confidence interval [CI]: 9.4-15.7). The median PFS was 9.4 months (95% CI: 6.5-12.3), and the 6-month PFS rate was 62.1%. The median OS was 12.7 months (95% CI: 9.7-15.7), and the 12-month OS rate was 48.3%. Evaluation of treatment response was performed according to RANO (response assessment in neuro-oncology, RANO) criteria, including 21 partial response, 6 stable disease, and 2 PFS events. The ORR and DCR were 72.4%, and 93.1%, respectively. Grade III AEs occurred in 2 patients, and the others were less than grade III. The most common AE was thrombocytopenia, with an incidence rate of 31.0%. All AEs were alleviated and controlled by symptomatic treatment. No treatment-related deaths occurred.

CONCLUSION: Anlotinib had a low incidence of AEs and good safety in the treatment of recurrent high-grade glioma. Moreover, it showed good short-term effectiveness and significantly prolonged the PFS of patients, which may become a promising therapeutic option for recurrent high-grade glioma and lay a foundation for further clinical studies.

KEYWORDS: Recurrent glioma, high-grade glioma, molecular targeted therapy, anlotinib

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Introduction

Globally, the annual incidence rate for glioma is estimated to be 6/100 000 per year. Every year, approximately 100 000 people worldwide are diagnosed as having diffuse gliomas.[1] Glioma is a common primary brain tumor that derives from glial cells, accounting for 40% to 50% of central nervous system tumors.[2] Meanwhile, the incidence rate of glioma is about 70% of all primary brain malignant tumors, and it is one of the major brain diseases with high mortality and disability rates.[3] According to the 2016 World Health Organization (WHO) classification of central nervous system tumors, gliomas are

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classified as grades I-IV, including low-grade glioma (LGG, grades I and II) and high-grade glioma (HGG, grades III and IV).[4] The biological characteristics of HGG, such as their invasive growth, abnormal proliferation of vascular tissue, and easy destruction of brain tissue, result in difficult treatment and poor prognosis.[5] The current standard treatment for HGG includes surgery, concurrent radiochemotherapy, adjuvant chemotherapy with temozolomide (TMZ), and Tumor Treating Fields. One of the most common contributing reasons driving HGG recurrence is resistance to therapeutic drugs.[6,7] In addition, drug-resistant glioblastoma multiforme (GBM) is more difficult to treat due to its limited repair mechanisms and anatomical complexities.[8-10] There is no standard second-line chemotherapy regimen for recurrent gliomas after STUPP treatment. How to overcome TMZ resistance and enhance the chemotherapy sensitivity of gliomas remains to be solved.

Previous studies have shown that conventional chemotherapy drugs such as nitrosourea, procarbazine, irinotecan, lomustine, vincristine, and platinum exhibited unsatisfactory effectiveness and obvious drug toxicity in the treatment of recurrent HGG.[11-13] Vascular proliferation is one of the pathological features of HGGs. Vascular endothelial growth factor (VEGF) and VEGF receptors (VEGFRs) are key drivers of tumor-associated neovascularization. Vascular endothelial growth factor, by binding to tyrosine kinase cell surface receptors (VEGFR-1, VEGFR-2, and VEGFR-3), has mitogenic effects on endothelial cells and increases endothelial permeability, which leads to tumor-related edema and stimulates the proliferation, migration, and survival of endothelial cells.[14] Preclinical evidence suggested that VEGF/VEGFR signaling constitutes an autocrine loop that stimulates glioma growth in vivo.[15-17]

Anlotinib is a novel tyrosine kinase inhibitor (TKI) independently developed in China, with the major anti-angiogenesis target of VEGFR-2.[18] It can inhibit downstream signaling pathways by preventing the phosphorylation of VEGFR-2,[19,20] thereby inhibiting angiogenesis. In a retrospective study of anlotinib monotherapy and in combination with TMZ for treating recurrent HGG, the median progression-free survival (PFS) and median overall survival (OS) were 4.5 months and 7.7 months, respectively, indicating the good effectiveness and tolerability of anlotinib in recurrent HGG.[21] As the study was only combined with TMZ chemotherapy and was a small single-center clinical study, more clinical studies are needed to validate the results. Herein, we conducted this study to explore the safety and effectiveness of anlotinib in the treatment of recurrent HGG by analyzing the effectiveness and prognosis of anlotinib as monotherapy or combination therapy.

Methods

Study design and patients

Patients with recurrent HGG (WHO grades III-IV) treated with anlotinib monotherapy or combination therapy in Sichuan Cancer Hospital from June 2019 to June 2022 were included. We retrospectively collected the general data, clinical data, treatment effectiveness, and follow-up time of the patients. The study was approved by the ethics committee institutional review board of Medical Research and New Medical Technology of Sichuan Cancer Hospital (Ethics Approval No. SCCHEC-02-2022-111).

The inclusion criteria were as follows: (1) receiving radiotherapy and chemotherapy after the first diagnosis of HGG; (2) meeting one of the following assessment principles for recurrence: (a) reference to RANO criteria and mRANO criteria, HGG with a clear enhancing lesion in enhanced magnetic resonance imaging (MRI) with a layer thickness of 5 mm, lesion diameter >10 mm, occupying not less than 2 levels, continued treatment and observation for 4 weeks, and then multimodal MRI examination confirmed by 2 associate chief physicians or higher confirmed as disease progression, and (b) pathology or biopsy after reoperation suggesting tumor recurrence; (3) not being managed with other anti-angiogenic agents 3 months prior to recurrence or progression; (4) Karnofsky performance status (KPS) ⩾60; and (5) neutrophil count $\geqslant 1.5 \times 10^9$/L, platelet count $\geqslant 100 \times 10^9$/L, and hemoglobin ⩾90 g/L, with good liver and kidney function. Patients were excluded if they met any of the following criteria: (1) pregnant and lactating women; (2) patients with less than 3 months since the end of the last radiotherapy; (3) patients with previous severe organ function and organic disease; (4) patients with severe mental illness; and (5) patients receiving anlotinib therapy for less than 1 month.

Treatment regimen

All patients received continuous oral anlotinib 8 to 12 mg once a day for 2 weeks as 1 course, followed by 1-week rest. Nineteen patients were treated with anlotinib in combination with other treatments, including 8 with combining with a continuously dose-intensive chemotherapy regimen of TMZ (orally 100 mg/m^2, d1-d7, q2w), 6 with combining with semustine chemotherapy (orally 0.1 g/m^2, d1, q6-8w), 1 with TMZ and semustine chemotherapy, 3 with irinotecan chemotherapy (intravenous infusion of 125 mg/m^2, d1, q2w), and 1 with vemurafenib targeted therapy (orally 960 mg, q12 h). Dose adjustment was made according to the degree of adverse events (AEs) after taking anlotinib until imaging indicates the progression of disease (PD) or severe intolerant side effects developing.

Treatment evaluation

The MRI evaluation was performed every 2 to 3 months or when there were symptoms. Clinical response was assessed according to RANO criteria[22]: complete response (CR), partial response (PR), stable disease (SD), and PD. Objective response rate (ORR) was defined as the proportion of patients who

achieved either PR or CR. Disease control rate (DCR) was defined as the total proportion of patients who achieved CR, PR, and SD. The primary endpoint was PFS (defined as the time from the first dose of anlotinib administered until disease progression or death from any cause or the last day of follow-up). Secondary endpoints were OS (defined as the time from the first dose of anlotinib administered until the date of the most recent follow-up or death from any cause or the last day of follow-up), the 6-month PFS rate, ORR, and DCR. All AEs were monitored and graded according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE 5.0).[23]

Statistical analysis

All statistical analyses were carried out using SPSS 22.0 software. Survival analysis was performed by the Kaplan-Meier method with 95% confidence intervals (CI), and differences in survival probabilities were compared using the log-rank test. Cox regression analysis was used for univariate and multivariate analyses. *P* values $<.05$ were considered statistically significant.

Results

Patient characteristics

A total of 29 patients (14 men, 15 women; median age, 50 years; range, 15-71 years) with recurrent HGG who received an anlotinib-containing treatment regimen were included in this retrospective study, including 20 with glioblastomas, 1 with diffuse midline glioma, 5 with anaplastic astrocytomas, and 3 with anaplastic oligodendroglioma. The baseline characteristics of the patients are described in Table 1. Among these patients, the first pathological diagnosis confirmed 7 patients with WHO grade III HGG and 22 patients with WHO grade IV HGG. All patients were in good general condition at entry, with a Karnofski performance status (KPS) score of 60 to 100. The therapeutic regimens before relapse were collected and statistically analyzed. All patients had received radiotherapy with concurrent chemotherapy with TMZ after the initial diagnosis, of which 4 patients had received concurrent irinotecan. During the maintenance adjuvant chemotherapy, TMZ therapy was continued in 26 patients, combination irinotecan in 5 patients, and vemurafenib therapy in 1 patient. Eleven of the 29 patients had been treated with targeted therapy with bevacizumab during initial treatment, 1 with nimotuzumab, and the remaining 17 patients had not received targeted therapy.

Effectiveness

All 29 patients receiving an anlotinib-containing treatment regimen were evaluable for response. Of these, 10 patients were in the anlotinib monotherapy group and 19 patients were in the combined treatment group. The median follow-up time

Table 1. Patient characteristics at baseline.

CHARACTERISTIC	N=29	
Age/year		Percentage
Median	50	
Range	15-71	
Sex		
Male	14	48.28
Female	15	51.72
Tumor location		
Multifocal/dissemination	14	48.28
Focal	15	51.72
KPS score		
≥80	23	79.31
<80	6	20.69
Histology		
Grade III	7	31.03
Grade IV	22	68.97
Previous operation		
Yes	27	93.10
No	2	6.90
Previous radiotherapy		
Yes	29	100.00
No	0	0.00
Previous anti-angiogenic agents		
Yes	12	41.38
No	17	58.62
Concurrent chemotherapy		
TMZ	29	100.00
Irinotecan	4	13.79
Other	1	3.45
Adjuvant chemotherapy		
TMZ	26	89.66
Irinotecan	5	17.24
Other[a]	1	3.45
MGMT promoter status		
Methylation	12	41.38
Unmethylation	17	58.62
IDH status		
Mutation	6	20.69
Wild type	23	79.31
1p19q codeletion		
Codeletion	2	6.90
Nocodeletion	11	37.93
Unknown	16	55.17

(Continued)

Table 1. (Continued)

CHARACTERISTIC	N = 29	
TERT status		
Mutation	21	72.41
Wild type	8	27.59
Baseline tumor diameters *D*/cm		
Median	4.5	
Range	2.7-8.0	
Study treatment		
Anlotinib	9	31.03
Anlotinib plus chemotherapy	20	68.97

Abbreviations: IDH, isocitrate dehydrogenase; KPS, Karnofsky performance status score; MGMT, O6-methylguanine-DNA methyltransferase; TERT, telomerase reverse transcriptase; TMZ, temozolomide.
[a]Other includes histologies of oligodendroglioma, anaplastic astrocytoma, and diffuse midline glioma.

was 11.6 months (95% CI: 9.4-15.7). The median PFS was 9.4 months (95% CI: 6.5-12.3; Figure 1A), with a 6-month PFS rate of 62.1%. The median OS was 12.7 months (95% CI: 9.7-15.7; Figure 1B), with a 6-month OS rate and 1-year OS rate of 79.3% and 48.3%, respectively.

Among all patients, the best responses to treatment were PR in 21 (72.4%) patients, the treatment effect of one of the patients is shown in Figure 2; SD in 6 (20.7%) patients; PD in 2 (6.9%) patients; and no patient experienced a CR. The ORR and DCR were 72.4% and 93.1%, respectively (Table 2). As of December 3, 2022, 2 patients survived in the monotherapy group, 5 patients survived in combination with TMZ, 2 patients survived in combination with semustine, and 1 patient survived in combination with irinotecan. Thus, 19 of 29 patients treated had died. In addition, 26 patients have reached the study endpoint, while 3 patients have not reached it (Figure 3).

Among 22 patients with WHO grade IV HGG, the median PFS was 6.7 months (95% CI: 3.8-9.6), with a 6-month PFS rate of 54.5%. The median OS was 9.9 months (95% CI: 5.6-14.2), with a 6-month OS rate and 1-year OS rate of 72.7% and 36.4%, respectively (Table 3). The disease remission rate was 65.0%, and the DCR was 90.0%. Of the 7 patients with WHO grade III HGG, the median PFS was 11.4 months (95% CI: 8.0-14.7), with a 6-month PFS rate of 85.7%. The median OS was 15.7 months (95% CI: 12.5-18.9), with a 6-month OS rate and 1-year OS rate of 100% and 85.7%, respectively (Figure 4A and B). The disease remission rate and DCR reached 88.9% and 100%, respectively.

Kaplan-Meier survival analysis showed that the KPS score, histology, and MGMT methylation status were significantly associated with PFS (Table 4). Patients with KPS scores ⩾80 had a significant treatment benefit over patients with KPS scores <80 (11.1 months vs 5.0 months, $P = .012$); patients with WHO grade IV had a significantly higher risk of progression than patients with WHO grade III, with a median PFS of 11.1 months versus 6.7 months ($P = .012$); and patients with

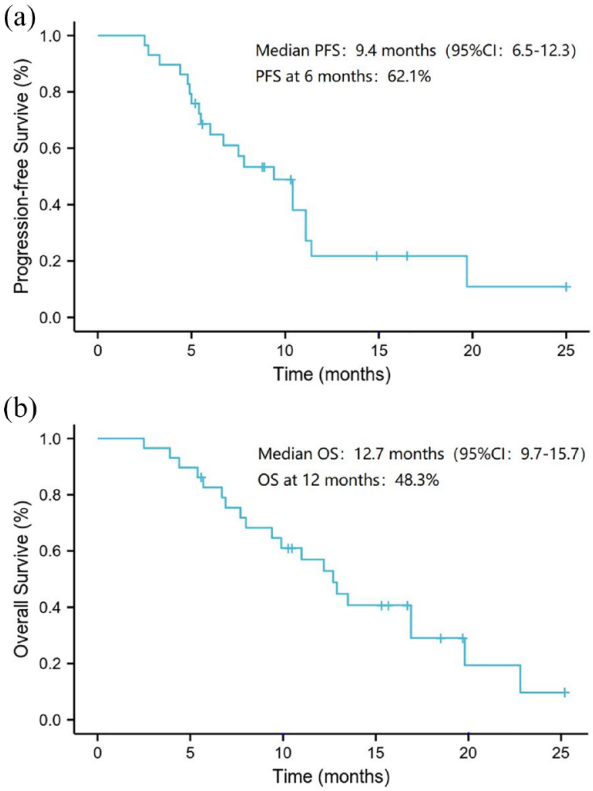

Figure 1. Kaplan-Meier plots of PFS (A) and OS (B) in all patients.
CI indicates confidence interval; OS, overall survival; PFS, progression-free survival.

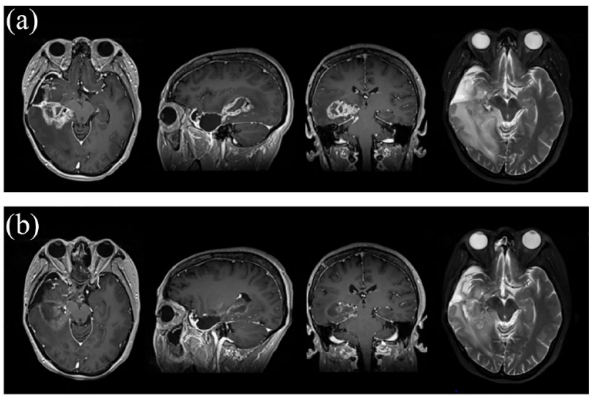

Figure 2. Effect of treatment with anlotinib in one of the patients: (A) MRI image at the time of relapse and (B) MRI image after 1 month of anlotinib treatment.
MRI indicates magnetic resonance imaging.

Table 2. Response assessment of 29 patients.

RESPONSE ASSESSMENT	CR	PR	SD	PD
Grade III (n = 7)	0	6 (85.7%)	1 (14.3%)	0
Grade IV (n = 22)	0	15 (68.2%)	5 (22.7%)	2 (9.1%)
Total (n = 29)	0	21 (72.41%)	6 (20.69%)	2 (6.90%)

Abbreviations: CR, complete response; PD, progression of disease; PR, partial response; SD, standard deviation.

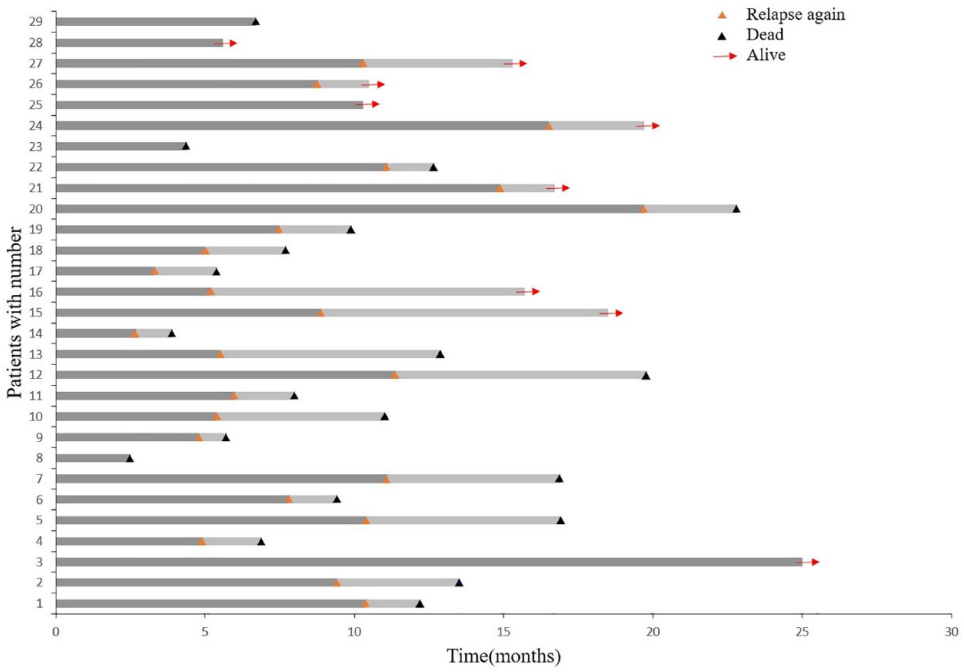

Figure 3. Chart of survival status of 29 patients.

Table 3. Efficacy of anlotinib or anlotinib plus chemotherapy in recurrent high-grade glioma.

	GRADE III (N=9)			GRADE IV (N=20)		
	ANLOTINIB (N=3)	ANLOTINIB PLUS CHEMOTHERAPY (N=4)	TOTAL (N=7)	ANLOTINIB (N=7)	ANLOTINIB PLUS CHEMOTHERAPY (N=15)	TOTAL (N=22)
Median PFS, months	11.1	–	11.4 (8.0-14.7)	5.0 (0-10.0)	6.7 (1.6-11.8)	6.7 (3.8-9.6)
Median OS, months	15.7	–	15.7 (12.5-18.9)	7.7 (2.9-12.5)	12.2 (6.6-17.8)	9.9 (5.6-14.2)
6-mo PFS, No. (%)	2 (66.7)	4 (100)	6 (85.7)	3 (42.9)	9 (60.0)	12 (54.5)
6-mo OS, No. (%)	3 (100)	4 (100)	7 (100)	5 (71.4)	11 (50.0)	16 (72.7)
1-y OS, No. (%)	3 (100)	3 (75.0)	6 (85.7)	1 (14.3)	7 (46.7)	8 (36.4)

Abbreviations: OS, overall survival; PFS, progression-free survival.

MGMT methylation status had a significantly higher median PFS than MGMT non-methylated There was also a significant difference in median PFS in patients (11.4 months vs 6.0 months, $P = .04$); however, these results need to be interpreted with caution as 7 of the 12 MGMT methylated patients were WHO grade IV patients compared with 15 of the 17 MGMT non-methylated patients. (Table 4). Multivariate analysis of baseline KPS score, histology, and MGMT methylation status did not reveal any independent prognostic factors for PFS. Similarly, KPS was found to be an independent prognostic factor in the analysis of OS, with a hazard ratio (HR) of 0.294 (95% CI: 0.118-0.80; $P = .016$; $\geqslant 80$ vs <80).

Safety and tolerability

Treatment-related AEs are listed in Table 5. The most common AEs were thrombocytopenia (31%) and leukopenia (27.6%). Grade I-II AEs occurred in 93.1% of patients, and grade III AEs (thrombocytopenia) occurred in only 2 patients (6.9%) with combination therapy. The incidence of only fatigue, arthrodynia, headache, palpitation, and hoarseness in the monotherapy group was higher than that in the combination group. All AEs were alleviated and controlled by symptomatic treatment, and no treatment-related fatal events by anlotinib occurred in all patients.

Discussion

Recurrent HGG has a poor prognosis, with a median PFS of only 12 weeks and a median OS of less than 6 months.[24,25] To date, there is no established standard of care for patients with recurrent HGG. In this study, the clinical effectiveness and safety of anlotinib monotherapy and anlotinib combined with TMZ, smolustine, irinotecan, or vemulafenib in the treatment of recurrent HGG were investigated. This single-center

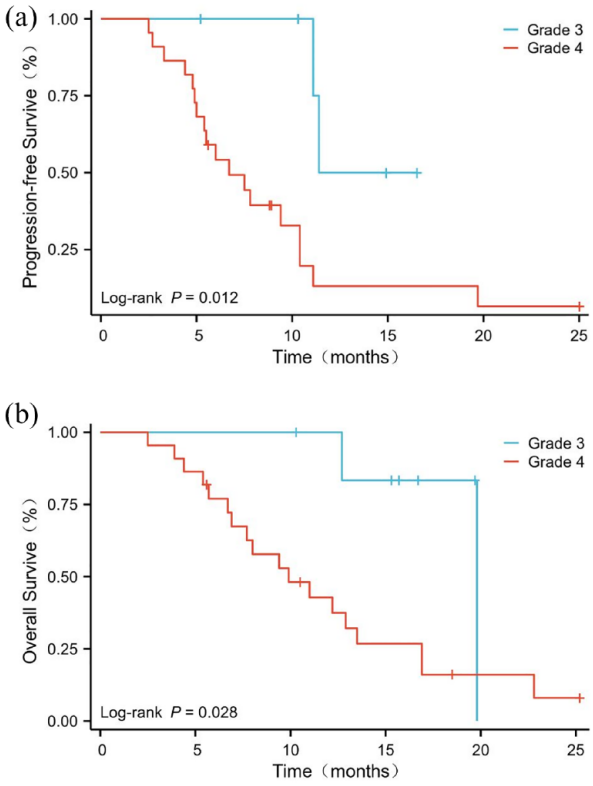

Figure 4. Kaplan-Meier plots of progression-free survival (A) and overall survival (B) for patients with grade III (blue) or grade IV (red) disease.

retrospective experience of 29 patients with recurrent HGG revealed a median PFS of 5.7 months (95% CI: 4.9-9.4) and a median OS of 9.4 months (95% CI: 6.4-12.2). In addition, grade III AEs occurred in only 1 patient and were controlled by symptomatic treatment. To our knowledge, this is the first clinical study for anti-angiogenic small-molecule TKI as monotherapy or combination with multiple typical clinical drugs in patients with recurrent HGG, which fully reflects clinical exploration and practice in the real-world setting. The results also suggested the favorable effectiveness and safety of anlotinib as an anti-angiogenic multi-target small-molecule TKI in the treatment of recurrent HGG.

Anti-epidermal growth factor receptor drugs have been widely used for treating various malignant tumors including GBM.[26] Bevacizumab is a humanized monoclonal antibody that acts on VEGF/VEGFR. Based on the positive results of phase II clinical trials,[27,28] single-dose bevacizumab was approved by the US Food and Drug Administration for the treatment of recurrent glioblastoma. A meta-analysis involving 548 patients with recurrent GBM treated with bevacizumab showed a median OS of 9.3 months and median PFS of 6.1 months, with a 6-month PFS rate of 45% and a 6-month OS rate of 76%, respectively.[29] Besides, the meta-analyses indicated that bevacizumab combined with or without chemotherapy showed a significantly improved PFS and ORR in relapsed GBM, but did not prolong OS. Bevacizumab combined with chemotherapy may lead to a higher incidence of AEs, while the incidence of grade III/IV and any grade of hypertension is higher in patients with bevacizumab monotherapy.[30,31] In this study, the results suggested that the median PFS and median OS of GBM were 6.7 months and 9.4 months, respectively, with the 6-month PFS rate of 55.0% and 6-month OS rate of 70.0%, which were comparable to those in the above-mentioned studies of bevacizumab.

In addition to macromolecular monoclonal antibodies, small-molecule TKIs such as sorafenib, sunitinib, and pazopanib have also been developed to inhibit VEGFRs and their downstream targets.[32] To date, several anti-angiogenic agents[33-42] for recurrent HGG have been reported (Table 6). In general, the median PFS and OS of other small molecule TKIs for recurrent HGG were 1.7-4.2 months and 3.9-10.2 months, respectively. Among these regimens, cediranib in combination with lomustine achieved relatively good median PFS and OS of 4.2 months and 9.4 months respectively, while its 6-month PFS rate of 35% was also the highest, and another study of Cediranib in combination with gefitinib showed the highest objective remission rate of 42.11%. Although the results of this study were retrospective, anlotinib showed more potential PFS and OS than other anti-angiogenic TKIs in the treatment of recurrent HGG, which is worthy of further study.

Anlotinib is a novel oral small-molecule receptor TKI that targets VEGFR, platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), and stem cell factor receptor (c-Kit), with a broad spectrum of inhibitory effects on tumor angiogenesis and growth.[43] It inhibits angiogenesis via blocking the activation of tyrosine kinases induced by their cognate cytokines and their downstream signaling.[44] In vitro studies have revealed that anlotinib occupies the ATP-binding pocket of VEGFR-2 tyrosine kinase and shows high selectivity and inhibitory potency for VEGFR-2 with 20-fold higher inhibitory activity than sunitinib.[18] In addition, the upregulation of FGFR and its ligand FGF can induce tumor angiogenesis and lead to the failure of anti-angiogenic treatment. Notably, it has been reported that anlotinib inhibited stronger phosphorylation of FGFR than sunitinib and sorafenib, which exhibited favorable anti-angiogenic and anti-tumor activities.[44] More importantly, anlotinib can induce autophagy in glioblastoma cells by increasing Beclin-1 and microtubule-associated protein 1 light chain 3B (LC3B) levels. Meanwhile, anlotinib combined with TMZ suppresses glioblastoma growth via the mediation of JAK2/STAT3 signaling pathway, indicating the potential application of anlotinib as a treatment option for glioblastoma.[45]

In this study, thrombocytopenia was the most frequent AE, with an incidence of 31.0%, and grade III thrombocytopenia only occurred in 2 cases with symptomatic recovery after symptomatic treatment. The other AEs observed were all grade <3, which were alleviative and manageable after symptomatic treatment. No treatment-related deaths occurred, indicating favorable tolerance of oral anlotinib. In a phase II study of

Table 4. Results of the univariate analysis.

CHARACTERISTICS	NO. OF PATIENTS	MEDIAN PFS MONTHS (95% CI)	*P* VALUE	HR (95%)
Year				
<50	14	9.4 (4.0-14.8)	0.711	0.99 (0.96-1.02)
⩾50	15	10.4 (4.1-16.7)	–	–
Sex				
Male	14	9.4 (6.5-12.3)	0.414	0.70 (0.29-1.69)
Female	15	11.1 (5.8-16.4)	–	–
Tumor location				
Multifocal/dissemination	14	10.4 (6.3-14.5)	0.321	0.64 (0.26-1.57)
Focal	15	7.8 (2.2-13.4)	–	
KPS score				
⩾80	23	11.1 (9.3-12.9)	0.012	0.29 (0.10-0.81)
<80	6	5.0 (2.2-7.8)	–	–
Histology				
Grade III	7	11.1 (8.0-14.7)	0.012	4.46 (1.02-19.42)
Grade IV	20	6.7 (3.8-9.6)	–	–
Previous operation				
Yes	29	7.8 (2.8-12.8)	0.745	1.28 (0.29-5.66)
No	0	–	–	–
Previous anti-angiogenic agents				
Yes	12	6.0 (3.0-9.0)	0.39	0.67 (0.27-1.68)
No	17	10.4 (8.6-12.2)	–	–
MGMT promoter status				
Methylation	12	11.4 (7.6-15.2)	0.04	2.74 (0.99-7.57)
Unmethylation	17	6.0 (3.2-8.8)	–	–
IDH status				
Wild type	23	7.8 (3.9-11.7)	0.062	5.40 (0.72-40.63)
Mutation	6	–	–	–
TERT status				
Mutation	21	7.8 (4.9-10.7)	0.373	0.63 (0.23-1.77)
Wild type	8	9.4 (3.9-14.9)	–	–
Baseline tumor diameters *D*/cm				
<4.5		7.8 (4.6-11.0)	0.206	0.53 (0.20-1.44)
⩾4.5		11.1 (6.0-16.2)	–	–
Study treatment				
Anlotinib	9	7.8 (4.2-11.4)	0.235	0.58 (0.23-1.46)
Anlotinib plus chemotherapy	20	10.4 (6.6-14.2)	–	

Abbreviations: CI, confidence interval; IDH, isocitrate dehydrogenase; KPS, Karnofsky performance status score; MGMT, O6-methylguanine-DNA methyltransferase; TERT, telomerase reverse transcriptase; PFS, progression-free survival.

Table 5. The most common treatment-related adverse events.

TOXICITY	ANLOTINIB (N = 10)	ANLOTINIB AND OTHER[a] (N = 19)	TOTAL (N = 29)
Thrombocytopenia, No. (%)	2 (20.0)	7 (36.8)	9 (31.0)
Leukopenia, No. (%)	2 (20.0)	6 (31.6)	8 (27.6)
Liver function impairment, No. (%)	1 (10.0)	5 (26.3)	6 (20.7)
Hypertension, No. (%)	3 (30.0)	3 (15.8)	6 (20.7)
Hypertriglyceridemia, No. (%)	1 (10.0)	5 (26.3)	6 (20.7)
Hand-foot reaction, No. (%)	2 (20.0)	4 (21.1)	6 (20.7)
Fatigue, No. (%)	4 (40.0)	1 (3.5)	5 (17.2)
Memory impairment, No. (%)	1 (10.0)	4 (21.1)	5 (17.2)
Renal function impairment, No. (%)	1 (10.0)	3 (15.8)	4 (13.8)
Anemia, No. (%)	1 (10.0)	2 (10.5)	3 (10.4)
Arthrodynia, No. (%)	2 (20.0)	1 (5.3)	3 (10.4)
Headache, No. (%)	3 (30.0)	0	3 (10.4)
Rash, No. (%)	1 (10.0)	2 (10.5)	3 (10.4)
Cerebral hemorrhage, No. (%)	1 (10.0)	2 (10.5)	3 (10.4)
Bleeding gums, No. (%)	0	3 (15.8)	3 (10.4)
Gastrointestinal reaction, No. (%)	0	3 (15.8)	3 (10.4)
Anorexia, No. (%)	0	2 (10.5)	2 (6.9)
Diarrhea, No. (%)	0	2 (10.5)	2 (6.9)
Palpitation, No. (%)	2 (20.0)	0	2 (6.9)
Hoarseness, No. (%)	1 (10.0)	0	1 (3.5)
Memory impairment, No. (%)	0	1 (5.3)	1 (3.5)
Edema, No. (%)	0	1 (5.3)	1 (3.5)
Sleepiness, No. (%)	0	1 (5.3)	1 (3.5)

Abbreviation: TMZ, temozolomide.
[a]Other includes semustine (6), TMZ (8), semustine plus TMZ (1), irinotecan (3), and vemurafenib (1).

bevacizumab monotherapy for relapsed GBM,[27] 46.4% of patients had grade III AEs, among which hypertension (8.3%) and convulsion (6%) were the most common AEs; besides, intracranial hemorrhage (grade I) occurred in 2 patients (2.4%). As can be seen, anlotinib has a significantly lower incidence of grade III AEs and more favorable effects on blood pressure compared with bevacizumab, with comparable bleeding risk. The results of our study showed that the effectiveness of anlotinib in the treatment of recurrent GBM is comparable to that of bevacizumab previously reported, with good tolerance. During the COVID-19 pandemic, patients traveling to the hospital for infusions increase the risk of contracting COVID-19 and increase the time and economic costs. Therefore, oral anlotinib targeted therapy may be one of the available therapeutic options during the epidemic.

At present, anlotinib has been widely used as the posterior-line treatment for non–small cell lung cancer, metastatic renal cell carcinoma, and sarcoma, with encouraging effectiveness and mild side effects.[42] However, studies on anlotinib use for treating recurrent HGG have been rarely reported. In a retrospective study involving 31 patients with recurrent HGG receiving anlotinib monotherapy or combination with TMZ continuous dose-intensive regimen (50 mg/m^2, every day), the results showed that anlotinib was effective and well-tolerated for the treatment of recurrent HGG, with the median PFS of 4.5 months and median OS of 7.7 months.[21] Unfortunately, there were no chemotherapy regimens in combination with irinotecan or semustine as applied in this study design; besides, the results still need to be verified by more clinical studies due to the limitation of single-center clinical studies with small

Table 6. Clinical trials of small-molecule anti-angiogenic drugs were reported for recurrent high-grade glioma.

AUTHOR (REF.)	DRUGS	CASES	HISTOLOGY	COMBINATION DRUG	ORR	MEDIAN PFS	MEDIAN OS	PFS 6 MO
Duerinck et al[33]	Axitinib	22	GBM	–	27.27%	3.0 mo	6.8 mo	34%
Batchelor et al[34]	Cediranib	131	GBM	–	13.74%	3.1 mo	8.0 mo	16%
		129	GBM	Lomustine	16.28%	4.2 mo	9.4 mo	35%
Brown et al[35]	Cediranib	19	GBM	–	26.32%	2.8 mo	5.5 mo	15.80%
		19	GBM	Gefitinib	42.11%	3.6 mo	7.2 mo	15.80%
Chheda et al[36]	Vandetanib	19	GBM	Sirolimus	10.53%	1.9 mo	7.2 mo	15.80%
Hutterer et al[37]	Sunitinib	40	GBM	–	0	2.2 mo	9.2 mo	12.50%
Schiff et al[38]	Sorafenib (no anti-VEGF before)	41	GBM	Temsirolimus	9.76%	2.6 mo	6.3 mo	17.10%
	Sorafenib (prior anti-VEGF before)	41	GBM	Temsirolimus	2.44%	1.9 mo	3.9 mo	9.80%
Sautter et al[39]	Imatinib	32	GBM	–	–	2.1 mo	6.5 mo	–
Lombardi et al[40]	Regorafenib	54	GBM	–	7.41%	2.3 mo	10.2 mo	18%
Lassman et al[41]	Infigratinib	26	HGG	–	3.85%	1.7 mo	6.7 mo	16%
Yao et al[42]	Apatinib	17	HGG	TMZ	23.5%	4.0 mo	9.1mo	–

Abbreviations: GBM, glioblastoma; HGG, high-grade glioma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS6 m, the PFS rate at 6 months; Ref., references; TMZ, temozolomide; VEGF, vascular endothelial growth factor.

samples. In our study, in addition to TMZ, some patients received anlotinib combined with irinotecan or semustine, which further demonstrated the promising prospect of anlotinib monotherapy and combination therapy in recurrent high-grade glioma. However, our study is also limited by a single-center retrospective clinical study with a small sample, and more clinical studies are needed to verify these findings in the future.

Conclusion and Prospect

Anlotinib, as a small-molecule multi-target TKI, is expected to be one of the drug options for patients with recurrent HGG. Anlotinib has a low incidence of ARs and a good safety profile in the treatment of recurrent HGG. It has also shown good near-term effectiveness and significantly prolonged PFS, which may be an effective treatment for recurrent HGG and provide a basis for further clinical studies. Anlotinib in combination with radiotherapy may also further improve the prognosis of patients with recurrent HGG. Future prospective clinical studies with expanded sample sizes may be conducted to obtain more clinical data to validate and guide clinical work.

Author Contributions

Jinyi Lang and Ke Xu designed the study and assisted in the preparation of the manuscript. Jun Yin and Wenya Yin contributed to the analysis and interpretation of our data and wrote the initial draft of the manuscript. All other authors have contributed to the data collection and interpretation and reviewed the manuscript. All authors approved the version of the manuscript finally and agree to be accountable for all aspects of the work.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This retrospective study was approved by the ethics committee institutional review board of Medical Research and New Medical Technology of Sichuan Cancer Hospital (Ethics Approval No. SCCHEC-02-2022-111).

Informed Consent

For this type of study, formal consent is not required.

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394-424. doi:10.3322/caac.21492
2. Dolecek TA, Propp JM, Stroup NE, Kruchko C. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005-2009. *Neuro Oncol*. 2012;14:v1-v49. doi:10.1093/neuonc/nos218
3. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin*. 2016;66:115-132. doi:10.3322/caac.21338

4. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol*. 2016;131:803-820. doi:10.1007/s00401-016-1545-1
5. Helseth R, Helseth E, Johannesen TB, et al. Overall survival, prognostic factors, and repeated surgery in a consecutive series of 516 patients with glioblastoma multiforme. *Acta Neurol Scand*. 2010;122:159-167. doi:10.1111/j.1600-0404.2010.01350.x
6. Messaoudi K, Clavreul A, Lagarce F. Toward an effective strategy in glioblastoma treatment. Part I: resistance mechanisms and strategies to overcome resistance of glioblastoma to temozolomide. *Drug Discov Today*. 2015;20:899-905. doi:10.1016/j.drudis.2015.02.011
7. Fan CH, Liu WL, Cao H, Wen C, Chen L, Jiang G. O6-methylguanine DNA methyltransferase as a promising target for the treatment of temozolomide-resistant gliomas. *Cell Death Dis*. 2013;4:e876. doi:10.1038/cddis.2013.388
8. Furnari FB, Fenton T, Bachoo RM, et al. Malignant astrocytic glioma: genetics, biology, and paths to treatment. *Genes Dev*. 2007;21:2683-2710. doi:10.1101/gad.1596707
9. Stupp R, Hegi ME, Gilbert MR, Chakravarti A. Chemoradiotherapy in malignant glioma: standard of care and future directions. *J Clin Oncol*. 2007;25:4127-4136. doi:10.1200/jco.2007.11.8554
10. Van Meir EG, Hadjipanayis CG, Norden AD, Shu HK, Wen PY, Olson JJ. Exciting new advances in neuro-oncology: the avenue to a cure for malignant glioma. *CA Cancer J Clin*. 2010;60:166-193. doi:10.3322/caac.20069
11. Parasramka S, Talari G, Rosenfeld M, Guo J, Villano JL. Procarbazine, lomustine and vincristine for recurrent high-grade glioma. *Cochrane Database Syst Rev*. 2017;7:CD011773. doi:10.1002/14651858.CD011773.pub2
12. Roci E, Cakani B, Brace G, et al. Platinum-based chemotherapy in recurrent high-grade glioma patients: retrospective study. *Med Arch*. 2014;68:140-143. doi:10.5455/medarh.2014.68.140-143
13. Seystahl K, Wick W, Weller M. Therapeutic options in recurrent glioblastoma-an update. *Crit Rev Oncol Hematol*. 2016;99:389-408. doi:10.1016/j.critrevonc.2016.01.018
14. Puputti M, Tynninen O, Sihto H, et al. Amplification of KIT, PDGFRA, VEGFR2, and EGFR in gliomas. *Mol Cancer Res*. 2006;4:927-934. doi:10.1158/1541-7786.mcr-06-0085
15. Knizetova P, Darling JL, Bartek J. Vascular endothelial growth factor in astroglioma stem cell biology and response to therapy. *J Cell Mol Med*. 2008;12:111-125. doi:10.1111/j.1582-4934.2007.00153.x
16. Lu L, Saha D, Martuza RL, Rabkin SD, Wakimoto H. Single agent efficacy of the VEGFR kinase inhibitor axitinib in preclinical models of glioblastoma. *J Neurooncol*. 2015;121:91-100. doi:10.1007/s11060-014-1612-1
17. Bao S, Wu Q, Sathornsumetee S, et al. Stem cell-like glioma cells promote tumor angiogenesis through vascular endothelial growth factor. *Cancer Res*. 2006;66:7843-7848. doi:10.1158/0008-5472.can-06-1010
18. Xie C, Wan X, Quan H, et al. Preclinical characterization of anlotinib, a highly potent and selective vascular endothelial growth factor receptor-2 inhibitor. *Cancer Sci*. 2018;109:1207-1219. doi:10.1111/cas.13536
19. Bergers G, Benjamin LE. Tumorigenesis and the angiogenic switch. *Nat Rev Cancer*. 2003;3:401-410. doi:10.1038/nrc1093
20. Holmes K, Roberts OL, Thomas AM, Cross MJ. Vascular endothelial growth factor receptor-2: structure, function, intracellular signalling and therapeutic inhibition. *Cell Signal*. 2007;19:2003-2012. doi:10.1016/j.cellsig.2007.05.013
21. Yang Q, Guo C, Lin X, et al. Anlotinib alone or in combination with temozolomide in the treatment of recurrent high-grade glioma: a retrospective analysis. *Front Pharmacol*. 2021;12:804942. doi:10.3389/fphar.2021.804942
22. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol*. 2010;28:1963-1972. doi:10.1200/jco.2009.26.3541
23. Freites-Martinez A, Santana N, Arias-Santiago S, Viera A. Using the common terminology criteria for adverse events (CTCAE—version 5.0) to evaluate the severity of adverse events of anticancer therapies. *Actas Dermosifiliogr (Engl Ed)*. 2021;112:90-92. doi:10.1016/j.ad.2019.05.009
24. Turkowski K, Brandenburg S, Mueller A, et al. VEGF as a modulator of the innate immune response in glioblastoma. *Glia*. 2018;66:161-174. doi:10.1002/glia.23234
25. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol*. 2009;10:459-466. doi:10.1016/S1470-2045(09)70025-7
26. Reardon DA, Turner S, Peters KB, et al. A review of VEGF/VEGFR-targeted therapeutics for recurrent glioblastoma. *J Natl Compr Canc Netw*. 2011;9:414-427. doi:10.6004/jnccn.2011.0038
27. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol*. 2009;27:4733-4740. doi:10.1200/jco.2008.19.8721
28. 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;27:740-745. doi:10.1200/jco.2008.16.3055
29. Wong ET, Gautam S, Malchow C, Lun M, Pan E, Brem S. Bevacizumab for recurrent glioblastoma multiforme: a meta-analysis. *J Natl Compr Canc Netw*. 2011;9:403-407. doi:10.6004/jnccn.2011.0037
30. Chen Z, Xu N, Zhao C, Xue T, Wu X, Wang Z. Bevacizumab combined with chemotherapy vs single-agent therapy in recurrent glioblastoma: evidence from randomized controlled trials. *Cancer Manag Res*. 2018;10:2193-2205. doi:10.2147/cmar.s173323
31. Zhang T, Xin Q, Kang JM. Bevacizumab for recurrent glioblastoma: a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci*. 2021;25:6480-6491. doi:10.26355/eurrev_202111_27092
32. Zirlik K, Duyster J. Anti-angiogenics: current situation and future perspectives. *Oncol Res Treat*. 2018;41:166-171. doi:10.1159/000488087
33. Duerinck J, Du Four S, Vandervorst F, et al. Randomized phase II study of axitinib versus physicians best alternative choice of therapy in patients with recurrent glioblastoma. *J Neurooncol*. 2016;128:147-155. doi:10.1007/s11060-016-2092-2
34. Batchelor TT, Mulholland P, Neyns B, et al. Phase III randomized trial comparing the efficacy of cediranib as monotherapy, and in combination with lomustine, versus lomustine alone in patients with recurrent glioblastoma. *J Clin Oncol*. 2013;31:3212-3218. doi:10.1200/jco.2012.47.2464
35. Brown N, McBain C, Nash S, et al. Multi-center randomized phase II study comparing cediranib plus gefitinib with cediranib plus placebo in subjects with recurrent/progressive glioblastoma. *PLoS ONE*. 2016;11:e0156369. doi:10.1371/journal.pone.0156369
36. Chheda MG, Wen PY, Hochberg FH, et al. Vandetanib plus sirolimus in adults with recurrent glioblastoma: results of a phase I and dose expansion cohort study. *J Neurooncol*. 2015;121:627-634. doi:10.1007/s11060-014-1680-2
37. Hutterer M, Nowosielski M, Haybaeck J, et al. A single-arm phase II Austrian/German multicenter trial on continuous daily sunitinib in primary glioblastoma at first recurrence (SURGE 01-07). *Neuro Oncol*. 2014;16:92-102. doi:10.1093/neuonc/not161
38. Schiff D, Jaeckle KA, Anderson SK, et al. Phase 1/2 trial of temsirolimus and sorafenib in the treatment of patients with recurrent glioblastoma: north central cancer treatment group study/alliance N0572. *Cancer*. 2018;124:1455-1463. doi:10.1002/cncr.31219
39. Sautter L, Hofheinz R, Tuettenberg J, et al. Open-label phase II evaluation of imatinib in primary inoperable or incompletely resected and recurrent glioblastoma. *Oncology*. 2020;98:16-22. doi:10.1159/000502483
40. Lombardi G, Caccese M, Padovan M, et al. Regorafenib in recurrent glioblastoma patients: a large and monocentric real-life study. *Cancers (Basel)*. 2021;13. doi:10.3390/cancers13184731
41. Lassman AB, Sepúlveda-Sánchez JM, Cloughesy TF, et al. Infigratinib in patients with recurrent gliomas and FGFR alterations: a multicenter phase II study. *Clin Cancer Res*. 2022;28:2270-2277. doi:10.1158/1078-0432.CCR-21-2664
42. Yao H, Liu J, Zhang C, et al. Clinical study of apatinib plus temozolomide for the treatment of recurrent high-grade gliomas. *J Clin Neurosci*. 2021;90:82-88. doi:10.1016/j.jocn.2021.05.032
43. Shen G, Zheng F, Ren D, et al. Anlotinib: a novel multi-targeting tyrosine kinase inhibitor in clinical development. *J Hematol Oncol*. 2018;11:120. doi:10.1186/s13045-018-0664-7
44. Lin B, Song X, Yang D, Bai D, Yao Y, Lu N. Anlotinib inhibits angiogenesis via suppressing the activation of VEGFR2, PDGFRbeta and FGFR1. *Gene*. 2018;654:77-86. doi:10.1016/j.gene.2018.02.026
45. Xu P, Wang H, Pan H, Chen J, Deng C. Anlotinib combined with temozolomide suppresses glioblastoma growth via mediation of JAK2/STAT3 signaling pathway. *Cancer Chemother Pharmacol*. 2022;89:183-196. doi:10.1007/s00280-021-04380-5