Original Article

Postoperative concurrent chemoradiotherapy plus apatinib for patients with high-grade glioma: a retrospective cohort study

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Background: Radiotherapy plus temozolomide followed by adjuvant temozolomide was the standard treatment for high-grade gliomas. This study aimed to explore the effectiveness and safety of the addition of apatinib in patients with high-grade gliomas after surgery.

Methods: In this retrospective cohort study, patients with high-grade glioma [World Health Organization (WHO) grade III or IV] treated with apatinib and concurrent chemoradiotherapy (cCRT) after surgery from October 2017 to February 2021 were reviewed. High-grade glioma patients used cCRT alone in the same period were reviewed as the control group. Progression-free survival (PFS), overall survival (OS), the grade of peritumoral brain edema (PTBE) and safety profiles were recorded. Cox regression analyses were used to determine the associated factors of PFS and OS.

Results: A total of 60 patients with high-grade glioma were reviewed, with 30 patients in the apatinib plus cCRT group and 30 patients in the cCRT group. The median PFS of the apatinib plus cCRT group compared with the cCRT group was 8.53 *vs.* 7.33 months (P=0.62), and the median OS was 13.70 *vs.* 14.30 months (P=0.93). Multivariate analysis revealed that only pathological grade was independently associated with PFS [hazard ratio (HR) =4.445, 95% confidence interval (CI): 1.857 to 10.641, P<0.001] and OS (HR =3.737, 95% CI: 1.530 to 9.123, P=0.004). The apatinib plus cCRT also improved PTBE (P=0.001), and decrease the corticosteroids use than cCRT alone (P=0.002). No grade 3 or higher adverse event was observed in both groups.

Conclusions: Post-operative cCRT plus apatinib was feasible for patients with high-grade glioma, with manageable toxicities.

Keywords: Glioma; angiogenesis inhibitors; apatinib; chemoradiotherapy

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Introduction

Currently, gliomas are the most common central nervous system tumors (1). Among them, anaplastic gliomas [grade III according to the World Health Organization (WHO) classification] accounted for about 20% of adult gliomas, with an overall survival (OS) of only 2–5 years (2,3). In addition, as the most malignant and invasive of all gliomas, glioblastomas account for 48.3% of primary malignant brain tumors, and the 5-year survival rate was only 6.8% (1).

For high grade gliomas (WHO grade III or IV), the guidelines recommended maximal safe resection (4,5). The extent of tumor resection for high-grade gliomas is an independent prognostic factor, and total resection may prolong the time to recurrence and patients' survival (6,7). In addition to surgery, postoperative concurrent chemoradiotherapy (cCRT) for high-grade gliomas provides significant survival benefits (8,9). The EORTC-NCIC trial has demonstrated that temozolomide plus radiotherapy showed more benefit for newly diagnosed glioblastoma than radiotherapy alone, with minimal additional toxicity (9). The 5-year updated results confirmed the long-term efficacy of temozolomide plus radiotherapy, especially in patients with methylated O6-methylguanine DNA-methyltransferase (MGMT) (8). Based on this result, radiotherapy plus temozolomide followed by adjuvant temozolomide (Stupp strategy) has become the standard treatment for high-grade gliomas (4). Regardless of the advances in the therapy, there was only a median OS of 37.6 months for anaplastic gliomas and 14.4 months for glioblastomas (10). More treatment options for high-grade gliomas are urgently warranted.

An important feature of glioblastomas is their high degree of vascularization, and it is believed that vascular endothelial growth factor (VEGF) plays a major role in angiogenic activities in glioblastomas (11). Glioblastoma cells have also been shown to increase VEGF when exposed to radiation (12). Therefore, a potential angiogenic response caused by radiation may be decreased by blocking VEGF. In 2014, a phase III randomized controlled trial has evaluated the efficacy of bevacizumab in combination with radiotherapy plus temozolomide for newly diagnosed glioblastoma (13). Although the trial failed to demonstrate the survival benefit of the addition of bevacizumab, it showed potential benefit of anti-angiogenic therapy in high-grade gliomas.

Apatinib, an oral small-molecule tyrosine kinase inhibitor (TKI), inhibits vascular endothelial growth factor receptor 2 (VEGFR-2) by selectively binding to it, which therefore decreases tumor microvascular density and inhibits tumor development (14). Previous studies have showed the potential benefit of apatinib plus temozolomide for recurrent glioblastoma (15,16). However, the role of apatinib in combination with cCRT for patients with high-grade gliomas after surgery was unidentified. Therefore, this retrospective cohort study aimed to evaluate the effectiveness and safety of postoperative radiotherapy plus temozolomide and apatinib, followed by maintenance temozolomide for patients with high-grade gliomas. Our study may provide more evidence of anti-angiogenic regimen for patients with gliomas. We present this article in accordance with the STROBE reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-24-51/rc).

Highlight box

Key findings

- There was no significant difference in progression-free survival (PFS) between post-operative concurrent chemoradiotherapy (cCRT) plus apatinib and cCRT alone for patients with high-grade glioma. However, the addition of apatinib numerically improved peritumoral brain edema (PTBE), and decrease the corticosteroids use.

What is known and what is new?

- Radiotherapy plus temozolomide followed by adjuvant temozolomide was the standard treatment for high-grade gliomas. However, there was only a median overall survival (OS) of 37.6 months for anaplastic gliomas and 14.4 months for glioblastomas.
- Based on standard treatment, explore the effectiveness and safety of the addition of apatinib in patients with high-grade gliomas after surgery.

What is the implication, and what should change now?

- Clinically, apatinib can be applied to improve PTBE and decrease the corticosteroids use in patients with high-grade glioma. Whether PFS and OS can benefit more needs to be confirmed by a larger sample, prospective, randomized controlled study in future.

Methods

Study design and patients

In this single-center, retrospective cohort study conducted at the 900th Hospital of the Joint Logistics Support Force, patients with high-grade glioma (WHO grade III or IV) treated with apatinib and cCRT between October, 2017 and February, 2021 were reviewed. High-grade glioma

patients used cCRT in the same period were reviewed as the control group. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the ethical review board committee of the 900th Hospital of the Joint Logistics Team (No. 2018016). Informed consent of patients was waived due to the retrospective nature of the study. This observation study was registered on Clinical Trials.gov (NCT03567135).

The inclusion criteria were: (I) aged between 18 and 70 years old; (II) received surgery and were confirmed as high-grade glioma (WHO grade III or IV) by postoperative pathological diagnosis; (III) adequate hematologic, renal and hepatic function based on biochemical profiles; (IV) received cCRT plus apatinib or cCRT after surgery. Patients with factor affecting oral medication (such as dysphagia, chronic diarrhea and intestinal obstruction, etc.), history of epilepsy, history of bleeding disorder or uncontrolled hypertension were excluded. Patients with incomplete data were also excluded.

Treatment

All patients received cCRT. For radiotherapy, patients were scanned using Brilliance Big Bore computerized tomography (CT) scanner (Philips Electronics, Eindhoven, Netherlands), and the treatment plan was performed using Eclipse system. Gross tumor volume (GTV) was defined as the all the tumor identified on the enhanced magnetic resonance imaging (MRI) or other imaging methods. GTVtb was defined as the surgical cavity based on the preoperative and postoperative enhanced MRI. Clinical target volume (CTV) 1 was defined as a 1.5 to 2 cm expansion of GTV or GTVtb, while CTV2 was defined as a 2 to 2.5 cm expansion of GTV or GTVtb. Planning target volume (PTV) 1/2 was defined as CTV 1/2 plus a 3-mm margin. The prescribed radiation dose of PTV1 and PTV2 were 60 and 54 Gy in 30 fractions (2.0 or 1.8 Gy per fraction, 5 fraction per week for 6 weeks). All patients received concurrent temozolomide at a dose of 75 mg/m^2 from the first to the last day of radiotherapy for 6 weeks. Patients in apatinib plus cCRT group also received apatinib (250 mg, qd) during the cCRT.

One month after cCRT, patients were administrated with maintenance therapy consisted of temozolomide (150 mg/m^2 on days 1–5 during the first cycle, and 200 mg/m^2 on days 1–5 during the subsequent cycle if no unacceptable toxicity was observed) for six 4-week cycles.

Outcomes and assessments

Enhanced MRI was performed to assess tumor response and peritumoral brain edema (PTBE) at baseline, one month after cCRT, and every two cycles of the maintenance therapy. After all treatment, assessments every 3 months in the first year, and every 6 months thereafter until disease progression were recommended. The tumor response was determined according to the Response Assessment in Neuro-Oncology (RANO) criteria (17). For patients with potential pseudoprogression, treatment was continued, and a confirmatory assessment was performed 4 weeks later.

The outcomes in this study included progression-free survival (PFS), defined as the time from radiotherapy to disease progression or death of any cause, whichever came first) and OS (defined as the time from radiotherapy to death of any cause). The PTBE was graded as follows: (I) no edema: no obvious edema was identified on imaging; (II) mild edema: the width of edema area ≤2 cm; (III) moderate edema: the width of edema area >2 and ≤3 cm; (IV) severe edema: the width of edema area >3 cm. Adverse events (AEs) during the treatment was recorded and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0.

Statistical analysis

SPSS version 16.0 was used for statistical analysis. Continues variables were described by median and interquartile range (IQR), and compared using Mann-Whitney *U* test between groups. Categorical variables were presented as numbers and percentages, and compared using Chi-squared or Fisher tests. The PTBE before and after treatment was compared using Wilcoxon test. Time to event data was estimated by Kaplan-Meier method, and compared using log-rank test between groups. Univariable and multivariable Cox regression analyses were used to determine the associated factor of PFS and OS. P value was a one-sided test. P<0.05 indicated statistically significant difference.

Results

Patient characteristics

From October, 2017 to February, 2021, a total 60 patients with high-grade glioma were reviewed, with 30 patients in the apatinib plus cCRT group and 30 patients in the cCRT

Table 1 Baseline demographic and clinical characteristics of patients

Variables	Apatinib plus cCRT (n=30)	cCRT (n=30)	P
Age (years)	49 [19–70]	47 [24–68]	0.61
<50	15 (50.0)	17 (56.67)	
≥50	15 (50.0)	13 (43.33)	
Sex			0.79
Male	20 (66.67)	19 (63.33)	
Female	10 (33.33)	11 (36.67)	
ECOG PS			0.80
0	16 (53.33)	17 (56.67)	
≥1	14 (46.67)	13 (43.33)	
Surgical status			0.79
Complete resection	11 (36.67)	12 (40.00)	
Incomplete resection	19 (63.33)	18 (60.00)	
Pathological grade (WHO)			0.17
III	7 (23.33)	12 (40.00)	
IV	23 (76.67)	18 (60.00)	
IDH mutation			0.16
No	18 (60.00)	11 (36.67)	
Yes	9 (30.00)	12 (40.00)	
Unknown	3 (10.0)	7 (23.33)	
MGMT status			0.11
Nonmethylated	7 (23.33)	3 (10.00)	
Methylated	21 (70.00)	20 (66.67)	
Unknown	2 (6.67)	7 (23.33)	

Data are presented as median [IQR] or n (%). cCRT, concurrent chemoradiotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; WHO, World Health Organization; IDH, isocitrate dehydrogenase; MGMT, O6-methylguanine DNA-methyltransferase; IQR, interquartile range.

group. The baseline characteristics of the patients were comparable between the two groups (*Table 1*). The median age was 49 (IQR, 19–70) years old in the apatinib plus cCRT group, and 47 (IQR, 24–68) years old in the cCRT group. Twenty-three patients (76.7%) were WHO grade IV in the apatinib plus cCRT group, and 18 (60.0%) were WHO grade IV in the cCRT group, respectively.

Effectiveness profiles

As the cut-off date (February 20th, 2021), there were 8 patients with stable disease (SD), and 22 patients showed progressive disease (PD) in the apatinib plus cCRT group. Among them, 18 patients died. One case in the apatinib plus cCRT group experienced pseudoprogression. In the cCRT group, all patients showed PD, and 26 patients died. All deaths were due to disease progression, and no death of other reasons were observed.

The median PFS was 8.53 [95% confidence interval (CI): 6.911–10.156] months in the apatinib plus cCRT group, compared to 7.33 (95% CI: 5.414–9.252) months in the cCRT group, no statistically significant difference between the two groups (P=0.62) (*Figure 1*, *Table 2*). The 12-month and 24-month PFS rate was 17.9% and 8.9% in

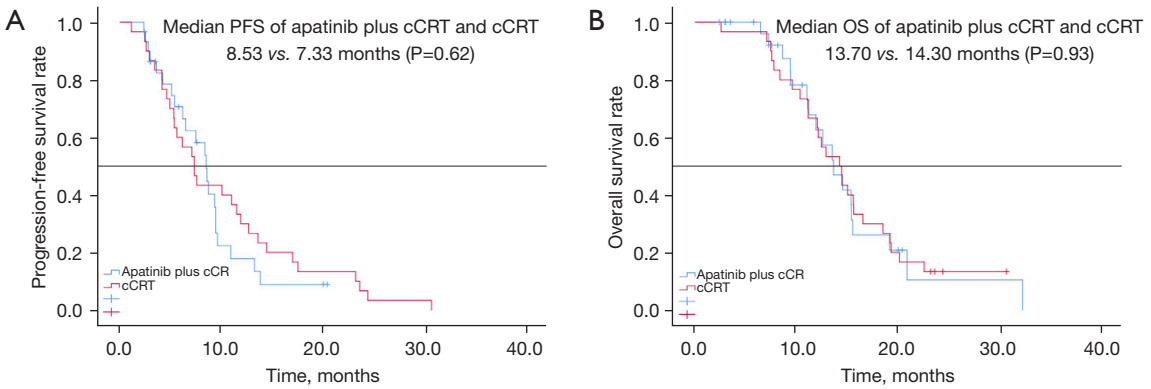

Figure 1 Kaplan-Meier curves of PFS (A) and OS (B). cCRT, concurrent chemoradiotherapy; PFS, progression-free survival; OS, overall survival.

Table 2 PFS and OS rates of two groups

Variables	Apatinib plus cCRT (n=30)	cCRT (n=30)	P
PFS (months), median (95% CI)	8.53 (6.911–10.156)	7.33 (5.414–9.252)	0.62
PFS rate (%)			
6-month	70.6	60.0	0.45
12-month	17.9	30.0	0.60
18-month	8.9	13.3	0.62
24-month	8.9	6.7	0.62
OS (months), median (95% CI)	13.70 (10.945–16.455)	14.30 (11.571–17.029)	0.93
OS rate (%)			
6-month	96.0	96.7	0.33
12-month	62.6	63.3	0.92
18-month	26.1	30.0	0.87
24-month	20.9	13.3	0.93

PFS, progression-free survival; OS, overall survival; cCRT, concurrent chemoradiotherapy; CI, confidence interval.

the apatinib plus cCRT group, and 30.0% and 13.3% in the cCRT group, respectively (*Table 2*). The median OS was 13.70 (95% CI: 10.945–16.455) months in the apatinib plus cCRT group, and 14.30 (95% CI: 11.571–17.029) months in the cCRT group. The difference was not statistically significant (P=0.93) (*Figure 1*). The 12-month OS rate was 62.6% in the apatinib plus cCRT group, and 63.3% in the cCRT group (P=0.92) (*Table 2*).

Group, age, surgical status, pathological grade, isocitrate dehydrogenase (IDH) mutation, MGMT methylated were included in the Cox regression model. The multivariable analyses showed only pathological grade was independently associated with PFS (HR =4.445, 95% CI: 1.857–10.641, P<0.001) and OS (HR =3.737, 95% CI: 1.530–9.123, P=0.004) (*Table 3*).

PTBE before and after treatment

In the apatinib plus cCRT group, the grade of PTBE was improved in 20 (66.7%) patients and stable in 10 (33.3%) patients. In the cCRT group, 7 patients (23.3%) showed improved PTBE, 20 patients (66.7%) were stable, while 3 (10.0%) were aggravated. The difference in the rate of edema relief between the two groups was

Table 3 Multivariate Cox regression analysis of PFS and OS

Variables	PFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Group (apatinib + cCRT *vs.* cCRT)	0.862 (0.484–1.537)	0.62	0.801 (0.411–1.562)	0.52	0.973 (0.526–1.802)	0.93	1.086 (0.548–2.153)	0.81
Age (≥50 *vs.* <50 years)	1.756 (1.004–3.073)	0.048	1.632 (0.892–2.987)	0.11	1.571 (0.855–2.886)	0.15	1.188 (0.620–2.275)	0.60
Surgical status (complete resection *vs.* incomplete resection)	0.849 (0.477–1.509)	0.58	0.774 (0.411–1.456)	0.43	0.818 (0.442–1.516)	0.52	0.727 (0.371–1.427)	0.36
Pathological grade (WHO) (IV *vs.* III)	3.008 (1.501–6.028)	0.002	4.445 (1.857–10.641)	<0.001	3.251 (1.517–6.966)	0.002	3.737 (1.530–9.123)	0.004
IDH mutation	0.785 (0.415–1.487)	0.46	1.725 (0.774–3.846)	0.18	0.812 (0.415–1.590)	0.54	1.054 (0.500–2.223)	089
MGMT methylated	1.715 (0.789–3.730)	0.17	2.305 (0.967–5.492)	0.059	1.559 (0.649–3.745)	0.32	2.470 (0.913–6.683)	0.08

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; cCRT, concurrent chemoradiotherapy; WHO, World Health Organization; IDH, isocitrate dehydrogenase; MGMT, O6-methylguanine DNA-methyltransferase.

Table 4 Adverse events

Events	Grade 1		Grade 2		Any grade	
	Apatinib plus cCRT (n=30)	cCRT (n=30)	Apatinib plus cCRT (n=30)	cCRT (n=30)	Apatinib plus cCRT (n=30)	cCRT (n=30)
Any adverse event	11 (36.6)	7 (23.3)	5 (16.7)	5 (16.7)	16 (53.3)	12 (40.0)
Fatigue	3 (10.0)	2 (6.7)	2 (6.7)	2 (6.7)	5 (16.7)	4 (13.3)
Decreased appetite	3 (10.0)	2 (6.7)	1 (3.3)	2 (6.7)	4 (13.3)	4 (13.3)
Gastrointestinal reaction	2 (6.7)	3 (10.0)	1 (3.3)	0	3 (10.0)	3 (10.0)
Myelosuppression	1 (3.3)	0	0	1 (3.3)	1 (3.3)	1 (3.3)
Hypertension	0	0	1 (3.3)	0	1 (3.3)	0
Hand-foot syndrome	1 (3.3)	0	0	0	1 (3.3)	0
Proteinuria	1 (3.3)	0	0	0	1 (3.3)	0

Data are presented as n (%). cCRT, concurrent chemoradiotherapy.

statistically significant (P=0.001). Six patients (20.0%) used corticosteroids for PTBE in the apatinib plus cCRT group, and 18 patients (60.0%) in the cCRT group needed corticosteroids for the management of PTBE (P=0.002).

Safety profiles

The AEs observed in the study were presented in the *Table 4*. Sixteen patients (53.3%) in the apatinib plus cCRT group and 12 (40.0%) in the cCRT group experienced AEs of any grade. All AEs were grade 1 or 2, with no grade 3 or higher AEs observed. The most common AE was fatigue, decreased appetite and gastrointestinal reaction in both groups. No AEs leading to dose reduction or treatment discontinuation occurred. No serious AEs occurred and all AEs were manageable.

Discussion

During the past decade, post-operative radiotherapy plus temozolomide followed by adjuvant temozolomide has become the standard treatment for high-grade gliomas (4).

However, the prognosis of patients was still suboptimal. Therefore, more treatment options for high-grade gliomas are urgently needed. In this study, we reviewed the data of high-grade gliomas patients received postoperative radiotherapy plus temozolomide and apatinib, followed by maintenance temozolomide. Our results showed that the addition of apatinib to post-operative cCRT was feasible for patients with high-grade gliomas.

In glioblastomas, vascularization is a prominent feature, and VEGF may play a significant role in angiogenic activity (11). Hypoxia inducible factor (HIF)-1α induces VEGF production under hypoxic conditions, which stimulates endothelial cells to migrate, proliferate, and breakdown the extracellular matrix. Besides, VEGF can also increase the vascular permeability (11). A strong association exists between the presence of VEGF within glioblastomas lesions and the presence of viable tumors immediately adjacent to necrotic areas (18). Based on the preclinical studies, several trials have evaluated the role of anti-angiogenic regimen such as bevacizumab in patients with glioblastomas (19-21). Based on these results, bevacizumab has been approved by the Food and Drug Administration (FDA) for the treatment of recurrent glioblastomas in 2009 (22). In 2014, bevacizumab combined with radiotherapy plus temozolomide was evaluated in a phase III randomized controlled trial for newly diagnosed glioblastoma (13). The results showed that the addition of bevacizumab to cCRT showed prolonged PFS (10.6 *vs.* 6.2 months; HR =0.64, 95% CI: 0.55–0.74; P<0.001) and maintenance of quality of life compared to cCRT alone. Nevertheless, bevacizumab failed to bring additional benefit on OS (16.8 *vs.* 16.7 months; HR =0.88, 95% CI: 0.76 to 1.02, P=0.10), and showed more safety concerns (13).

Apatinib is an oral small-molecule TKI, which highly selectively binds and inhibits the VEGFR2, and therefore decreases tumor microvascular density and inhibits tumor development (14,23,24). Researchers have demonstrated that apatinib increases Bax and caspase-9 expression and lowers caspase-9 expression in tumor cells through inhibiting the PI3K/Akt signaling pathway (25). Further, apatinib reverses multidrug resistance of tumor by inhibiting multiple ATP-binding cassette transporters (23,26). Previous studies have shown that apatinib can not only inhibit the proliferation, colony formation and invasion of glioma cells by inducing apoptosis, but also promote the proliferation inhibition of glioma cells mediated by temozolomide, and play a synergistic anti-tumor role with temozolomide in the treatment of glioma (27). Recent research showed that apatinib was able to induce ferroptosis vis inhibiting VEGFR2/Nrf2/Keap1 pathway in glioma cells (28).

Based on potential benefit of apatinib in preclinical studies, some pilot clinical studies have also been conducted. Wang *et al.* (29) treated recurrent high-grade glioma with apatinib plus irinotecan. The PFS was 8.3 months in ten patients, with the objective response rate (ORR) of 55% and disease control rate (DCR) of 78%. Wang *et al.* (16) reported a phase II clinical trial of apatinib combined with dose-dense temozolomide for 20 patients with recurrent glioblastoma. The results showed the ORR and DCR was 45% and 90%, and the median PFS and OS was 6 and 9 months, respectively. Another retrospective study has showed the median PFS and OS were 4.9 and 8.2 months for patients with recurrent glioblastoma treated by apatinib plus temozolomide (15). All these studies demonstrated the potential role of apatinib in patients with high-grade glioma. Nevertheless, the effect of apatinib in newly diagnosed patients with high-grade glioma was unknown. Our study showed that no statistically significant difference in PFS with apatinib plus CCRT compared to the CCRT group (8.53 *vs.* 7.33 months, P=0.615), and had a comparable OS (13.70 *vs.* 14.30 months, P=0.932).

Age and the extent of tumor resection are independently prognostic factors in high-grade gliomas (6,7). Previous studies have showed patients with age of less than 60 years old showed better prognosis, and total resection but not incomplete resection may prolong the time to recurrence and patients' survival (6,7). MGMT methylation is also an associated factor with patients' survival in patients received cCRT (8,30). The median OS of patients with MGMT methylation is 22–26 months, compared to 12–15 months for non-MGMT methylated patients (31). IDH mutation status is another biomarker related to prognosis, and gliomas with IDH wild-type have a poorer prognosis and shorter survival than those with IDH mutants (32). In our study, the multivariable analysis showed that pathological grade IV was the risk factor for both PFS and OS, which was well documented in the previous studies (3). However, other variables including age, extent of tumor resection, IDH mutation status, MGMT methylated status was not associated with the PFS and OS, which may be related to the small sample size of our study and should be further evaluated in the future studies.

The majority of malignant glioma patients have obvious PTBE, which can cause or aggravate neurological dysfunction and intracranial hypertension, significantly

affecting the patient's quality of life and increasing the mortality and disability rate (33,34). PTBE is caused by increased blood-brain barrier permeability, and radiotherapy can damage the vascular endothelium, destroy the blood-brain barrier, and exacerbate edema (35). Anti-edema treatment is particularly important for glioma patients undergoing postoperative cCRT. Previous studies have shown bevacizumab exhibited anti-edema role in glioma patients (33). There is a close relationship between VEGF/VEGFR pathway and PTBE, among which VEGFR2 plays a primary role in monitoring the functionality of the vascular endothelium (36,37). Compared with other TKI, apatinib shows a strong inhibitory effect on VEGFR2, effectively blocking VEGF/VEGFR2 signal pathway, and thus reduces vascular permeability and PTBE (38). In our study, the PTBE in apatinib plus cCRT group also improved than cCRT alone (P=0.001), and the percentage of patients received corticosteroids for PTBE lowered (20.0% *vs.* 60.0%, P=0.002).

Our study had some limitations. First, the study was a retrospective single-center study, which can be susceptible to bias. Second, there were few patients in this study, the follow-up period was insufficient, and the multivariable analysis may not have yielded highly reliable results. Further large-scale studies with long-term follow-up are needed to confirm our results. Third, the WHO Classification of Tumors of the Central Nervous System published in 2021 highlighted the importance of molecular diagnosis (3), but this study was not precise enough to differentiate between 1p/19q deletion status, TERT, TP53, and BRAF mutation status. Fourth, apatinib was only used during the cCRT, and the maintenance treatment consisted of apatinib plus temozolomide can be studied in the future.

Conclusions

In conclusion, our study demonstrated that there was no significant difference in PFS between post-operative cCRT plus apatinib and cCRT alone for patients with high-grade glioma. However, the addition of apatinib numerically improved PTBE, and decrease the corticosteroids use, with manageable toxicities. Further trials are needed to confirm our results.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://cco.amegroups.com/article/view/10.21037/cco-24-51/rc

Data Sharing Statement: Available at https://cco.amegroups.com/article/view/10.21037/cco-24-51/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-24-51/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the ethical review board committee of the 900th Hospital of the Joint Logistics Team (No. 2018016). Informed consent of patients was waived due to the retrospective nature of the study.

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