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Safety and Efficiency of Anlotinib in Patients with Recurrent Grade 4 Glioma: A Single-Center Retrospective Analysis

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Abstract:

Purpose: Anlotinib is a multi-target TKI which has been used in different advanced tumors. However, its efficiency and safety in patients with glioblastoma are still not well discussed. This retrospective study aimed to discover the safety and efficiency of anlotinib in recurrent grade 4 glioma.

Methods: The clinical data of patients with recurrent grade 4 glioma treated with anlotinib in our center were collected and analyzed. The progression-free survival (PFS), overall survival (OS), and OS after recurrence were calculated by Kaplan–Meier method and compared by log-rank test. Sub-group analysis was used to find possible variables that affect survival.

Results: From October 2017 to December 2020, seventeen patients with recurrent grade 4 glioma treated with anlotinib were enrolled. The median age was 50 with 13 males. The median KPS was 70. All patients received standard STUPP mode treatment before recurrence. The median PFS was 7 months [95% confidence interval (CI) 5.3–8.6]. The median OS after first diagnosis was 17 months (95% CI 15.7–18.3). The median OS after recurrence was 10 months (95% CI 7.6–12.4). The objective response rate was 33.33% (5/15), and the disease control rate was 60% (9/15). The existence of target genes was identified as a variable affecting the survival after recurrence. The median OS after recurrence in patients with target genes was 12 months (95% CI 6.9–17.1), whereas for patients without targets, the median OS was 4 months (95% CI 1.9–6.1) and for patients with an unknown status, the median OS was 10 months (95% CI 8.4–11.6) ($P = 0.013$).

Conclusion: For recurrent grade 4 glioma, anlotinib can be considered as a supplement to the standard STUPP treatment, especially for the patient with anlotinib target genes.

Key Words:

Anlotinib, gliomblastoma, recurrent, retrospective analysis

Key Message:

For recurrent grade 4 glioma, anlotinib can be considered as a supplement to the standard STUPP treatment with reliable security and effectiveness

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Glioblastoma (GBM) is the most common primary malignant brain tumor. Although regressive treatment consists of maximum tumor resection under maximal safety, followed by radiotherapy and temozolomide (TMZ) concurrent and adjuvant chemotherapy, the median overall survival (OS) of newly diagnosed GBM is 14.6 months (95% CI 13.2–16.8) and the median progression-free survival (PFS) time is 6.9 months (95% CI 5.8–8.2).[1] CBTRUS reported a 2 years survival rate of 18.5% (95% CI 18.2–18.7) for newly diagnosed GBM in United States from 2001 to 2015.[2] For recurrent GBM (rGBM), there is no standard treatment procedure. The National Comprehensive Cancer Network (NCCN) guideline for CNS tumor recommended clinical trials for rGBM. Bevacizumab is mostly used in rGBM, which is also recommended in NCCN guideline. The combination of lomustine and bevacizumab brings rGBM with a median overall survival (OS) after recurrence of 9.1 months (95% CI 8.1–10.1) and a median PFS of 4.2 months (95% CI 3.7–4.3).[3] Regorafenib is an oral

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angiogenic, stromal, and oncogenic receptor multi-target tyrosine kinase inhibitor (TKI), which is also recommended in NCCN guideline for rGBM. Clinical trial REGOMA indicated that median OS was significantly improved in regorafenib group compared with the lomustine group, with a median OS of 7.4 months (95% CI 5.8–12.0) in regorafenib group and 5.6 months (95% CI 4.7–7.3) in lomustine group.[4]

Anlotinib is an oral small-molecule TKI, which can suppress tumor development and angiogenesis by directly inhibiting multiple targets, including platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR), c-Kit, and fibroblast growth factor receptor (FGFR).[5] Several clinical trials have proved that anlotinib is effective in the treatment of a variety of recurrent tumors, including advanced NSCLC (ALTER0303),[6] advanced soft tissue sarcoma (NCT01878448),[7] advanced hepatocellular carcinoma (ALTER0802),[8] and refractory metastatic colorectal cancer (ALTER0703).[9] In recent years, several cases of recurrent GBM treated with anlotinib have been reported.[10-13] Here, we tried to use anlotinib in the treatment of patients with recurrent grade 4 glioma. Through follow-up, we found that treating recurrent grade 4 glioma with anlotinib alone or combined with other methods can obtain acceptable OS with no serious adverse events.

Methods

This is a retrospective study of recurrent grade 4 glioma (GBM or diffuse midline glioma with H3K27M mutant) patients who were treated with anlotinib and TMZ in Jinling hospital from October 2017 to December 2020. The inclusion criteria included the following: 1) recurrent grade 4 glioma (GBM or diffuse mid-line glioma with H3K27M mutant), which is based on the WHO classification of tumor of the central nervous system (2016 edition and follow-up cIMPACT-NOW updates); 2) age ≥18 years old; 3) previously standard surgery, radiotherapy, and TMZ chemotherapy; 4) treatment with anlotinib after recurrence; 5) at least one measurable lesion; 6) evaluation of recurrence by multi-disciplinary treatment (MDT) composed of neurosurgeons, radiologists, radiation therapists, and pathologists according to the Response Assessment in NeuroOncology (RANO) criteria through clinical symptoms and magnetic resonance imaging (MRI) re-examination; and 7) no other systemic diseases that could not tolerate follow-up treatment. The exclusion criteria were as follows: insufficient follow-up data. Data collected included age, gender, primary pathology, tumor molecular information, KPS at recurrence, treatment after recurrence, cycles of anlotinib treatment, combined therapy, dosage, and therapeutic toxicity.

All tumor specimens were tested for molecular phenotypes at different depths, such as IDH, 1p, 19q, MGMT, TP53, ATRX, EGFR, TERT, and targets of anlotinib, such as PDGFR, FGFR, VEGFR, and c-Kit.

When a progressive lesion is suspected, it is necessary to rule out the possibility of pseudo-progression. Pseudo-progression was excluded by clinical symptoms, resection extent of surgery, time of recurrence, molecular pathology, MRI, perfusion, and spectrum. MDT was performed by neurosurgeons, radiologists, radiation therapists, and pathologists, who would discuss together to decide whether there is recurrence or pseudo-progression.

The dosing of the regimen of all patients received was as follows: 12 mg anlotinib orally once daily on days 1–14. Each cycle was 21 days (2 weeks on and 1 week off). Dose reduction (12 to 10 mg or 8 mg; 10 mg to 8 mg) or interruption for drug-related adverse events (AE) was allowed. Other treatments combined with anlotinib are allowed after recurrence. Each patient received MRI and functional MRI assessment of treatment efficacy every 2 cycles. Follow-up lasted until December 2021. Anlotinib would be stopped in the case of definite tumor progression and intolerable grade 4 drug-related adverse reaction. The study was approved by the ethics committee of Jinling Hospital. Informed consent was obtained from all involved participants. The safety was evaluated throughout the study. AEs were graded according to the NCI Common Terminology Criteria for AEs (CTCAE), version 4.0. The efficacy was estimated by RANO criteria.

Statistical analysis was processed using SPSS version 18.0. Survival curves were created using the Kaplan–Meier method in GraphPad Prism5.0. The log-rank test was used for univariate analysis of OS after recurrence between groups. Statistical significance was defined as $P < 0.05$.

Results

Patients' characteristics

After searching the database of our hospital, 17 cases with recurrent GBM or H3K27M mutant diffuse mid-line glioma treated with anlotinib were recruited to meet the requirements. Table 1 shows demographics and patient baseline characteristics. The median age was 49 years (16–75y) with 13 males. The median KPS before anlotinib treatment was 70 (50–90). All patients received standard glioma treatment including surgery, radiotherapy, and concurrent and adjuvant TMZ chemotherapy before recurrence. Pathological diagnosis of primary glioma includes GBM (n = 15) and diffuse mid-line glioma with H3K27M mutant (n = 2). Eight patients received salvage surgery after recurrence. All tumor specimens were subjected to gene detection. Sixteen patients showed IDH mutation, while one patient had wild-type IDH. All patients did not show 1p/19q co-deletion. Seven patients showed TERT mutation, while 10 patients were wide-type. Five patients showed MGMT promoter methylation, and 12 patients showed unmethylation. The target genes of anlotinib were detected in 12 patients. Target genes were found to be positive in seven cases. Other treatments were combined with anlotinib after recurrence including TMZ (n = 6), radiotherapy (n = 1), TTF (n = 2), and other target therapies (n = 2). Three patients received only one cycle of anlotinib, and then the drug was stopped because of economic reasons instead of tumor progression or drug-related adverse events. These three patients were excluded from the follow-up survival analysis between different groups. The other patients received anlotinib treatment for 11 cycles (n = 2), 9 cycles (n = 1), 6 cycles (n = 3), 3 cycles (n = 2), and 2 cycles (n = 6).

Efficiency

The median PFS of 19 patients in this cohort was 7 months (95% CI 5.3–8.6). The median OS after first diagnosis (overall

Table 1: Baseline demographic, clinical, and molecular characteristics of patients treated with anlotinib

Characteristic	Number of patients
Age, median (range)	49 (16-75)
Male: Female	13:4
KPS, median (range)	70 (50-90)
Prior TMZ/RT	17
Salvage surgery at time of recurrence	8
Tumor location	
frontal lobe	3
temporal lobe	4
parietal lobe	2
occipital lobe	2
insular lobe	3
thalamus	3
Prior pathologic diagnosis	
GBM	15
Diffuse midline glioma, H3K27M-mutant	2
Target gene	
with	7
without	5
unknown	5
IDH mutation	
yes	1
No	16
1p/19q co-deletion	
yes	0
no	17
MGMT promoter methylation status	
methylation	5
unmethylation	12
Treatment after recurrence (instead of anlotinib)	
surgery	7
TMZ	6
Other treatment	5
Dose of anlotinib	
10 mg	6
12 mg	11
Cycles of anlotinib	
≥6 cycles	6
<6 cycles	11

survival) was 17 months (95% CI 15.7–18.3). The median OS after recurrence (recurrent OS) was 10 months (95% CI 7.6–12.4) [Figure 1a-c].

Three patients who received only one cycle of anlotinib were excluded from the efficacy analysis. Fifteen patients with recurrent GBM were evaluated according to the RANO criteria, including five cases of partial response (PR), four cases of stable disease (SD), and six cases of progressing disease (PD). No complete response (CR) was identified. The objective response rate (ORR) was 33.33% (5/15), and the disease control rate (DCR) was 60% (9/16) [Table 2].

In order to better evaluate the therapeutic effect of anlotinib, patients were divided into sub-groups to evaluate the effect of anlotinib on recurrent OS. Three patients who received only one cycle of anlotinib were not included in this analysis. Grouping factors included age, gender, KPS, MGMT promoter methylation status, secondary surgery after recurrence, target genes existed, and anlotinib cycles. Univariate analysis showed that a significant difference was only identified in the group of target genes ($P = 0.01$). The median recurrent OS in patients with target genes was 12 months (95% CI 6.9–17.1), while for patients without targets, the median recurrent OS was 4 months (95% CI 1.9–6.1) and for patients with an unknown status, the median recurrent OS was 10 months (95% CI 8.4–11.6) [Figure 1d]. There is no significant difference between groups of age, gender, KPS, MGMT promoter methylation status, TERT status, secondary surgery, and anlotinib cycles [Table 3].

Adverse events

The adverse events we observed through the whole follow-up period include hypertension (7/17), hand-foot skin reaction (8/17), mouth ulcers (6/17), myelosuppression (10/17), and elevated liver enzymes (6/17). Most of AD were in grade 1–2, which can be adjusted by dose reduction or symptomatic treatment with no interruption of treatment cycles. Grade 3–4 AD can be adjusted through dose reduction, symptomatic treatment, or delayed treatment cycles. No treatment-related death occurred. Dose reductions occurred in five patients [Table 4].

Discussion

Despite the comprehensive treatment of surgical resection combined with radiotherapy and chemotherapy, GBM is still the most difficult malignant tumor to deal with. The majority of patients recurred at about 12 months, and about 85% of patients died in about 2 years. There is no standard treatment for rGBM. Many guidelines give recommendations of comprehensive treatment or clinical trials for rGBM. However, the OS of rGBM was only 6–12 months from different clinical trials.[14-16]

In recent years, NCCN guidelines have recommended the use of bevacizumab and regorafenib in recurrent GBM. Bevacizumab is a humanized monoclonal antibody targeted against VEGF, which is widely used in the treatment of rGBM. Many clinical trials have found that bevacizumab alone or combined with other drugs can prolong PFS, but it has no significant effect on OS. In 2009, Friedman compared bevacizumab alone or in combination with irinotecanb in rGBM. The OS of this phase 2 clinical trial was 9.2 months (95% CI 8.2–10.7) and 8.7 months (95% CI 7.8–10.9) in monotherapy and combination groups, respectively.[15] No significant difference was found. Other phase 2 trials also showed similar results, that is, bevacizumab alone or in combination with chemotherapy (including carboplatin, irinotecan, lomustine) brought no significant difference in OS for rGBM.[16-18] Then randomized phase 3 trial EORTC 26101 enrolled 437 patients with rGBM to receive lomustine plus bevacizumab (288 patients) or lomustine alone (149 patients). The median OS was 9.1 months (95% CI 8.1–10.1) in combination group and 8.6 months (95% CI 7.6–10.4) in monotherapy group. No significant difference of OS was found between two groups. However, combination treatment prolonged PFS compared to lomustine alone: 4.2 months versus 1.5 months (HR = 0.49; 95% CI 0.39–0.61; $P < 0.001$).[3] From these clinical trails, it can be concluded

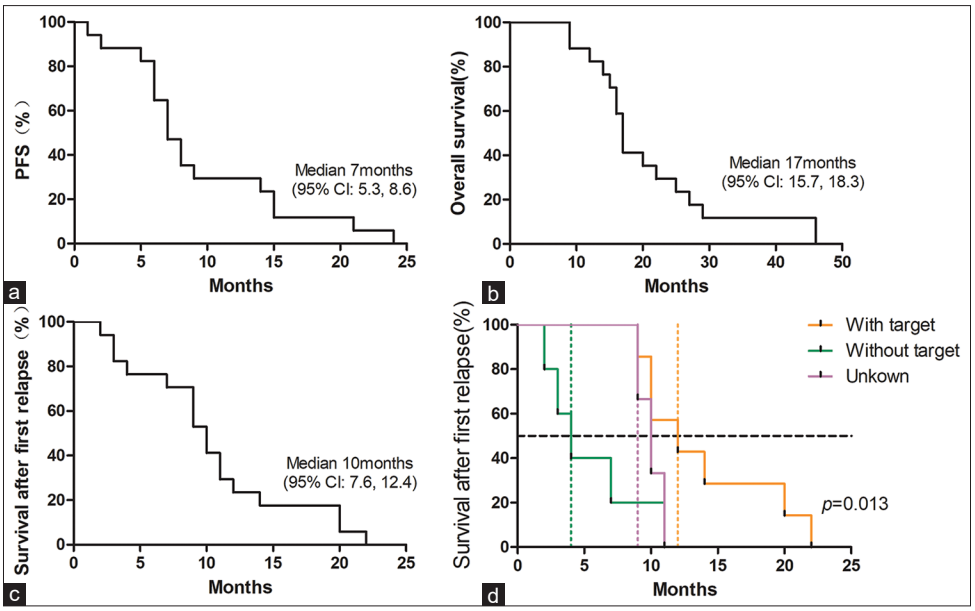

Figure 1: Survival curve of recurrent grade 4 glioma patients treated with anlotinib. (a) PFS, (b) OS, (c) overall survival after first relapse, and (d) overall survival of 16 patients in groups according to anlotinib target. Three patients only received 1 cycle and were excluded from sub-group analysis

Table 2: Summary of tumor response to anlotinib

	Number in 2 months
Complete response (CR)	0
Partial response (PR)	5
Stable disease (SD)	4
Progressive disease (PD)	6
Objective response rate (ORR)	(5/15) 33.33%
Disease control rate (DCR)	(9/15) 60%
Missing data	3

Note. The missing data included 3 patients who received only 1 cycle of anlotinib

that bevacizumab alone or in combination with chemotherapy can prolong the PFS but has no benefit for the OS of rGBM.

Regorafenib is an orally available inhibitor of several kinases, such as VEGFR1–3, TIE2, KIT, RET, RAF1, BRAF, PDGFR, and FGFR. In 2019, Lombardi reported the results of REGOMA, a randomized multi-center open-label phase 2 trial, which aimed to assess the efficacy and safety of regorafenib in the treatment of rGBM. A total of 119 patients were included in this study, including 59 in the regorafinib group and 60 in the lomustine group. OS was significantly improved in the regorafenib group compared with the lomustine group, with a median OS of 7.4 months (95% CI 5.8–12.0) in the regorafenib group and 5.6 months (95% CI 4.7–7.3) in the lomustine group.[4] No statistical difference was found in clinically meaningful worsening for any adverse effect between two groups.[19] A large and monocentric real-life study to investigate clinical outcomes and the safety of regorafenib in rGBM enrolled 54 consecutive patients. The median OS was 10.2 months (95% CI 6.4–13.9), and the 12 month OS rate was 43%. No death was considered to be drug-related.[20] These studies confirmed that regorafenib can effectively prolong the OS of rGBM.

Anlotinib is also a multi-target TKI inhibitor which has similar targets to regorafenib. Anlotinib can effectively inhibit VEGFR, FGFR, PDGFR, c-Kit, and MET.[5,21,22] Two multi-center, double-blinded, placebo-controlled, randomized phase III trials confirmed the efficacy and safety of anlotinib in advanced NSCLC (ALTER 0303)[6] and refractory metastatic colorectal cancer (ALTER0703).[9] Results from ALTER 0303 confirmed that anlotinib prolonged the PFS and OS in advanced NSCLC. The median OS in the anlotinib group was 9.6 months (95% CI 8.2–10.6) compared with 6.3 months (95% CI 5.0–8.1) in the placebo group ($P = 0.002$). For refractory metastatic colorectal cancer, ALTER0703 indicated that median PFS was improved in anlotinib group (4.1 months; 95% CI 3.4–4.5) over placebo group (1.5 months; 95% CI 1.4–1.5) ($P < 0.0001$). However, median OS was similar between two groups (8.6 months; 95% CI 7.8–9.7 vs. 7.2 months; 95% CI 6.2–8.8; $P = 0.870$). Based on the above studies, anlotinib has been approved for the treatment of advanced NSCLC and refractory metastatic colorectal cancer.

For glioma, there are also many case reports of the application of anlotinib in GBM.[10-12] Our recently published case report showed effectiveness of anlotinib in the treatment of diffuse mid-line gliomas with PDGFR mutation.[13] Our previous basic research results from *in vivo* and *in vitro* indicated that anlotinib can suppress proliferation and migration and promote apoptosis and autophagy of glioma through mediation of JAK2/STAT3 signal pathway.[23] Based on these results, we performed salvage treatment of anlotinib in patients with rGBM or diffuse mid-line glioma with H3K27M mutation. Our results indicated that median OS after recurrence was 10 months (95% CI 7.6-12.4) with 33.33% for ORR and 60% for DCR, which is close to the therapeutic effect of bevacizumab and regorafenib in recurrent GBM.[3,4] Most adverse events of anlotinib were in grade 1–2. No treatment-related death occurred.

Four retrospective studies about anlotinib in rGBM from different centers have been published recently [Table 5]. Lei She reported 20 rGBM treated with anlotinib and TMZ in the

Table 3: Univariate analysis of survival after first relapse

Variable (*n*) *	OS after first relapse (month)	95% CI	*P*
Gender			
Male (12)	10	6.6-13.3	0.897
Female (3)	9	8.2-9.8	
Age			
≥60 y (6)	9	6.6-11.4	0.111
<60 y (9)	11	8.1-13.9	
KPS			
>60 (11)	10	7.4-12.6	0.520
≤ 60 (4)	10	3.2-16.9	
MGMT promoter methylation status			
Methylation (5)	12	1.3-22.7	0.140
Unmethylation (10)	10	9.1-11.0	
TERT status			
wide type (10)	10	9.1-10.9	0.966
mutation (4)	7	0-14.8	
unknown (1)	11		
Salvage surgery at time of recurrence			
yes (6)	10	8.4-11.6	0.491
no (9)	8	3.1-14.8	
Target gene			
with target (7)	12	6.9-17.1	0. 013
without target (5)	4	1.9-6.1	
unknown (3)	10	8.4-11.6	
Cycles			
≥6 cycles (6)	11	7.4-14.6	0.234
<6 cycles (9)	10	9.2-10.8	

Note. * 3 patients treated only 1 cycles was excluded from analysis

Table 4: Adverse event

Adverse event	Grade 1-2 *n* (%)	Grade 3-4 *n* (%)	Total *n* (%)
Hypertension	6 (35.3)	2 (11.8)	8 (47.1)
Hand-foot skin reaction	7 (41.2)	2 (11.8)	9 (52.9)
Mouth ulcers	3 (17.6)	3 (17.6)	6 (35.3)
Myelosuppression	6 (35.3)	2 (11.8)	8 (47.1)
Increase in liver enzymes	4 (23.5)	2 (11.8)	6 (35.3)

dose dense mode.[24] The 1-year OS rate was 47.7%. The 6-month PFS rate was 55%. The median PFS and median OS of these 20 patients were 6.1 months and 11.9 months, respectively (95% CI = 4.9–7.3). The ORR was 70% (14/20), and the DCR was 95% (19/20). Qunying Yang *et al* reported 31 recurrent high-grade glioma (21 of grade 4 and 10 of grade 3) treated with anlotinib alone or combined with TMZ.[25] The median PFS was 4.5 months and the median OS was 7.7 months for the whole cohort. The 6 months PFS rate was 43.5% and the 12 months OS rate was 26.7% for the whole cohort. For 21 grade 4 patients, the 6 months PFS rate and 12 months OS rate were 40.2 and 27.9%, respectively. The ORR for grade 4 glioma patient was 33.3%. Sub-group analysis demonstrated that patients with a KPS score ≥60 had a significant PFS and OS benefit from treatment than those with a KPS score <60, which is also confirmed through multi-variate analysis [HR was 0.22 for PFS (95% CI: 0.079–0.634; $P = 0.005$) and 0.29 for OS (95% CI: 0.11–0.77; $P = 0.013$; ≥60 vs. <60)]. Multi-focal or disseminated disease and previous anti-angiogenesis treatment with bevacizumab slightly increased risk of recurrence, but no statistical significance was identified. However, diffusion lesion increased risk of death. MGMT promoter status and IDH status did not affect the prognosis of patients treated with anlotinib. Yun Guan *et al*.[26] reported five patients with rGBM treated with anlotinib and hypo-fractionated stereotactic radiotherapy (HSRT). The median number of cycles of anlotinib was 21. The ORR was 100%. Three patients achieved PR (60%), and two achieved CR (40%). Fangcheng Shen *et al*.[27] reported 26 patients with newly diagnosed or recurrent high-grade glioma treated with anlotinib alone or combined with TMZ. The median KPS score was 80 (60–90). The DCR after oral anlotinib was 96.2% (25/26), and the ORR was 73.1% (19/26). The median OS (calculated from the surgical diagnosis) was 25.6 months (2.7–101.6 months). The median PFS was 8.9 months (0.8–15.1 months), and the PFS rate at 6 months was 72.5% [Figure 1a]. The median OS was 12 months (1.6–24.4 months), and the OS rate at 12 months was 42.6%. In the multi-variate analysis of the PFS, patients with higher KPS scores (above 80) had a median PFS of 9.9 months ($P = 0.02$). The gender, age, IDH mutation, MGMT methylation, whether anlotinib was combined with chemoradiotherapy, and whether there was maintenance treatment had no effect on the PFS.

Our results were familiar with the previous two single-center retrospective studies. In our cohort, sub-group analysis also indicated that age, gender, MGMT promoter status, and TERT status have no effect on recurrent OS after anlotinib treatment, which is similar with previous two studies. Also, we verified that re-surgery after recurrence and anlotinib treatment cycle has no effect on recurrent OS. Most of our patients are IDH wild-type (16/17), so the IDH status was not analyzed here. However, for the first time to our knowledge, the presence of anlotinib target genes was proved to be a factor to improve recurrent OS of rGBM patients treated with anlotinib; the median recurrent OS in patients with target genes was 12 months; for patients without targets, it was 4 months; and for patients with an unknown status, it was 10 months ($P = 0.013$). This result indicated that molecular analysis should be performed in rGBM for more effective screening of targeted therapeutic drugs.

In conclusion, anlotinib has similar therapeutic effects to bevacizumab and regorafenib in the treatment of rGBM. The presence of anlotinib-related target genes may suggest that such patients are more sensitive to anlotinb treatment. For recurrent GBM, anlotinib can be considered as a treatment option. Multi-center, double-blind, randomized controlled phase 3 clinical trials should be carried out as soon as possible to further verify the therapeutic effect of anlotinib in glioblastoma.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the

Table 5: Literature review of anotlinib treatment in glioma (excluding case reports)

	Patient characteristics	Treatment	Efficiency	Safety
QY Yang *et al*.[25]	31 patients with recurrent high-grade gliomas (21 of grade 4 and 10 of grade 3). M: F=19:12. Median age 42Y. Median KPS 60 (40-80). MGMT methylation 12 (38.7%), IDH mutation 9 (29.0%).	17 cases of anlotinib alone and 14 cases combination with TMZ. The initial dose of anlotinib was 12 mg OD for 10 patients and 10 mg OD for 21 patients. The median duration of follow-up was 15.9m. The median duration of treatment was 4 cycles	For all patients, median PFS was 4.5m (95% CI 3.6-5.4) and median OS was 7.7m (95% CI 4.6-10.8). ORR and DCR were 41.9 and 77.4%. For 21 patients with grade 4 disease, median PFS was 4.5m (95% CI 3.1-5.8) and median OS was 6.2m (95% CI 4.3-8.2). ORR and DCR were 33.3 and 71.4%. For 10 patients with grade 3 disease, median PFS was 4.6m (95% CI 1.6-7.6) and median OS was 8.1m (95% CI 5.0-11.3). ORR and DCR were 60 and 90%. Multivariate analysis indicated KPS was prognostic factor for PFS, while KPS and lesion diffusion were prognostic factors for OS.	All treatment-related AD were grade 1-2. No treatment-related discontinuation of anlotinib occurred.
L She *et al*.[24]	20 patients with rGBM. Median age 52Y. M: F=10:10. Median KPS 80 (60-90). MGMT methylation 8 (40%), IDH mutation 2 (10%).	Anlotinib (12 mg OD, 2 weeks on and 1 week off, repeated every 3 weeks) combined with TMZ (100 mg/m^2 daily on a 28-day cycle, orally for 7 days on with 7 days off).	The median PFS and median OS of all patients were 6.1 months and 11.9 months, respectively (95% CI 4.9–7.3). The median PFS and median OS of patients with IDH1 wild type were 6.1 (95% CI 4.9–7.3) months and 11.9 (95% CI 5.7–18.1) months, respectively. The ORR was 70% (14/20), and the DCR was 95% (19/20).	The doses of two patients were reduced from 12 to 10 mg because of grade 3 AD, and one patient stopped taking because of cerebral infarction and seizure. No treatment-related deaths.
Y Guan *et al*.[26]	5 rGBM patients. M: F=3:2. Median age 51 years (range 43–60 years). KPS 70-90. MGMT methylation 5 (100%) and IDH mutation 0.	anlotinib (12 mg OD, 2 weeks on and 1 week off, repeated every 3 weeks) combined with HSRT (25.0 Gy in 5 fractions).	ORR 100%. PR 3 (60%) and CR 2 (40%). 1and 2 years OS rates were 100% and 80%, and PFS rates were 60% and 40%.	Grade 2 hand-foot syndrome was observed in two patients. No treatment-related deaths.
FC Shen *et al*.[27]	26 newly diagnosed or recurrent high-grade gliomas. M: F=18:8. Median age 50y (27-74). Median KPS 80 (60-90). MGMT methylation9 (34.6%). IDH mutation 4 (15.4%).	anlotinib 12 mg OD, 2 weeks on and 1 week off, repeated every 3 weeks. 15 patients took anlotinib together with concurrent chemoradiotherapy. 11 patients took anlotinib after the completion of concurrent chemoradiotherapy.	DCR was 96.2% (25/26), and ORR was 73.1% (19/26). Median PFS after oral anlotinib was 8.9 months (0.8–15.1), and the PFS at 6 months was 72.5%. Median OS after oral anlotinib was 12 months (1.6–24.4), and the OS at 12 months was 42.6%.	Except for one patient presenting with grade 3 hypertension (who had a previous history of hypertension), all the treatment-related adverse effects were at grade 1–2.

Institutional Research Ethics Committee of Jinling hospital. Informed consent was obtained from all individual participants included in the study.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Qiang Wang, Wuting Wei, Xiangjun Ji, Kangjian Sun and Chiyuan Ma. The first draft of the manuscript was written by Qiang Wang and Hao Pan. Jianrui Li, Jing Li and Nan Wu participate in the diagnosis and treatment of patients as a member of MDT. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Headings

1. Anlotinib has similar therapeutic effects to bevacizumab and regorafenib in the treatment of rGBM.
2. The patients with target genes for anlotinib would obtain longer survival than those without target genes.

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Conflicts of interest

There are no conflicts of interest.

References

1. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, *et al*. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-96.
2. Ostrom QT, Cioffi G, Gittleman H *et al*. CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2012-2016. Neuro Oncol 2019;21(Suppl 5):v1-100.
3. Wick W, Gorlia T, Bendszus M, Taphoorn M, Sahm F, Harting I, *et al*. Lomustine and bevacizumab in progressive glioblastoma. N Engl J Med 2017;377:1954-63.
4. Lombardi G, De Salvo GL, Brandes AA, Eoli M, Rudà R, Faedi M, *et al*. Regorafenib compared with lomustine in patients with relapsed

glioblastoma (REGOMA): A multicentre, open-label, randomised, controlled, phase 2 trial. Lancet Oncol 2019;20:110-19.

5. 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.
6. Han B, Li K, Wang Q, Zhang L, Shi J, Wang Z, *et al*. Effect of anlotinib as a third-line or further treatment on overall survival of patients with advanced non-small cell lung cancer: The ALTER 0303 phase 3 randomized clinical trial. Jama Oncol 2018;4:1569-75.
7. Chi Y, Fang Z, Hong X, Yao Y, Sun P, Wang G, *et al*. Safety and efficacy of anlotinib, a multikinase angiogenesis inhibitor, in patients with refractory metastatic soft-tissue sarcoma. Clin Cancer Res 2018;24:5233-8.
8. Sun Y, Zhou A, Zhang W, Jiang Z, Chen B, Zhao J, *et al*. Anlotinib in the treatment of advanced hepatocellular carcinoma: An open-label phase II study (ALTER-0802 study). Hepatol Int 2021;15:621-9.
9. Chi Y, Shu Y, Ba Y, Bai Y, Qin B, Wang X, *et al*. Anlotinib monotherapy for refractory metastatic colorectal cancer: A double-blinded, placebo-controlled, randomized phase III trial (ALTER0703). Oncologist 2021;26:e1693-703.
10. Lv Y, Zhang J, Liu F, Song M, Hou Y, Liang N. Targeted therapy with anlotinib for patient with recurrent glioblastoma: A case report and literature review. Medicine (Baltimore) 2019;98:e15749. doi: 10.1097/MD.0000000000015749.
11. Li C, Li W, Dai S, Sharma A, Sharma HS, Wu Y. Targeted therapy with anlotinib for a leptomeningeal spread recurrent glioblastoma patient. Prog Brain Res 2021;265:407-14.
12. Wang Y, Liang D, Chen J, Chen H, Fan R, Gao Y, *et al*. Targeted therapy with anlotinib for a patient with an oncogenic FGFR3-TACC3 fusion and recurrent glioblastoma. Oncologist 2021;26:173-7.
13. Wang Q, Niu W, Pan H. Targeted therapy with anlotinib for a H3K27M mutation diffuse middle glioma patient with PDGFR-alpha mutation: A case report. Acta Neurochir (Wien) 2021;26:173-7. doi: 10.1002/onco. 13530.
14. Kreisl TN, Smith P, Sul J, Salgado C, Iwamoto FM, Shih JH, *et al*. Continuous daily sunitinib for recurrent glioblastoma. J Neurooncol 2013;111:41-8.
15. Friedman HS, Prados MD, Wen PY, Mikkelsen T, Schiff D, Abrey LE, *et al*. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol 2009;27:4733-40.
16. Taal W, Oosterkamp HM, Walenkamp AM, Dubbink HJ, Beerepoot LV, Hanse MC, *et al*. Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): A randomised controlled phase 2 trial. Lancet Oncol 2014;15:943-53.
17. Field KM, Simes J, Nowak AK, Cher L, Wheeler H, Hovey EJ, *et al*. Randomized phase 2 study of carboplatin and bevacizumab in recurrent glioblastoma. Neuro Oncol 2015;17:1504-13.
18. Reardon DA, Desjardins A, Peters KB, Gururangan S, Sampson JH, McLendon RE, *et al*. Phase II study of carboplatin, irinotecan, and bevacizumab for bevacizumab naive, recurrent glioblastoma. J Neurooncol 2012;107:155-64.
19. Lombardi G, Del BP, Brandes AA, Eoli M, Rudà R, Ibrahim T, *et al*. Patient-reported outcomes in a phase II randomised study of regorafenib compared with lomustine in patients with relapsed glioblastoma (the REGOMA trial). Eur J Cancer 2021;155:179-90.
20. Lombardi G, Caccese M, Padovan M, Cerretti G, Pintacuda G, Manara R, *et al*. Regorafenib in recurrent glioblastoma patients: A large and monocentric real-life study. Cancers (Basel) 2021;13:4731. doi: 10.3390/cancers13184731.
21. Wang G, Sun M, Jiang Y, Zhang T, Sun W, Wang H, *et al*. Anlotinib, a novel small molecular tyrosine kinase inhibitor, suppresses growth and metastasis via dual blockade of VEGFR2 and MET in osteosarcoma. Int J Cancer 2019;145:979-93.
22. Xie C, Wan X, Quan H, Zheng M, Fu L, Li Y, *et al*. Preclinical characterization of anlotinib, a highly potent and selective vascular endothelial growth factor receptor-2 inhibitor. Cancer Sci 2018;109:1207-19.
23. 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;89:183-96.
24. She L, Su L, Shen L, Liu C. Retrospective study of the safety and efficacy of anlotinib combined with dose-dense temozolomide in patients with recurrent glioblastoma. Front Oncol 2021;11:687564. doi: 10.3389/fonc. 2021.687564.
25. Yang Q, Guo C, Lin X, Luo L, He Z, Lin F, *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.
26. Guan Y, Li J, Gong X, Zhu H, Li C, Mei G, *et al*. Safety and efficacy of hypofractionated stereotactic radiotherapy with anlotinib targeted therapy for glioblastoma at the first recurrence: A preliminary report. Brain Sci 2022;12:471. doi: 10.3390/brainsci12040471.
27. Shen F, Li J, Liu F, Sun N, Qiu X, Ding W, *et al*. The efficacy and adverse effects of anlotinib in the treatment of high-grade glioma: A retrospective analysis. Front Oncol 2023;13:1095362. doi: 10.3389/fonc. 2023.1095362.