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Efficacy of Anlotinib in Treating Progressive Glioblastoma: Insights From a Single-Center Study

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Background: Glioblastoma (GBM) is the most common and aggressive malignant tumor in the central nervous system, with limited therapeutic options and poor prognosis. Anlotinib, a novel multi-targeted tyrosine kinase inhibitor, has shown promise in treating various malignancies. This study systematically analyzed the treatment outcomes of 10 typical patients with progressive GBM in our institution who were treated with anlotinib.

Material/Methods: Ten progressive GBM patients treated with anlotinib between 2020 and 2022 were included. Tumor progression was assessed using modified Response Assessment in Neuro-Oncology (mRANO) criteria. Disease progression was evaluated via conventional MRI and physical examinations. Patient condition was measured using the Karnofsky performance status (KPS) scale and the European Organization for Research and Treatment Core Quality of Life Questionnaire (EORTC QLQ-C30). Median progression-free survival (PFS) and overall survival (OS) were calculated from anlotinib initiation. Adverse effects were graded using CTCAE 5.0.

Results: According to the mRANO criteria, 3 patients had a complete response, 3 had a partial response, 1 had stable disease, and 3 had progressive disease, resulting in a 70% disease control rate and a 60% objective response rate. Median PFS was 5.42 months, and median OS was 6.30 months. KPS scores significantly improved after treatment ($P<0.05$), and QLQ-C30 scores were higher in 11 of 15 items ($P<0.05$). No grade 3 or 4 adverse events were observed.

Conclusions: Through small-sample real-world research, anlotinib, either as monotherapy or in combination with temozolomide, demonstrated promising therapeutic effects in patients with progressive GBM, suggesting its potential as a targeted treatment option.

Keywords: Glioblastoma • Therapeutics

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Introduction

Glioblastoma (GBM) is the most prevalent tumor in the central nervous system [1]. Due to its high malignancy, patients with GBM experience lower progression-free survival (PFS), overall survival (OS), and 5-year survival rates [2,3]. At present, newly diagnosed GBM is treated with maximal safe resection, postoperative concomitant chemoradiation, and adjuvant chemotherapy using temozolomide (TMZ) [4,5]. Due to its malignancy, GBM progresses despite standard therapy [2]. This aggressive progression typically includes postoperative residual tumor cell invasion and migration, aberrant tumor vascularization, an immunosuppressive tumor microenvironment, genetic alterations, and treatment resistance, clinically reflected by symptom deterioration and evident radiological progression (eg, new or enlarging lesions on contrast-enhanced MRI). However, there are no treatment guidelines for progressive GBM [6]. Despite attempts by neurosurgeons to utilize various therapeutic measures such as second surgeries, radiotherapy and chemotherapy, patients with progressive GBM have a poor prognosis [7].

Glioma is characterized by several clinically significant molecular biomarkers, including but not limited to isocitrate dehydrogenase status, O-6-methylguanine-DNA methyltransferase, epidermal growth factor receptor (EGFR) copy number variation and mutation status, as well as 1p-19q co-deletion [8,9]. These diverse molecular biomarkers are closely associated with treatment modalities and patient prognosis [9]. Recently, targeted therapy for these markers and individualized treatment strategies tailored to specific patients have been gradually implemented in the management of glioma, particularly GBM [5,10]. However, when regards to target therapy for newly diagnosed GBM, only bevacizumab has progressed to phase III trials, and the research outcomes have not been ideal [11,12]. For recurrent glioblastoma (rGBM), bevacizumab may offer limited improvements in patients' quality of life and PFS, but it does not appear to extend OS [13-15].

Anti-angiogenic therapy now plays a vital role in targeting the multifaceted mechanisms of glioma progression. Anlotinib, a novel oral molecular multi-target tyrosine kinase inhibitor (TKI), exerts its inhibitory effect by targeting vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptors (PDGFR), and stem cell factor receptor c-Kit [16,17]. As a newly developed molecular targeted therapy, anlotinib can suppress tumor angiogenesis and growth. For pharmacokinetics, anlotinib exhibits favorable bioavailability and membrane permeability, as well as notable blood–brain barrier permeability [17,18]. Given these advantages, anlotinib holds broader prospects in clinical application. Currently, anlotinib has been increasingly applied, expanding from treatment of refractory non-small cell lung cancer and small cell lung cancer to other malignant tumors such as medullary thyroid cancer and soft tissue sarcoma [19-21]. Beyond its use in these malignancies, the evidence on anlotinib in the treatment of GBM has progressed from case reports to clinical trials [22-25]. Due to its multi-target inhibition feature, we believe that this drug could exert a deeper antineoplastic effect on GBM.

This study aims to further investigate the clinical efficacy and safety profile of anlotinib in an expanded cohort of progressive glioblastoma patients. We conducted retrospective analysis of 10 progressive GBM patients and assessed the clinical outcomes after anlotinib was used.

Material and Methods

Patient Inclusion

We retrospectively included and analyzed 10 patients with progressive GBM in Tianjin Medical University General Hospital from March 2020 to December 2022. The patient inclusion criteria were: 1) age >18 years; 2) diagnosed as having GBM by integrated pathology and molecular biomarkers, including the latest WHO guidance; 3) previous first-line treatment measures with Stupp protocol; 4) tumor progression verified by neurosurgeons and radiologists using mRANO criteria [26]; 5) normal bone marrow, liver, and kidney function; 6) treatment with anlotinib after tumor progression; and 7) complete neuroimaging. Exclusion criteria were: 1) presence of other malignant tumors; 2) severe cardiovascular and cerebrovascular diseases; and 3) absence of clinical data. Additionally, we meticulously collected clinical data on all patients, including sex, age, surgical procedures, duration of anlotinib use, additional treatment measures, and toxicity. During the treatment process, we performed neuroimaging examinations every 2 months, and hemograms were performed monthly to assess clinical status of each patient. Neuroimaging follow-up was performed primarily with non-contrast and contrast-enhanced MRI, while blood tests included basic assessments of red blood cells, white blood cells, platelets, and key liver and kidney function tests. Postoperative glioma progression was primarily defined by new intracranial MRI contrast-enhancing lesions or progressive clinical worsening, assessed jointly by neurosurgeons and neuroradiologists.

Treatment Process

All enrolled patients initially received the standard Stupp protocol. Upon confirmation of tumor progression, treatment was switched to a regimen consisting of anlotinib (12 mg once daily, administered orally in 3-week cycles: 2 weeks on, 1 week off) and TMZ (150-200 mg/m^2 once daily, given on a 7-days-on/7-days-off schedule within a 28-day cycle). Treatment continued

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until the occurrence of second progression, grade III-IV toxicity, or death, in accordance with the standard Stupp criteria [4,27]. The dosage of anlotinib could be adjusted as appropriate (8-12 mg) according to adverse effects.

Efficacy and Adverse Effects Evaluation

We evaluated treatment efficacy according to the mRANO criteria. For patients who maintain a stable condition, we conducted neuroimaging using magnetic resonance imaging (MRI) and systematic physical assessment every 2 chemotherapy cycles (2 months). For patients with new clinical symptoms presentation, we promptly conducted physical examinations and neuroimaging to assess their status. Based on clinical data and mRANO criteria, we systematically evaluated disease status and classified them as complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD) [28]. Based on the above data and definitions, we calculated the overall response rate (ORR) and disease control rate (DCR). In accordance with the National Cancer Institute-Common Terminology Criteria Adverse Events (CTCAE, version 5.0), we systematically evaluated the adverse effects of each patient. In addition, the general condition of every patient was assessed using the European Organization for Research and Treatment core quality of life questionnaire (EORTC QLQ-C30, version 3.0) [29]. Lastly, we established the definitions of OS and PFS following the administration of anlotinib. The primary endpoints for assessing patient survival were 6-month PFS and 1-year OS.

Statistical Analysis

The survival data of this cohort were analyzed after anlotinib use. Statistical analysis of KPS and QLQ-C30 was conducted using SPSS (version 26.0) with a 2-tailed *t* test. Because of the small sample size, no multivariate analysis was conducted.

Ethics Approval

This study was authorized by the Ethics Committee of Tianjin Medical University General Hospital (approval no. IRB2023-wz-163). Informed consent has been obtained from all patients, and strict confidentiality measures have been implemented to protect patient data.

Results

Patient Characteristics

From March 2020 to December 2022, a total of 10 patients diagnosed with progressive GBM were enrolled (6 males and 4 females). Their mean age was 58 years, ranging from 41 to 70 years.

The mean preoperative KPS score was 70 (40-90), while the mean corresponding score for tumor progression was 50 (20-80). Although the histopathology of this cohort covered astrocytoma, anaplastic astrocytoma, pleomorphic xanthoastrocytoma, and GBM, GBM was diagnosed in all patients after the integration of molecular identification. Most patients underwent tumor resection (8 of 10), with 2 undergoing stereotactic biopsy (2 of 10) due to the deep tumor location. In addition, more patients had at least 1 negative prognostic factor, including unmethylated MGMT promoter, IDH wild type, and EGFR mutation. Patient clinical characteristics and detailed treatment information are presented in **Tables 1 and 2**.

Treatment Process and Clinical Outcome

All patients in this cohort received anlotinib, and all except 1 were also treated with TMZ at the same time. The 1 exception discontinued TMZ due to hyperemesis induced by the drug. At the statistical endpoint, 7 patients had died and 3 were alive, with no censoring. The dosage of anlotinib administered was 12 mg/QD for 8 out of 10 patients and 8 mg/QD for the remaining 2. Each patient was followed up until 31 December 2022. According to mRANO criteria, there were 3 cases of CR, 3 cases of PR, 1 case of SD, and 3 cases of PD. Furthermore, the DCR was 70% and the ORR was 60%. Survival analysis showed the median PFS was 5.42 months (range 0.80-27.40 months) and the median OS was 6.30 months (range 4.17-27.40 months). **Figure 1** illustrates the patient outcomes, ranging from anlotinib treatment to tumor progression or death.

To estimate the physical status during treatment, we conducted an analysis of KPS and QLQ-C30 scores. Firstly, a line chart was systematically presented for KPS scores at 4 different time points (preoperative, postoperative, tumor progression and anlotinib use) using GraphPad (version 9.4.0) (**Figure 2**). A 2-tailed paired *t* test revealed a significant difference between tumor progression and anlotinib use conditions ($P<0.05$). The results of the analysis suggested that there are benefits to using KPS scores. Secondly, QLQ-C30 scores in tumor progression and anlotinib use were analyzed and are presented in **Table 3**. The analysis showed statistically significant differences between tumor progression and anlotinib use across most items of the questionnaire.

Adverse Effects

Some patients experienced treatment-related adverse effects, but no severe toxic events (CTCAE °III-IV) occurred. Adverse effects were observed in the hematological, gastrointestinal, cardiovascular, and mucocutaneous systems. The most frequent adverse effect was decrease in white blood cells (8 out of 10, 80%), as well as elevations in AST and ALT levels (2 out of 10, 20%), increased GGT (2 out of 10, 20%), and hypertension (3 of 10 patients, 30%). There were no adverse effects over CTCAE 3.

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Table 1. Characteristics of enrolled patients.

Patient No.	Age	Sex	Dose	PFS (months)	OS (months)	Present condition	Operation type
1	46	Male	12 mg	27.40	27.50	Live	Resection
2	66	Female	12 mg	0.80	4.17	Died	Resection
3	69	Male	12 mg	4.23	5.83	Died	Resection
4	58	Male	8 mg	10.80	10.83	Died	Resection
5	41	Female	12 mg	3.60	4.60	Died	Resection
6	42	Male	12 mg	3.70	6.07	Died	Resection
7	69	Male	12 mg	5.73	6.53	Died	Resection
8	58	Female	8 mg	7.33	7.50	Live	Biopsy
9	61	Male	12 mg	7.23	7.30	Live	Biopsy
10	70	Female	12 mg	5.10	5.10	Died	Resection

No. – number, PFS – progression-free survival; OS – overall survival.

Table 2. Clinical characteristics of enrolled patients.

Patient No.	MGMT methylated	1p/19q co-deletion	IDH1/IDH2	CDKN2A/B deletion	EGFR Co-deletion	Other treatment
1	No	No/yes	Wild type	Yes/yes	Yes	None
2	Yes	No/no	Wild type	No/no	No	None
3	No	No/no	Wild type	No/no	No	None
4	Yes	No/no	Wild type	Yes/yes	Yes	Enzastaurin
5	Yes	No/no	Wild type	Yes/yes	Yes	TTF
6	No	No/no	Wild type	No/no	No	Bevacizumab
7	Yes	No/no	Wild type	Yes/yes	Yes	None
8	No	No/no	Wild type	Yes/yes	No	None
9	Yes	No/no	Wild type	Yes/no	Yes	None
10	No	No/no	Wild type	Yes/yes	No	TTF

MGMT methylated – MGMT O-6-methylguanine-DNA methyltransferase; 1p/19q co-deletion – co-deletion of chromosomal arms 1p and 19q; IDH – isocitrate dehydrogenase; CDKN2A/B deletion – CDKN2A/B homozygous deletion; EGFR co-deletion – epidermal growth factor receptor co-deletion, TTF – tumor treating fields.

For lower-grade adverse events, symptomatic management was implemented. Other adverse effects can be found in **Table 4**. No deaths were deemed to be treatment-related. We cannot confirm whether the adverse effects were attributable to anlotinib or TMZ.

Illustrative Cases

Case 1

Case 1, a 40-year-old man had glioma located in frontal lobe. This patient underwent tumor resection, and histopathology confirmed the GBM diagnosis. He had seizure and weakness 4.07 months after surgery, and radiological examination showed tumor progression. After the use of anlotinib combined with TMZ as the new treatment strategy, he achieved CR. Presently, this patient is still alive, with improved quality of life. The main neuroimaging in treatment process is shown in **Figure 3**.

Case 2

Case 2 was a 58-year-old woman with a tumor located in the callosum. Due to its deep location, biopsy was necessary, and

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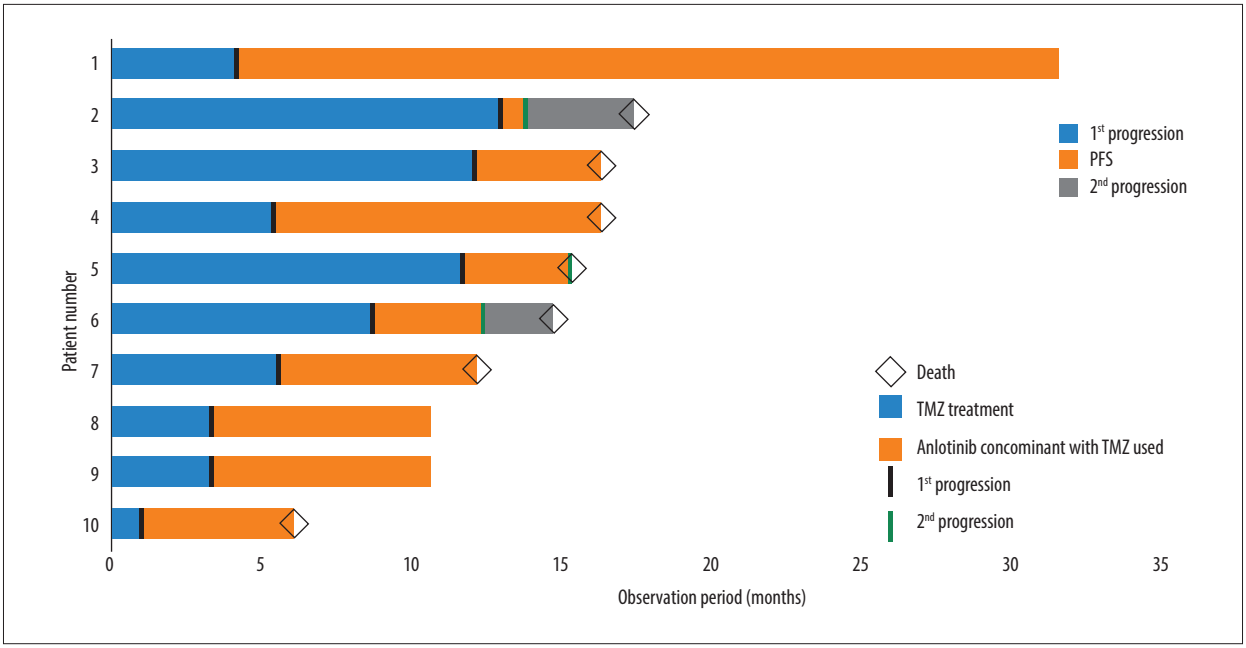
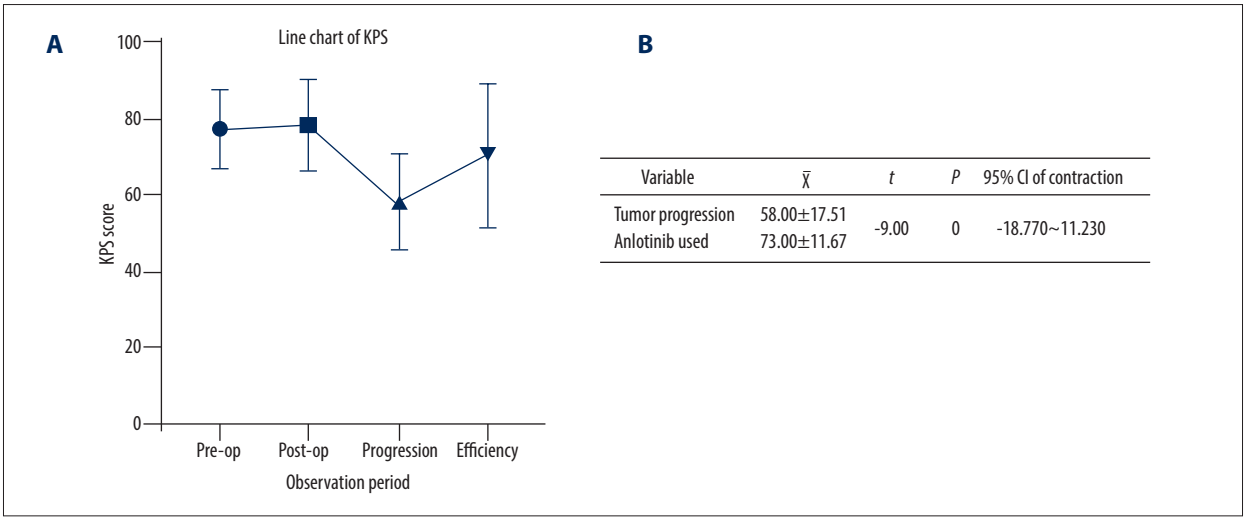


Figure 1. Summary of treatment process. Swimmer plot of 10 patients with GBM at admission and treated with anlotinib after the tumor has progressed. The plot was sorted by overall survival. The line chart began after the resection of each patient's lesion. The blue line represents the process of TMZ treatment, while the orange line depicts the procedure of concurrent anlotinib and TMZ use. The gray line shows patients had a second tumor progression. Between those 3 periods of treatment, we used blue and green string to distinguish them. Rhombus symbolized the patients' death. Some of the patients have passed away (7 of 10), and some of them is living (3 of 10).



B

Variable	$\bar{X}$	*t*	*P*	95% CI of contraction
Tumor progression	58.00±17.51	-9.00	0	-18.770~11.230
Anlotinib used	73.00±11.67			

Figure 2. Changes of KPS scores across different conditions. (A) Line chart of Karnofsky performance status score. The line chart shows mean KPS score of 10 patients. A comparison of pre- and postoperative status shows the status has improved after tumor resection. Among patients who received anlotinib treatment, an improvement in KPS score was commonly observed, suggesting a potential beneficial effect on functional status during therapy. **(B) An improvement in KPS was observed following the administration of anlotinib.** Table shows the distinction between tumor progression and anlotinib used. According to the result of the 2-tailed *t* test, we could easily identify anlotinib has significantly improve the KPS score ($P<0.05$).

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Table 3. Contrast of QLQ-C30 scores between tumor progression and anlotinib used in this cohort (2-tailed *t* test).

Item	Progression		Efficiency		*T*	*P*
	Mean	Standard deviation	Mean	Standard deviation		
PF	45.333	18.571	70.000	24.810	-7.150	0.000
RF	43.333	20.000	62.000	21.510	-3.107	0.013
EF	65.833	16.436	92.500	8.700	-6.249	0.000
CF	63.334	23.333	90.000	13.333	-4.310	0.002
SF	43.333	21.344	65.000	11.667	-3.881	0.004
QL	35.000	15.723	60.000	15.275	-9.000	0.000
FA	45.556	17.533	18.889	11.166	4.609	0.001
NV	11.667	13.017	3.333	10.000	2.236	0.052
PA	36.667	22.111	8.333	11.180	4.295	0.002
DY	3.333	10.000	0.000	0.000	1.000	0.343
SL	30.000	17.951	3.333	10.000	4.000	0.003
AP	26.666	13.333	6.667	13.333	3.674	0.005
CO	6.667	20.000	3.333	10.000	1.000	0.343
DI	0.000	0.000	0.000	0.000	—	—
FI	46.667	26.667	46.667	26.668	0.000	1.000

PF – physical functioning score; RF – role functioning; EF – emotional functioning; CF – cognitive functioning; SF – social functioning; QL – global health status; FA – fatigue; NV – nausea and vomiting; PA – pain; DY – dyspnea; SL – insomnia; AP – appetite loss; CO – constipation; DI –diarrhea; FI – financial difficulties.

Table 4. Adverse effects during by CTCAE grade.

CTCAE grade	1	2	3	4	5
Blood and lymphatic system					
White blood cells decreased	4	4	0	0	0
Thrombocytopenia	1	2	0	0	0
Anemia	3	2	0	0	0
Gastrointestinal system					
AST increased		1	0	0	0
ALT increased	1	1			0
GGT increased	1	1	0	0	0
Cholesterol increased	4	1	0	0	0
Alkaline phosphatase	1	1	0	0	0
Gastrointestinal symptoms	0	1	0	0	0
Cardiovascular system					
Hypertension	2	1	0	0	0
Mucocutaneous system					
Hand-foot skin reaction	1	0	0	0	0

CTCAE – Common Terminology Criteria for Adverse Events; AST – aspartate transaminase; ALT – alanine transaminase, GGT – gamma-glutamyl transferase.

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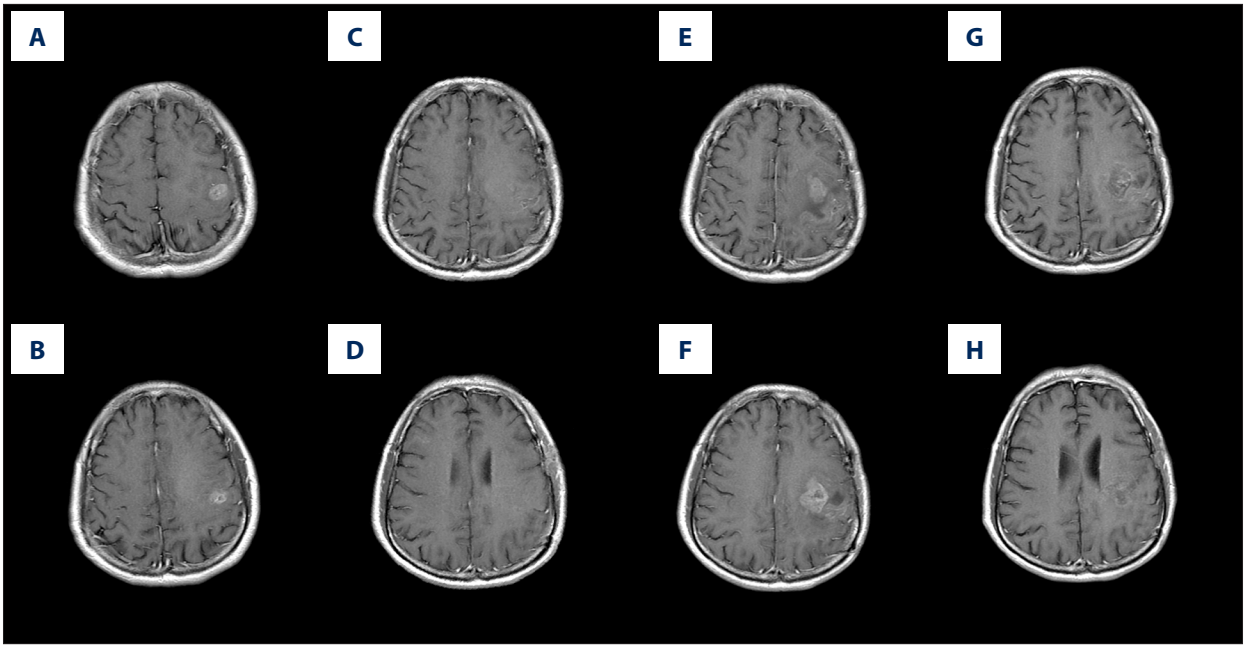

Figure 3. Main neuroimaging of illustrative case 1 during treatment process. Illustrative case 1 shows anlotinib treatment efficacy. In Figure 3, 8 separate figures show preoperative, postoperative, tumor progression, and anlotinib efficacy in MRI (contrast-enhanced T1 sequence). Figure **A and B** show the patient's preoperative condition. Postoperative MRI in Figures **C and D** demonstrates gross total resection of the tumor. Subsequent tumor progression was identified based on MRI findings and clinical symptoms (**E, F**). After anlotinib treatment, neuroimaging shows enhancement in MRI was relieved (**G, H**), and the symptoms caused by tumor progression were alleviated.

GBM diagnosis was confirmed through histopathology and molecular identification. Tumor progression was detected by MRI, and syndromes appeared 3.33 months after tumor resection. She received anlotinib without TMZ because of emesis. At present, she is in good health. Interestingly, this illustrative case showed that anlotinib can restrain GBM progression without combined use of TMZ (the main neuroimaging in treatment is shown in **Figure 4**).

Case 3

Case 3 was a 69-year-old man with tumor widely located in the temporo-parietal occipital lobe. After tumor resection, GBM was diagnosed through the integration of histopathology and molecular identification. He had tumor progression 4.07 months after surgery, presenting seizure and weakness. He died in 2022 because of coronary heart disease. Until his death, we observed no second progression of tumor (the main imaging during treatment is shown in **Figure 5**).

Discussion

GBM is a highly malignant tumor that exhibits hypervascularization. Currently, there are no recommended treatments for progressive GBM. Targeted therapies for malignant tumors involve specific drugs that pharmacologically block molecules involved in tumor growth and progression, thereby preventing their spread [30]. GBM has a poor prognosis, few treatments, and short survival. Patients often experience tumor progression following surgery. Targeted therapies have provided new options for patients with progressive GBM [7]. Due to its production of VEGF and its hypervascular nature, targeted therapies for GBM always focus on anti-vascular therapy [7,31]. Bevacizumab, an earlier targeted agent for recurrent GBM, is a single-target inhibitor of angiogenesis (VEGF) and has shown promising results in previous clinical studies [11-15]. Although bevacizumab dose not confer a survival benefit, phase III clinical trials have confirmed its positive effect in improving PFS [14]. In addition to single-target angiogenesis inhibitors, multi-target inhibitors such as sunitinib and regorafenib have also been investigated and utilized in the treatment of recurrent and progressive GBM, with several studies reporting promising outcomes [32,33].

As a multi-target angiogenesis inhibitor, anlotinib has gradually extended its application from lung cancer to other malignant tumors such as thyroid cancer and colorectal cancer [34-37]. In this study, we retrospectively investigated 10 patients with progressive GBM who received anlotinib treatment. The main clinical outcomes were analyzed in detail. Compared to the Phase III clinical trials conducted by Wick W et al [14],

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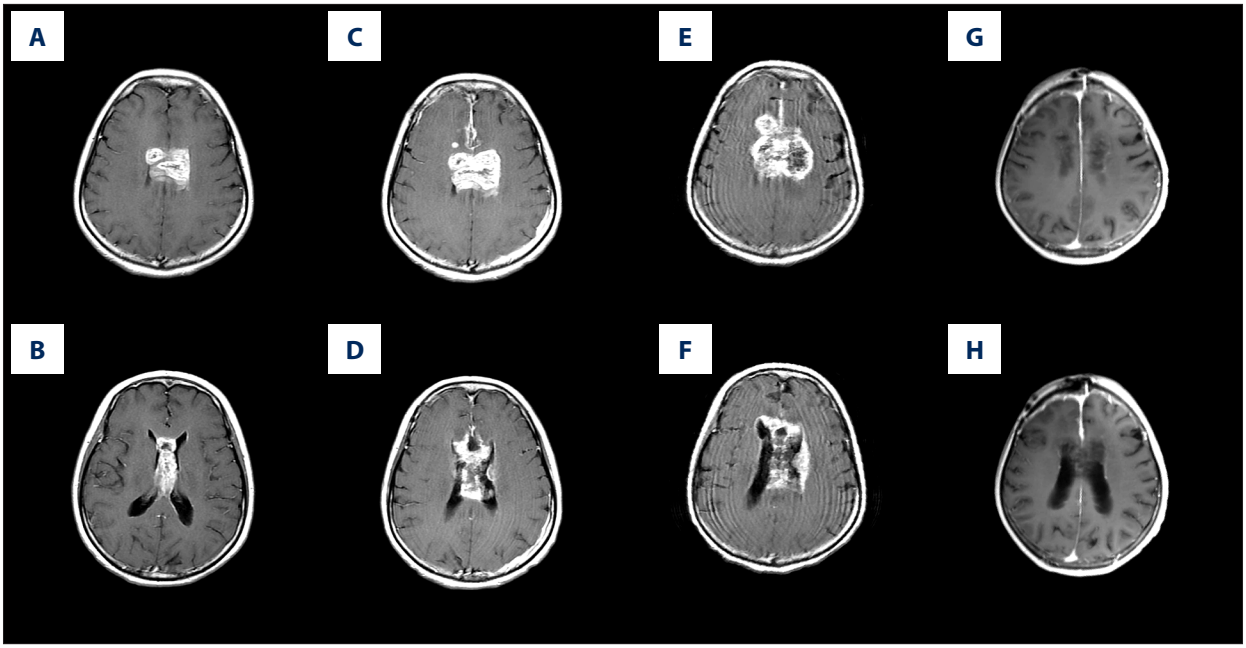

Figure 4. Main neuroimaging of illustrative case 2 during treatment process. Neuroimaging of the treatment process in illustrative case 2. There were 8 separated figures showing preoperative (**A, B**), postoperative (**C, D**), tumor progression (**E, F**), and anlotinib efficiency (**G, H**) in MRI (contrast-enhanced T1 sequence). Preoperatively, **A and B** show the tumor located in the callosum. Because of its deep location, we used stereotactic biopsy to detect tumor grade and determine further treatment measures. In neuroimaging after biopsy, we could easily notice that the lesion has been partial resected (**C, D**). After months of TMZ treatment, the tumor has progressed and enhancement was detected on MRI (**E, F**). With anlotinib use, neuroimaging showed relieved tumor progression and the symptoms caused by tumor progression were alleviated (**G, H**).

patients treated with anlotinib showed a lower median OS of 6.30 months, compared to 9.10 months in those treated with bevacizumab. However, patients receiving anlotinib treatment had a greater median PFS benefit of 5.42 months, compared to 4.20 months with bevacizumab. Additionally, a comparable outcome was observed with regorafenib treatment for progressive GBM (median OS: 6.30 months versus 7.40 months; median PFS: 5.42 months versus 2.0 months) [33]. The survival results and comparison showed that patients with progressive GBM who were treated with anlotinib had a greater benefit in PFS.

We conducted a systematic analysis of anlotinib therapy for progressive GBM in this real-world study. Interestingly, in comparison of other targeted drugs (regorafenib and bevacizumab), the patients included in this study did not achieve significantly better clinical results [14,33]. Considering the clinical findings of our study, we attribute this observation to the following factors. Firstly, some patients in this study were of advanced age and had poor admission status, as well as underlying conditions such as cerebral infarction and coronary heart disease. These factors may have contributed to their relatively poor prognosis and survival outcomes. Secondly, for patients with deep lesions, we used a combination of stereotactic biopsy and standard Stupp protocol of care. Partial tumor resection could potentially affect subsequent therapy statistics and follow-up data. Finally, the presence of diverse ages and admission conditions may account for the statistical heterogeneity observed in the data.

Tumor progression plays a crucial role in the therapeutic process of GBM. It typically occurs following standard therapy (Stupp protocol), including tumor progression, pseudoprogression, and radiation necrosis [38]. Pseudoprogression refers to radiographic evidence of disease progression that spontaneously enhances after the gadolinium administration. It often occurs within 3-6 months after treatment, and although pseudoprogression is accompanied with symptoms in some patients, most of them are self-healing. Radiation necrosis often occurs 9-12 months after treatment and can last for several years. In radiologic findings, radiation necrosis has novel areas of MRI enhancement, which has clear boundaries with initial radiation fields. Microscopically, radiation necrosis is characterized by injury to oligodendrocytes, activation of autoimmune mechanisms, and endothelial cell death. Those microscopic reactions often lead to irreversible fibrosis, vascular hyalinization, and other pathological changes, resulting in severe neurological decline and poor prognosis. Besides worsening symptoms, patients with radiation necrosis experience a worsened prognosis. Tumor progression, also identified as

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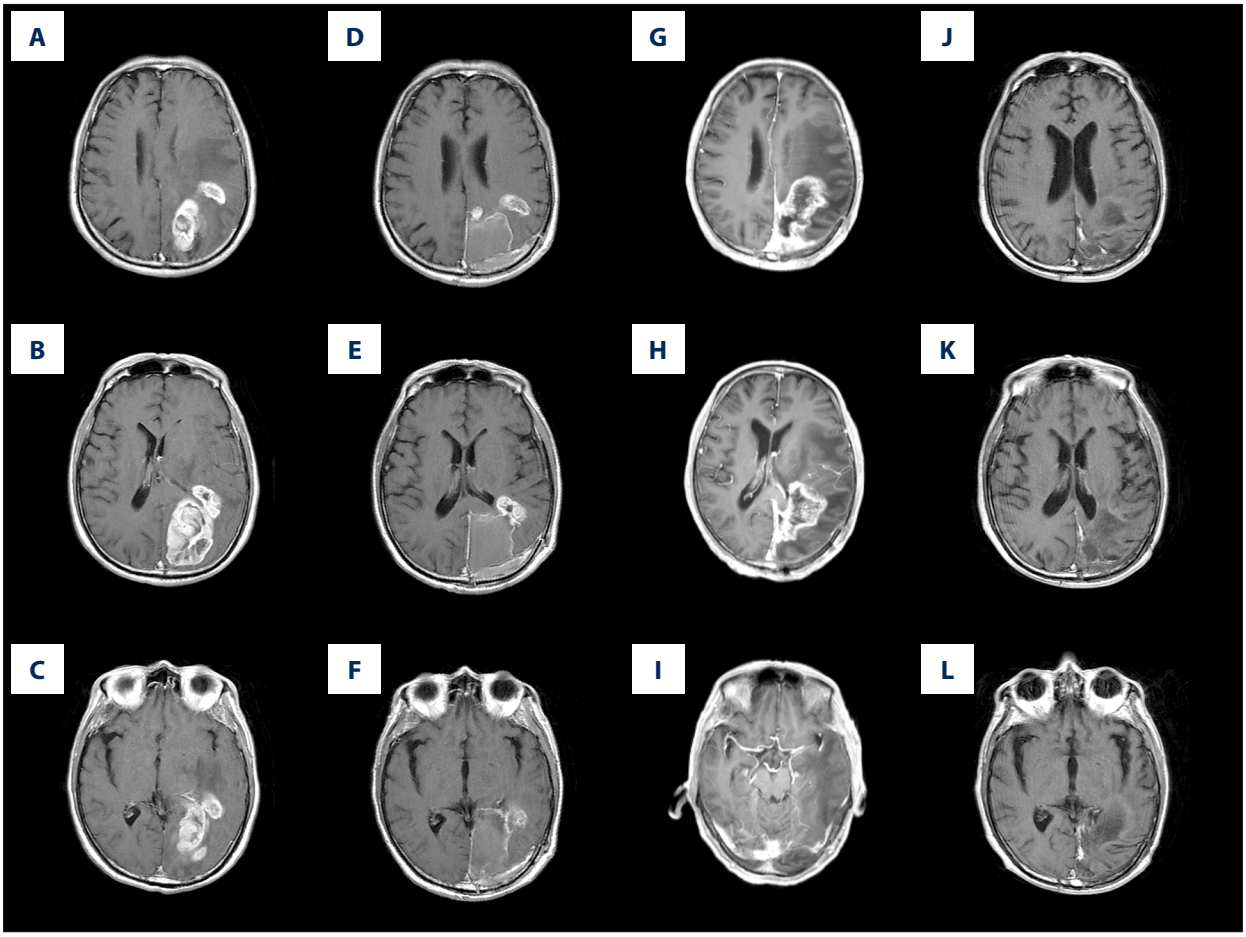

Figure 5. Main neuroimaging of illustrative case 3 during treatment process. The treatment process of illustrative case 3. Preoperative (**A-C**), postoperative (**D-F**), tumor progression (**G-I**), and anlotinib used (**J-L**) in neuroimaging (MRI, contrast-enhanced T1 sequence). In postoperative neuroimaging (**A-C**), the lesion is easily observed in the temporo-parietal occipital lobe, with significant enhancement in contrast-enhanced T1 sequence. Postoperatively, MRI confirmed gross total resection of the tumor (**D-F**). However, follow-up MRI performed several months after completion of the Stupp protocol revealed radiographic evidence of tumor progression (**G-I**). After anlotinib use, MRI showed enhancement was relieved, as were the symptoms caused by tumor progression (**J-L**).

recurrent GBM, is often characterized by radiographic hyperintensity on T2-FLAIR and restricted diffusion on DWI. Patients with rGBM invariably present with worsening symptoms and resistance to standard treatment. For neurosurgeons, distinguishing among tumor progression, pseudoprogression, and radiation necrosis is challenging. Furthermore, there is no established therapeutic regimen for recurrent GBM [39]. Hence, we used the new definition of "tumor progression" in current study, which include the 3 kinds of tumor progression mentioned above. Anlotinib was used as the primary intervention for managing progressive GBM. The analysis findings demonstrated that this treatment not only extended PFS, but improved patients' quality of life. For neurosurgeons, specific therapeutic measures are required for patients with progressive GBM. Due to the challenges in distinguishing among recurrent tumor, pseudoprogression, and radiation necrosis, we used anlotinib as an advanced intervention. The clinical results were satisfactory and the treatment approach met ethical and therapeutic criteria, which makes it worth recommending.

Previously, anlotinib was primarily used for the treatment of rGBM. Lv et al [22] first investigated its use in a patient with rGBM. Although the patient had partial remission, the tumor eventually progressed and the patient died, with the OS of 3.67 months. Subsequently, Yang et al [25] and She et al [40] performed larger retrospective clinical studies. In the cohort study by Yang et al, 31 patients with recurrent high-grade glioma had a median OS of 7.7 months and the 12-month OS rate was 26.7%. In the study by She et al [40], 20 patients with rGBM were treated with anlotinib combined with dose-intensive TMZ: 5 of the cohort had achieved SD, 13 patients achieved PR, 1 had CR, and 1 had PD. In that study, the patients

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Table 5. Ongoing clinical trials of anlotinib in the treatment of glioma.

Trial	Title	Drug	Conditions	Phase	Status	Estimated completion date
NCT05033587	Study of AK105 with anlotinib and radiotherapy adjuvant therapy in MGMT-unmethylated newly diagnosed glioblastoma	Anlotinib, AK105	MGMT-unmethylated glioblastoma	Phase II	Recruiting	November 2023
NCT04959500	Addition of anlotinib hydrochloride to the stupp regimen versus the stupp regimen alone for newly diagnosed glioblastoma: A randomized double-blind multicenter prospective phase II study	Anlotinib, hydrochloride, temozolomide	Glioblastoma	Phase II	Recruiting	October 2023
NCT04725214	Anlotinib combined with stupp for MGMT nonmethylated glioblastoma	Anlotinib	MGMT-unmethylated Glioblastoma	Phase II	Recruiting	December 2023
NCT04547855	Anlotinib combined with dose-dense temozolomide for the first recurrent or progressive glioblastoma after stupp regimen	Anlotinib, dose-dense temozolomide	glioblastoma	Phase II	Unknown	March 2023
NCT04157478	Addition of anlotinib hydrochloride to the stupp regimen versus the stupp regimen alone for newly diagnosed glioblastoma	Anlotinib, hydrochloride, hydrochloride	Glioblastoma	Phase II	Not yet recruiting	December 2024

AK 105 – penpulimab.

had a mean 1-year OS rate of 47.7% and a 6-month PFS rate of 55%. Previous studies have demonstrated that anlotinib has tolerable adverse effects, including hyperlipidemia and hypertension. No serious toxic reactions were observed. The therapeutic targets of these studies encompass FGFR3-TACC3, JAK/STAT3, EGFR-L858R mutation, and other targets associated with the efficacy of anlotinib in treating rGBM [23,24,41]. However, previous relevant studies had limited sample sizes and produced inconsistent results. Currently, there are several ongoing studies investigating the efficacy of anlotinib in treating glioma (**Table 5**). Thus, the effectiveness of anlotinib in treating glioma needs further assessment in larger studies.

Limitations

The present study has several limitations. Firstly, as a single-center retrospective study, it had a small sample size and limited generalizability to other settings. Second, differences in patient conditions upon admission may have affected not only the clinical outcomes, but also caused heterogeneity in the statistical analysis. Thirdly, certain patients within the cohort had either undergone or were currently undergoing additional therapeutic interventions (such as tumor treating fields, gamma knife radiosurgery, or bevacizumab), which may have affected clinical outcomes.

Conclusions

Anlotinib, a multi-target tyrosine kinase inhibitor, is a promising new option for patients with progressive glioblastoma. This exploratory study provides preliminary evidence of therapeutic efficacy and good tolerability, highlighting its potential clinical efficacy. To gain deeper insights into the clinical potential of this drug, large-scale studies are needed.

Consent to Publication

The authors affirm that human research participants provided informed consent for publication of the images in Figures 3, 4, and 5.

Consent to Participate

Informed consent was obtained from all participating patients, ensuring the protection and confidentiality of their data.

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Availability of Data and Materials

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

Department and Institution Where Work Was Done

Department of Neurosurgery, Tianjin Medical University General Hospital, Tianjin, PR China.

Ethic Statement

The present study was granted approval by the Ethics Committee of Tianjin Medical University General Hospital (Ethical NO: IRB2023-wz-163).

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

Abbreviations

GBM – glioblastoma; **OS** – overall survival; **PFS** – progression-free survival; **TMZ** – temozolomide; **KPS** – Karnofsky performance status; **EORTC QLQ-C30** – European Organization for Research and Treatment core quality of life questionnaire; **CTCAE 5.0** – National Cancer Institute-Common Terminology Criteria for Adverse Events 5.0; **CR** – complete response; **PR** – partial response; **SD** – stable disease; **PD** – progressed disease; **DCR** – disease control rate; **ORR** – objective response rate; **EGFR** – epidermal growth factor receptor.

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