Anlotinib Combined with Temozolomide Therapy for Recurrent Glioblastoma (IDH-wt and TERTp-mut) After Standard Treatment

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Research Article

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Abstract

Purpose

IDH1-wt glioblastoma patients with TERTp-mut had the worst prognosis, and no effective management strategy was established after tumor recurrence. The median overall survival (OS) of recurrent GBM patients who only received supportive therapy was approximately 1.0 month. We reported survival outcomes of recurrent glioblastoma (rGBM) treated with anlotinib combined with temozolomide therapy (ACTT), and to explore the management strategy of rGBM.

Methods

The clinical data of 14 rGBM patients treated with ACTT was collected. Therapeutic efficacy and adverse effects were evaluated in every 2 months of treatment. We also included 16 patients treated with bevacizumab (Bev), 22 with TMZ, 28 with re-operation, 21 with re-irradiation, and 75 with supportive care to make comparison. Kaplan-Meier analysis was used to compare the survival of ACTT group versus other treatment groups.

Results

Fourteen rGBM patients treated with ACTT were enrolled. After 2-month of ACTT, the overall response and disease control rate were 50.0% and 92.9%, respectively. The 6-months PFS rate was 78.6%, and the 1-year survival rate was 50.0%. The median PFS and OS in ACTT group were 11.0 and 13.0 months, respectively. The median PFS and OS in Bev-group was 4.0 and 8.0 months. The patients treated with ACTT had better PFS than that in Bev-group. And compared to all the others treatment groups, ACTT could prolong survival.

Conclusion

The treatment regimen of ACTT maybe reliable, safe, and effective for rGBM. The patients can gain survival benefits from ACTT, and prolonged survival were observed compared with other treatment regimens.

Introduction

Glioblastoma (GBM) is the most common intracranial malignant tumor with poor prognosis[1, 2], the patients with IDH1 wild-type (IDH1-wt) had a worse prognosis[3], and the patients with IDH1-wt and TERT promoter mutation (TERTp-mut) had the worst survival outcome[4]. At present, although comprehensive therapies are performed to improve survival in patients, approximately 85% of them suffer tumor recurrence in 2 years[5]. The prognosis of patients with recurrent GBM (rGBM) is worse, with a median

overall survival (OS) less than 6 months[6], and patients only received supportive care even had a median OS of 1.0 month. Some previous studies showed that repeated surgery can prolong survival in recurrent GBM[7–9] , however, some patients are reluctant to redo-surgery for the incidence of complications cause by re-operation was higher than that in the initial operation[9]. The bevacizumab therapy is the preferred drug for recurrent glioma in the National Comprehensive Cancer Network guidelines, however, it only can improve progression-free survival (PFS), while the OS benefits was not observed[10, 11].

Anlotinib is a multitarget tyrosine kinase inhibitor, and it can inhibit vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor-4 (FGFR), platelet-derived growth factor receptors α/β (PDGFRα/β), c-Kit, and Ret[12–15]. Anlotinib can inhibit both tumor angiogenesis and tumor cell proliferation, and it was approved as a third-line treatment for refractory advanced non-small cell lung cancer by the China Food and Drug Administration in 2018[13]. In addition, the patients with metastatic renal cell carcinoma or sarcoma treated with anlotinib can also gain PFS and OS benefits[16–20]. By July 2021, there were only two cases of rGBM treated by anlotinib had been reported, and those 2 patients gained survival benefits from therapy[21, 22] . In Liu et.al.'s study[23], they performed a retrospective study of anlotinib combined TMZ therapy for rGBM, and evaluated the safety and efficacy of ACTT, and they hold the view that the anlotinib was effective for rGBM and the AEs were tolerant. To have a better assessment of the effectiveness of anlotinib therapy for rGBM, we retrospectively collected 14 patients in our hospital to make a survival analysis. What is important, we further compared survival outcome in the ACTT group to bevacizumab monotherapy, temozolomide monotherapy, re-operation, reirradiation and supportive care groups, respectively.

Materials And Methods

We analyzed the data of 14 patients with rGBM (IDH-wt and TERTp-mut) from January 2020 to December 2021 in Renji Hospital affiliated to Shanghai Jiaotong University School of Medicine. The inclusion criteria included the following: a) Age≥18 years; b) Karnofsky performance scale at recurrence≥60; c) GBM was confirmed by pathology, IDH 1 wild-type and TERT promoter mutation was confirmed by direct gene sequencing; d) The patients received gross total resection at initial operation followed by concurrent chemoradiotherapy and TMZ adjuvant chemotherapy; e) Measurable lesions were presented on MRI; f) the GBM recurrence was confirmed by neurosurgeons, radiologists, and oncologists assessment based on Response Assessment in Neuro-Oncology (RANO) criteria; g) Good bone marrow, liver and kidney function; h) rGBM patients treated with ACTT. Exclusion criteria are as follows:1) patients with other malignant tumors or serious diseases; 2) cases of pseudo progression; 3) patients with hypertension whose blood pressure cannot be controlled to normal levels after treatment. Patients with myocardial infarction, arrhythmias, and grade II cardiac insufficiency; arteriovenous thrombosis events occurred within 6 months. 4) lacking of follow-up data. The collected clinical data included: gender, age, pathology, extent of resection at initial operation, history of radiotherapy and chemotherapy, initiation and end time of anlotinib therapy, combination therapy and therapeutic toxicity. The changes bone marrow, liver and kidney functions, thyroid function and urinary protein; and clinical symptoms on blood pressure, hand and foot skin, and ect were recorded before and after each treatment cycle. The changes of imaging

findings on MRI and MRS were recorded every 2 months. In order to better evaluate the efficacy of ACTT in the treatment of recurrent GBM, 16 patients received Bev-monotherapy, 22 patients received TMZ monotherapy, 28 patients received re-operation, 21 patients received re-irradiation, and 75 patients received supportive care after recurrence were included. PFS and OS in ACTT group were compared with those patients treated with Bev-monotherapy. OS in ACTT group was compared with those patients who received TMZ monotherapy, re-operation, re-irradiation, and supportive care. The study was approved by the ethics committees of Renji Hospital, Shanghai Jiao Tong University School of Medicine, according to principles of the Declaration of Helsinki.

Treatment Methods

All 14 patients received anlotinib (10 mg daily, orally for 2 weeks, discontinued for 1 week, repeated every 3 weeks) in combination with TMZ therapy (100 mg/m^2 daily, orally for 5 days, rest for 23 days, 28-day cycle) until disease progression (PD) or AEs above grade 4 appeared. Grade 3 AEs need to be restored to grade 2 before continuing therapy.

Efficacy and Adverse Events

Therapeutic effect was evaluated by RANO criteria, including complete remission (CR), partial remission (PR), stable disease (SD), and disease progressed PD. The overall response ratio (ORR) was defined as the ratio of the number of patients reaching CR and PR to the total number of patients, and the disease control rate (DCR) as the ratio of the number of patients reaching CR, PR, and SD to the total number of patients. MRI scans are routinely performed after 2 months of treatment. Clinicians assess the disease status based on MRI images and clinical symptoms. AEs were evaluated based on the National Cancer Institute-Common Terminology Criteria Adverse Events version 4.03 (NCI-CTCAE 4.03). We define PFS as the time from tumor recurrence to disease progression again, and overall survival (OS) as the time from tumor recurrence to death or the end of follow-up. The main endpoints were 6-month, 1-year PFS and 1-year OS.

Statistical analysis

All statistical analyses were performed using SPSS 23.0 statistical software (IBM Corporation, Armonk, New York, USA). Patients' baseline data and adverse events data were calculated by direct counting method, and the cut-off points of continuity variables and categorical variables were determined by median. Kaplan-Meier survival curve was used for survival analysis. A bilateral test was used to determine the significance of time to survival in the two groups of patients with different treatment regimens. The significance level was $P < 0.05$.

Results

A total of 14 adult patients with rGBM treated with ACTT were identified. Their characteristics are summarized in Tables 1 and 2. All patients were diagnosed as GBM with IDH1-wt and TERTp-mut. The

median age at tumor recurrence was 55.0 years (range: 28.0-71.0y); 50% (7/14) of them were male. The tumor locations were the parietal lobe (n = 5, 35.7%), frontal lobe (n =4, 28.6%), occipital lobe (n = 2, 14.3%), cerebellum (n = 2, 14.3%), and basal ganglia region (n = 1, 7.1%). All patients received gross total resection at initial surgery followed by concurrent chemoradiotherapy and TMZ adjuvant chemotherapy. All 14 patients were treated with ACTT for the first-line therapy after tumor recurrence. After 2 months of ACTT, CR occurred in 5 patients, PR in 2 patients, SD in 6 patients, and PD in 1 patient. The ORR was 50.0% (7/14), DCR was 92.9% (13/14). There were 3 patients had AEs, and no treatment-related death.

The median treatment cycle of ACTT was 6.0 cycles (1.0-15.0 cycles). We were highly vigilant of pseudo progression when making a diagnosis of tumor recurrence, especially for patients with tumor progression within 3 months. The distinction between tumor recurrence and pseudo progression based on the extent of resection at initial operation, recurrence time, molecular pathological features, and multiple MRI and MRS examinations. Tumor recurrence is determined by the neurosurgeons, oncologists, and radiologists based on patient's clinical symptoms and examination results. For patients suspected of short-term recurred, we chose dynamic observation, and then dynamic examination of MRI and MRS were performed**.** And subsequently repeated MRI showed tumor enlargement, and MRS showed the Cho/NAA ratio in the region of interest was higher than that in the first suspected recurrence, and the Cho/NAA ratio >2.0. These patients were eventually identified as GBM recurrence. In addition, the symptoms of those patients had improved after ACTT, the tumor volume decreased and the Cho/NAA ratio in the region of interest decreased, these findings also confirmed that these patients should be diagnosed as GBM recurrence rather than pseudo progression. The interval of MRI and MRS was 1-3 months, and the time point of efficacy evaluation was 2 cycles after the therapy (approximately 2 months after tumor recurrence).

Survival comparison of ACTT and different treatment regimens

The follow-up time ranged from 2.0 to 24.0 months. The 6-month and 1-year of PFS rate were 78.6% and 42.9%, respectively. The 1-year survival rate was 50.0%. And the median PFS and OS were 11.0 and 13.0 months, respectively (Table 3). And then we compared survival outcome for ACTT with other treatment regimens (Tables 2). The Median PFS in Bev-group after GBM recurrence was 4.0 months, which was significantly shorter than that in ACTT group (median PFS: 4.0 vs. 11.0 months, P<0.001, Figure 1A). And the Median OS between these two groups was significantly different (median OS: 8.0 in BEV group vs. 13.0 months in ACTT group, P<0.001, Figure 1B). Twenty-eight patients (without considering IDH1 status) received re-operation after tumor recurrence, with the median OS being 12.0 months, this survival outcome was similar with ACTT group (Figure 1C). However, for the IDH1-wt GBM patients, the ACTT group had prolonged OS than that in re-operation group (median OS: 7.0 vs. 13.0 months, Figure 1D). The median OS in re-irradiation TMZ monotherapy, and supportive care groups were 4.0, 4.0 and 5.0 months, which were worse than that in ACTT group (Figure 1E-G). And compared to all the other treatment groups, the patients treated with ACTT had the best survival (Figure 1H).

Illustrative Cases

Case1

A 65-year-old female presented with 1-month history of headache. The MRI showed a ring-enhanced right parietal occipital lobe lesion with peritumoral edema and the midline shift (Figure 2A). After admission, a gross total resection of lesion was performed, and the mass was confirmed as GBM. Immunohistochemical results showed that IDH1 (-), TERT C250T promoter (+), Ki67 index was 30%, GFAP (+), ATRX (+), Oligo2 (+), P53 (+), MGMT (+), MGMT promoter unmethylation. Direct gene sequencing showed IDH1 was wild-type and TERT C250T promoter mutation. The patients received concurrent chemoradiotherapy and temozolomide adjuvant chemotherapy after surgery. However, the MRI suggested the tumor recurrence 6 months later (Figure 2B). And then she received anlotinib combined with temozolomide therapy. Two months after treatment, the enhanced lesion basically disappeared on MRI (Figure 2C), and she achieved complete remission. She continued to receive ACTT, and after tumor recurrence 4, 6, 7, 9, 11 and 13 months, the lesions had completely disappeared and the disease was stable (Figure 2D-I). Unfortunately, the MRI suggested that the tumor recurred again after 15 months treatment (Figure 2J), and the Cho/NAA ratio in the region of interest increased(Figure 2K). She continued to receive ACTT and survived with symptom-free 21 months after tumor recurrence, despite a progressive increase in tumor volume (Figure 2L-N).

Case 2

A 66-year-old woman with a chief complain of headache for 2 weeks was admitted to our department. Brain MRI showed a right parietal occipital lobe lesion with heterogeneous enhanced (Figure 3A). She received gross total resection of lesion, and the lesion was confirmed as GBM. Immunohistochemistry showed that IDH1 (-), TERT C228T promoter (+), Ki67 index 30%, GFAP (+), ATRX (+), Oligo2 (+), P53 (+), MGMT (-), and MGMT promoter unmethylation. IDH1 wild-type and TERT C250T promoter mutation was confirmed by gene sequencing. Postoperative she received concurrent chemoradiotherapy and TMZ adjuvant chemotherapy. Four months after surgery, the MRI suggested tumor recurrence with the Cho/NAA ratio increased on MRS (Figure 3B, K), and ACTT was initiated. After 2 months of treatment, the lesion was stable without progression (Figure 3C). She continued to receive ACTT, and the disease was stable at 4, 6, 8, 10, 13, 15 and 18 months after tumor recurrence (Figure 3D-J). Although there was no significant change in tumor volume, a gradual decreasing in CHO/NAA ratio in region of interest was observed (Figure 3L, M), and she remained symptom-free survival for 19 months.

Adverse Events

According to the Phase III clinical study of ALTER0303 and the Adverse reaction Management Manual of antlotinib, the adverse effects of antlotinib mainly include fatigue, gastrointestinal reaction, oral mucitis, hypertension, rash, proteinuria, hypothyroidism, bone marrow suppression, abnormal liver and kidney function, dyslipidemic, etc[23]. There were 3 patients had AEs in our study, nasal bleeding and mental symptom in 1 patient; pain, blisters, and cerebral hemorrhage in 1 patient; and mild abnormal liver function in 1 patient. These AEs were assessed as grade 1 based on NCI-CTCAE 4.03. All the AEs could be

tolerated after symptomatic treatment. Although the AEs were mild, 2 patients refused to continue ACTT. There was no treatment-related deaths in the study.

Discussion

The survival outcome of IDH-wt rGBM is poor, and those patients with TERTp-mut have shorter OS than patients without TERTp-mut[4]. And the treatment strategies for rGBM remain challenging. Here we perform a retrospective study on the prognosis of rGBM (IDH1-wt and TERTp-mut) treated with ACTT, and we found the median PFS and OS were prolonged. No unexpected toxicity or treatment-related adverse event was observed. The patients treated with ACTT had prolonged survival compared with other treatment regimens. These findings are encouraging that the rGBM patients can gain benefit from ACTT, and this treatment regimen was well tolerated. Our findings may offer a potential treatment option for rGBM, especially for those patients with IDH-wt and TERTp-mut.

In recent years, a variety of management strategies for rGBM were explored. Re-resection was proved to be a favorable independently prognostic factor for rGBM[24–27]. In Ringel's study [9], the median OS of patients who received re-operation without considering IDH1 status was 11.9 months. The median OS in our whole re-operation group was 12.0 months, which was similar with their results[9]. IDH1 status has an important effect on survival, and the patients with IDH1 mutation had a better survival[28, 29]. Without considering IDH1 status, we found no difference in the survival between re-operation group and ACTT group in our study. While when compared the OS between these two groups in patients with IDH1-wt rGBM, we found that the OS in ACTT group was significantly prolonged (median OS=12.0 vs 7.0 months).

For the patients who refused re-operation, single-agent bevacizumab was granted by US Food and Drug Administration approval, and it is the preferred drug for recurrent glioma in the National Comprehensive Cancer Network (NCCN) guidelines[30–33] . Bevacizumab can inhibit VEGF, and it has been used as a later-line treatment for rGBM patients in 2009[34]. Currently, bevacizumab has become the standard treatment for rGBM patients in the NCCN guidelines. However, it was confirmed that bevacizumab can only improve PFS, while no OS benefit was observed[35, 36]. In addition, bevacizumab combined with lomustine can also improves PFS compared with lomustine alone (4.2 months vs 1.5 months), however, no OS benefit was presented as well[37]. In our study, we found the median PFS and OS in Bev-group were 4.0 and 8.0 months, and the median OS in Bev-group was longer than that in TMZ monotherapy group (median OS=8.0 vs 4.0 months), our results were consistent with previous study[38].

Anlotinib is a multitarget tyrosine kinase inhibitor, and it can inhibit tumor angiogenesis and tumor cell proliferation from multiple targets. In our study, the 6-months PFS rate was 78.6%, and the 1-year survival rate was 50.0%. The patients treated with ACTT can gain survival benefits, with the median PFS and OS being 11.0 and 13.0 months, respectively. As shown above, Bev-monotherapy had improved survival compared with TMZ monotherapy in rGBM patients, however, both the PFS and OS benefit in Bev-group was lower than that in ACTT group (median PFS= 11.0 vs 4.0 months, median OS=14.0 vs 8.0 months),

showing significant differences in survival. Meanwhile, we found that the survival outcome in ACTT group was better than TMZ monotherapy, re-irradiation and supportive care groups. In Liu er. al.' study[23], they perform a retrospective study on safety and efficacy of ACTT in 20 patients with rGBM, and their results showed that the median PFS and median OS were 6.1 and 11.9 months, respectively. Their findings were in accordance with our results, indicating that anlotinib combined with TMZ may can improve the PFS and OS in rGBM patients.

What is important, there were 35.7% (5/14) of patients had CR after 2 courses of treatment, with recurrent lesions disappeared completely on enhanced MRI and the Cho/NAA rate decreased gradually on MRS. Two patients had PR, although the recurrent lesions disappeared not completely, they gain PFS benefits. Six patients were in SD, although the lesion almost unchanged on MRI, the MRS showed that the Cho/NAA rate in the region of interest decreased. And they also gain PFS benefits after treatment, even one patient survived with symptom-free for 18.0 months (patient no.5). Unfortunately, 1 patient had disease progressed, and he dead 2 months later after tumor recurrence. The reason why this patient had no response for treatment may due to the lesion have already invaded the brain stem by the time of tumor recurrence. The ORR was 50% (7/14), and the DCR was 92.9% (13/14), this finding was consistent with previous published study[23], demonstrating ACTT maybe effective for rGBM.

Although this is a retrospective study, we carefully recorded the adverse effects of all patients. Regarding tolerability and compliance, there were 3 patients had AEs in our study, including pain, skin vesicle and cerebral hemorrhage in 1 patient, nosebleed in 1 patient, and minor liver dysfunction in 1 patient. All AEs were assessed as graded 1 based on NCI-CTCAE 4.03. The AEs rate in our study was lower than that in Liu et. al.' study[23], this may due to our patients were on a 10mg daily dose, while their patients were on a 12mg daily dose. No treatment-related death was presented. The dosage of anlotinib was 10 mg daily in our study, which was lower than the dosage of anlotinib in non-small cell lung cancer and soft tissue sarcoma and previous study on rGBM therapy. The optimal dose of anlotinib in the management of rGBM remains unclear, and further trail is needed to be explored.

The management of rGBM still remains challenging. Although some targeted therapies can increase several months in survival, the prognosis is still dismal. To date, there is no effective targeted drug having been proven to improve survival, which may be associated with drug resistance. Some studies have suggested that GFR3-TACC3 fusion may be a new marker for the treatment of glioma by anlotinib[22], but the specific molecular biomarkers related to the evaluation of the treatment effect of anlotinib remain to be further explored. Although this is a retrospective study based on a small sample, our findings can provide a potential option for the treatment of rGBM to some extent. To date, there are several relevant clinical trials on the treatment of recurrent GBM by anlotinib conducted in China. It is believed that anlotinib monotherapy or combined therapy may can bring more hope for the clinical management of rGBM.

In conclusion, the treatment regimen of ACTT maybe reliable, safe, and effective for rGBM. The patients can gain survival benefits from treatment, and the survival outcome is better than re-operation, TMZ

monotherapy, re-irradiation, and Bev-monotherapy. And we will perform prospective clinical trials in the future to further explore the clinical value of anlotinib combined with TMZ in rGBM.

Abbreviations

rGBM
Recurrent glioblastoma
IDH1
Isocitrate dehydrogenase1
ACTT
Anlotinib combined with temozolomide therapy
TMZ
temozolomide
Bev
bevacizumab
OS
Overall survival
PFS
Progression-free survival
RANO
Response Assessment in Neuro-Oncology
AEs
Adverse effects

Declarations

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Acquisition of data: Tianwei Wang, Zhijun Liao, Ruizhi Wang, Ming Ye, Yongrui Bai, Meimei Gao, Zhao Jiang, Renhua Huang;

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Study supervision: Yongming Qiu and Renhua Huang.

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Tables

Table 1 Details of patients with recurrent glioblastoma treated with anlotinib combined with temozolomide.

No	Age	Sex	Location	Anl-C	TE	PFS(m)	OS(m)	Status	AEs
1	32	M	L cerebellum	1	PD	0	2	Death	-
2	62	M	R frontal	5	SD	12	20	Death	-
3	28	M	R frontal	1	PR	15	≥15	AS	-
4	71	M	R parietal	9	CR	7	≥9	AS	-
5	66	F	R occipital	1	SD	18	≥19	AS	Epistaxis
6	59	M	L occipital	7	PR	22	≥22	AS	Pain, blisters, CH
7	50	F	R frontal	7	SD	6	≥11	AS	-
8	55	F	R BG	15	SD	11	≥11	AS	-
9	65	F	R occipital	6	CR	15	≥22	AS	-
10	56	M	L parietal	3	SD	6	9	Death	-
11	50	M	L frontal	7	CR	13	≥13	AS	-
12	42	F	L cerebellum	1	SD	8	≥8	AS	HD
13	69	F	L parietal	7	CR	7	≥10	AS	-
14	47	F	R parietal	6	CR	11	15	Death	-

M, male; F, female; L, left；R, right；BG, basal ganglia; Anl-C, anlotinib cycles; TE, therapeutic effect; PD， disease progressed; CR, complete remission; PR, partial remission; SD, stable disease; PFS, Progression-free survival; OS, overall survival; AS, Asymptomatic survival; AEs, adverse Events; CH, cerebral hemorrhage; HD, hepatic dysfunction.

Table 2 Demographic, clinical and molecular characteristics of patients in different groups.

ACTT, anlotinib combined with TMZ treatment; Bev, bevacizumab; TMZ, temozolomide; SC, supportive

Characteristics	ACTT (n=14)	Bev (n=16)	TMZ (n=22)	Re-operation (n=28)	Re-RT (n=21)	SC (n=75)
Age, years						
Median	55.0	56.0	55.0	51.0	55.0	58.0
Range	28.0-71.0	30.0-71.0	31.0-72.0	30.0-74.0	31.0-67.0	20.0-74.0
Gender						
Male	7 (50.0%)	8 (50.0%)	13 (59.1%)	19 (67.9%)	12 (57.1%)	50(66.7%)
Female	7 (50.0%)	8 (50.0%)	9 (40.9%)	9 (32.1%)	9 (42.9%)	25(33.3%)
EOR						
GTR	14 (100.0%)	16 (100.0%)	7 (31.8%)	10 (35.7%)	10 (47.6%)	41 (54.7%)
STR	0 (0.0%)	0 (0.0%)	12 (54.5%)	14 (50.0%)	8 (38.1%)	20 (26.7%)
PR	0 (0.0%)	0 (0.0%)	3 (13.7%)	4 (14.3%)	3 (14.3%)	14 (18.6%)
RT						
Y	14 (100.0%)	16 (100.0%)	22 (100.0%)	28 (100.0%)	21 (100.0%)	75 (100.0%)
N	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CoCT						
Y	14 (100.0%)	16 (100.0%)	15 (68.2%)	19 (67.9%)	13 (61.9%)	50 (66.7%)
N	0 (0.0%)	0 (0.0%)	7 (31.8%)	9 (32.1%)	8 (38.1%)	25 (33.3%)
AdCT						
Y	14 (100.0%)	16 (100.0%)	16 (72.7%)	26 (92.9%)	15 (71.4%)	60 (80.0%)
N	0 (0.0%)	0 (0.0%)	6 (28.3%)	2 (7.1%)	6 (28.6%)	15 (20.0%)
IDH1						
Mutation	0 (0.0%)	4 (25.0%)	2 (9.1%)	5 (17.9%)	0 (0.0%)	0 (0.0%)
Wild-type	14 (100%)	12 (75.0%)	12 (54.5%)	13 (46.4%)	4 (19.0%)	30 (37.9%)
NOS	0 (0.0%)	0 (0.0%)	8 (36.4%)	10 (35.7%)	17 (81.0%)	45 (62.1%)
TERT promoter						

Mutation	14 (100%)	4 (25%)	1 (4.5%)	2 (7.1%)	1 (4.8%)	8 (10.7%)
Wild-type	0 (0.0%)	12 (75%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (4.0%)
NOS	0 (0.0%)	0 (0.0%)	21 (95.5%)	26 (92.9%)	20 (95.2%)	64 (85.3%)

care; EOR, extent of resection; GTR, gross total resection; STR, subtotal, resection; PR, partial resection; RT, radiotherapy; CoCT, Concurrent chemotherapy; AdCT, adjuvant chemotherapy; Y, yes; N, no.

Table 3. K-M survival analysis of progression-free survival and overall survival of recurrent GBM with different treatment regimens.

Treatment regimens	Median PFS (mons)	Median OS (mons)	P value	95%5 CI
ACTT vs Bev	11.0 vs 4.0	-	<0.001	4.470, 7.530
ACTT vs Bev	-	13.0 vs 8.0	<0.001	8.705, 13.295
ACTT vs TMZ	-	13.0 vs 4.0	<0.001	2.629, 6.371
ACTT vs Re-operation (all patients)	-	13.0 vs 12.0	0.100	11.171, 18.829
ACTT vs Re-operation (IDH1 wilt-type)	-	13.0 vs 9.0	0.006	8.267, 21.733
ACTT vs Re-RT	-	13.0 vs 4.0	<0.001	8.309, 15.522
ACTT vs SC	-	13.0 vs 5.0	<0.001	4.320, 7.680

Figures

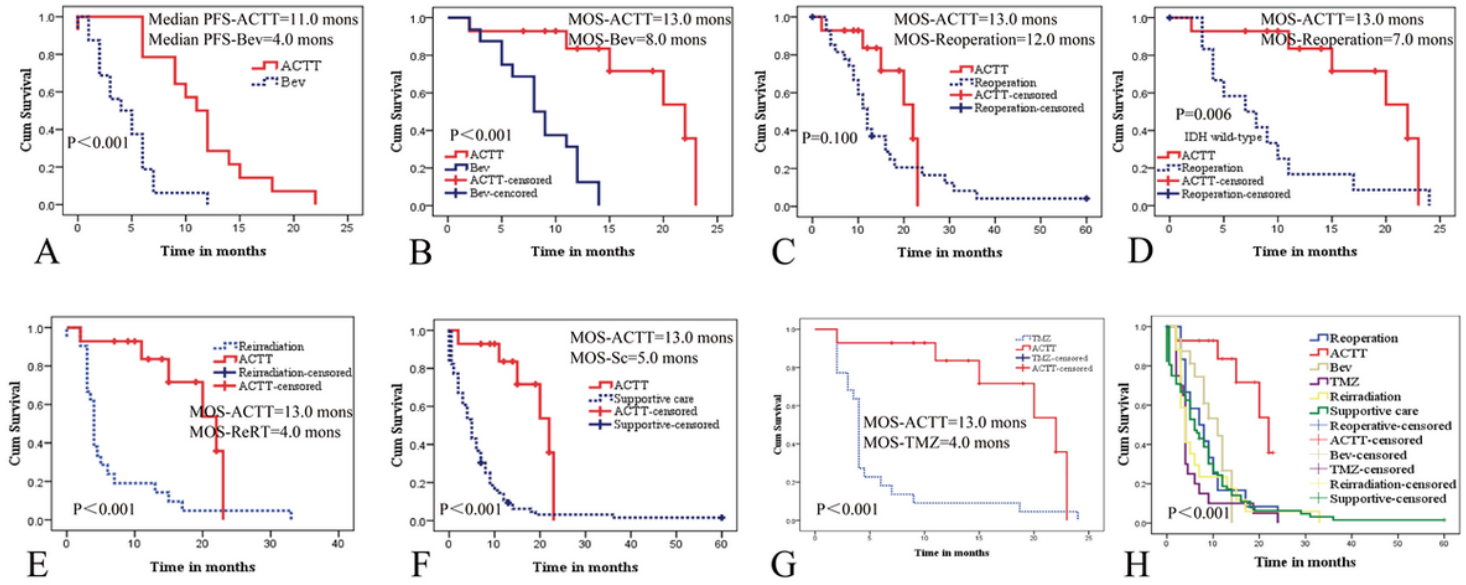

Figure 1

Kaplan–Meier survival curve of different treatment regimens of recurrent GBM. The patients treated with ACTT had better PFS and OS than bevacizumab monotherapy (A, B). The OS in between ACTT group and re-operation group (without considering IDH1 status) were similar (C), however, the IDH1-wt GBM patients treated with ACTT had better OS than that in re-operation group (D). The patients treated with ACTT had prolonged OS compared with reirradiation (E) and supportive care (F) and TMZ monotherapy (G). Representing ATG patients stratifed by treatment regimens (H).

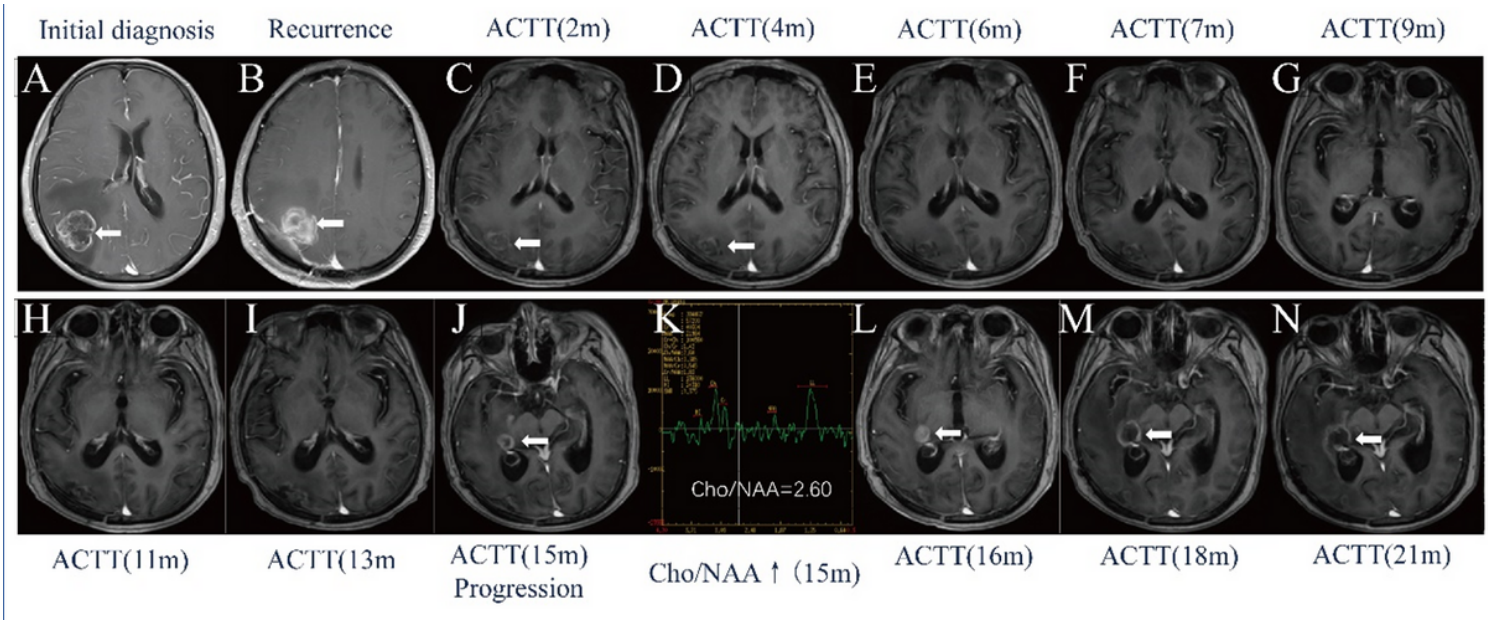

Figure 2

Brain MRI scan of patient no.9. A right parietal occipital lobe ring-enhanced lesion was presented on MRI (A). Tumor recurred 6 months after surgery (B). After 2 months of ACTT, the enhanced tumor shadow

disappeared on MRI (C). The MRI showed disease was stable at 4, 6, 7, 9, 11 and 13 months after ACTT treatment (D-I). The tumor progressed again after 15 months of ACTT treatment (J) and the ratio of Cho/NAA increased on MRS (K). After 16 (L), 18 (M) and 21 (N) months of ACTT treatment, the lesion gradually increased, while the patient remained symptom-free survival.

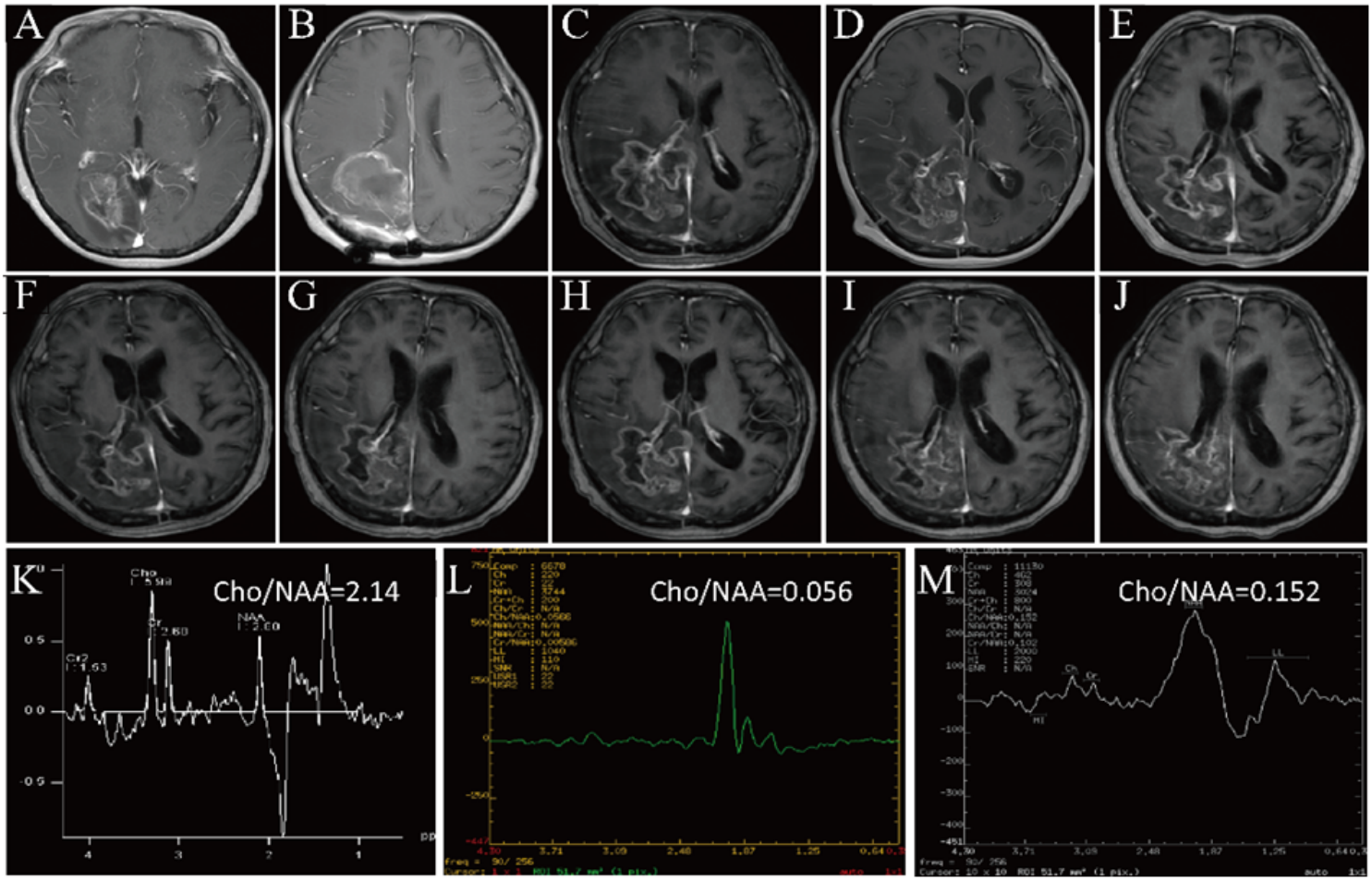

Figure 3

Brain MRI scan of patient no.5. A right parietal occipital lobe heterogeneous -enhanced lesion was observed on MRI (A). Tumor recurrence occurred in situ 4 months after surgery with the ratio of Cho/NAA increased on MRS (K). After 2 months of ACTT, the enhanced tumor shadow showed partial remission on MRI (C). MRI scan showed the disease was stable at 4, 6, 8, 10, 13, 15 and 18 months after ACTT treatment (D-J). Although the tumor lesion remained, a gradual decreasing in CHO/NAA ratio was observed on MRS (L, M).