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Original Article

Radiotherapy Plus Temozolomide With or Without Nimotuzumab Against the Newly Diagnosed EGFR-Positive Glioblastoma: A Retrospective Cohort Study

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Abstract

Background: Glioblastoma (GBM) has a poor prognosis, and patients with epidermal growth factor receptor (EGFR) amplification have an even worse prognosis. Nimotuzumab is an EGFR monoclonal antibody thought to play a significant role in the treatment of GBM. This paper presents a retrospective cohort study that evaluates the clinical efficacy and safety of nimotuzumab in GBM.

Materials and Methods: A total of 56 newly diagnosed patients with EGFR-positive GBM were included in our study. The patients were divided into radiotherapy (RT) + temozolomide (TMZ) + nimotuzumab (39 patients) and RT + TMZ (17 patients) groups based on whether or not nimotuzumab was added during RT. Progression-free survival (PFS), overall survival (OS), and toxicities were assessed.

Results: The median follow-up time was 27.9 months (95% confidence interval [CI], 25.1-30.8). The median PFS was 12.4 months (95% CI, 7.8-17.0) and 8.2 months (95% CI, 6.1-10.3) in the 2 groups, respectively, $P = .052$. The median OS was 27.3 months (95% CI, 19.0-35.6) and 16.7 months (95% CI, 11.1-22.2), respectively, $P = .018$. In patients with unmethylated O6-methylguanine-DNA methyltransferase (MGMT) promoter, the PFS and OS were significantly better in patients treated with nimotuzumab than in those without nimotuzumab (median PFS: 19.3 vs 6.7 months, $P = .001$; median OS: 20.2 vs 13.8 months, $P = .026$). During the treatment period, no statistically significant difference in toxicity was noted between the 2 groups.

Conclusion: Our retrospective cohort study suggests the efficacy of Nimotuzumab combined with concurrent RT with TMZ in patients with newly diagnosed EGFR-positive GBM, and specifically those with unmethylated MGMT promoter. Further prospective studies are warranted to validate our findings. Besides, nimotuzumab demonstrated good safety and tolerability.

Key words: glioblastoma; epidermal growth factor receptor; nimotuzumab; temozolomide; radiotherapy; survival.

Implications for Practice

This study recruited treatment-naïve patients with glioblastoma (GBM) with positive EGFR expression. Of note, this is arguably the first case-control study in China that targeted patients with EGFR-positive GBM. It was found that nimotuzumab combined with concurrent radiotherapy with temozolomide demonstrated efficacy in patients with newly diagnosed EGFR-positive GBM. The progression-free survival (PFS) and overall survival (OS) of patients in the group that used nimotuzumab were superior to those that did not use nimotuzumab. Multivariate analysis showed that the use of nimotuzumab is an independent prognostic factor for PFS and OS in patients with EGFR-positive GBM. Further analysis showed that nimotuzumab could further improve the survival rate of patients with unmethylated O6-methylguanine-DNA methyltransferase (MGMT) promoter. Nimotuzumab demonstrated good safety and tolerability. This may provide a clinical reference for the treatment of GBM.

Introduction

Glioblastoma (GBM) is the most prevalent primary brain tumor in adults, accounting for approximately 60%-70% of gliomas.[1] It is poorly differentiated, aggressive, highly malignant, and has a poor prognosis.[2,3] At present, its standard treatment includes the maximum extent resection under the premise of ensuring safety, concurrent chemoradiotherapy (CCRT) with temozolomide (TMZ), and adjuvant

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chemotherapy (AC) with TMZ. Nonetheless, these therapeutic approaches only prolong progression-free survival (PFS) to 6.9 months and overall survival (OS) to 14.6 months. Even with regular treatment, GBM with unmethylated O6-methylguanine-DNA methyltransferase (MGMT) promoter has a worse prognosis, with a PFS of only 5.3 months and an OS of only 12.7 months.[4] To enhance the survival of GBM, clinical studies of CCRT with TMZ combined with targeted therapy, immunotherapy, or other chemotherapeutic drugs have been actively implemented in China and abroad with most still in phase I and II research stages, and few studies demonstrated the positive results.[5-7] As such, it is necessary to identify novel treatments to further improve the outcome.

The epidermal growth factor receptor (EGFR) is expressed to varying degrees in more than 40% of gliomas. Activation of the EGFR pathway is linked to tumor angiogenesis, tumor invasion, and metastasis, as well as resistance to chemoradiotherapy.[8,9] Nimotuzumab is a humanized monoclonal antibody against EGFR that specifically binds to EGFR, hinders EGFR binding to its ligand, and finally impedes EGFR-mediated downstream signaling as well as suppresses tumor growth. Secondly, nimotuzumab mediates immune effects, including antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) that directly kill tumor cells. Furthermore, it forms a complex after binding to EGFR; this complex then enters the cell through endocytosis and is degraded to achieve the anti-tumor effect. Radioimmunoassay has proven that nimotuzumab would cross the blood-brain barrier.[10] Besides, it could improve the sensitivity of TMZ and radiotherapy (RT).[11,12] Therefore, scholars believe that nimotuzumab could improve OS in primary GBM theoretically. However, in clinical practice, there is little consensus on whether nimotuzumab improves the prognosis of primary GBM. A single-arm study in Shanghai Huashan Hospital enrolled 26 patients with GBM. All patients were subjected to CCRT and nimotuzumab. The PFS and OS were 10.0 and 15.9 months, respectively. Analysis showed that the PFS and OS were not correlated with EGFR expression. Nevertheless, the 12-month OS rate was better in EGFR-negative patients than that in EGFR-positive patients (90% vs. 53.8%, $P = .07$).[13] A German-based randomized controlled study revealed that the OS and PFS of patients in the nimotuzumab + CCRT group were superior to those of patients in the CCRT group. However, there was no statistically significant difference (22.3 vs. 19.6 months, $P = .4856$; 7.7 vs. 5.8 months $P = .7898$). Further analysis showed that the PFS and OS of patients with EGFR amplification treated with nimotuzumab are superior to those of patients without EGFR amplification (8.9 vs. 8.2 months, 21.2 vs. 17.2 months); besides, the 12-month PFS rate between the 2 groups was similar in patients without EGFR amplification.[14] A single-arm multicenter study in Sun Yat-sen University Cancer Center enrolled 36 patients with positive EGFR expression, and as a result, the PFS was 11.9 months and the OS was 24.5 months following the combined treatment with nimotuzumab. These findings are encouraging, however, the study had no control group and was a single-arm study.[15] Taken together, nimotuzumab maybe exerts more benefit to patients with EGFR-positive GBM. Moreover, in head and neck squamous cell carcinomas, such as nasopharyngeal carcinoma, EGFR positivity is a biomarker for nimotuzumab. GBM patients with EGFR amplification had a poorer prognosis.[16-18] Whether nimotuzumab improves survival in patients with EGFR-positive GBM remains unclear. The clinical efficacy and safety of nimotuzumab combined with concurrent irradiation and TMZ in newly diagnosed patients with EGFR-positive GBM were evaluated in this single-center retrospective cohort study from China; the study matched other known factors that may affect the prognosis of GBM.

Patients and Methods

Patient Characteristics

Data of 56 patients were retrospectively analyzed between March 2018 and November 2020 at the Xiangya Hospital of Central South University. The main inclusion criteria included: (1) newly diagnosed patients; (2) histological diagnosis of GBM; (3) immunohistochemical EGFR positive (more than 10% of tumor cells stained brownish-yellow were considered positive for EGFR expression.); (4) aged 18-70 years; (5) KPS score ≥60; (6) good blood routine, liver and kidney function; (7) all patients experienced surgery and CCRT; and (8) complete follow-up data. On the other hand, the exclusion criteria included: (1) EGFR negative; (2) previous craniocerebral RT; (3) combined with other malignant tumors or serious diseases; (4) missing reexamination data or follow-up data; and (5) patients could not tolerate combined therapy or refuse. Based on different treatment strategy patients were divided into RT + TMZ + nimotuzumab or RT + TMZ groups and matched the baseline data.

Treatment Methods

Surgical Stage

Surgical stage involves the removal of the tumor to the greatest extent under the premise of ensuring safety. Patients in both groups underwent tumor resection surgery. Based on the degree of surgical resection, surgery was divided into gross total resection (GTR) (degree of resection 100%) and subtotal resection (STR) (degree of resection 80%-90%).

CCRT Stage

In CCRT stage, patients in both groups received intensity-modulated radiotherapy (IMRT). On CT localization images, we determined and delineated the tumor target area (total tumor volume (GTV), clinical tumor volume (CTV), and planned tumor volume (PTV) as well as vital tissues and normal organs that need protection using preoperative and postoperative magnetic resonance imaging (MRI) as well as surgical records and surgeon suggestions according to the EORTC target delineation principle. Oncologists and radiologists identified residual GTV and tumor bed (GTVtb) as GTV under joint reading. The CTV was a margin of 2 cm from the GTV. The PTV was placed an additional 0.3 cm around the CTV. RT was 2.0 Gy/day, 5 days a week for 60 Gy for 6 weeks. Starting on the first day of RT, a dose of 75 mg/m^2/day of TMZ capsules was orally administered until the end of RT. Patients in the RT + TMZ + nimotuzumab arm received nimotuzumab weekly for 6 doses during RT. Nimotuzumab Injection 200 mg was diluted in 250 mL 0.9% sodium chloride solution, IVGTT, over 60 minutes.

AC Phase

In AC phase, TMZ regimen was administered 4 weeks of rest after RT. The dose of the first cycle was 150 mg/m^2/day for 5 consecutive days, with 23 days of rest, ie, 28 days as a course

of treatment. In the absence of grade 3 or 4 neutropenia or thrombocytopenia in the first cycle, the dose was 200 mg/m^2/day for 5 days with 23 days of rest, ie, 28 days as a course of treatment from the second cycle. There were 6 cycles of AC if no progression occurred.

Efficacy and Toxicities

MRI re-examinations were performed at an interval of every 2-3 months after CCRT until disease progression or death. Efficacy was assessed based on RANO criteria, which were divided into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). For the differential diagnosis of tumor recurrence, particularly for the presence of new lesions in the radiation field within 3 months after CCRT, the following factors were integrated for comprehensive determination: the extent of surgical resection, molecular pathology, time to recurrence, clinical symptoms, dynamic MRI T1-enhanced image changes, MRS, and PWI. If necessary, multidisciplinary discussion was held. Patients were evaluated for toxicity based on the Common Terminology Criteria for Adverse Events (CTCAE; version 5.0).

Statistical Analysis

The primary study endpoints were PFS and OS. PFS was defined as the time interval from diagnosis (date of surgery) to determination of tumor recurrence. OS was defined as the time interval from the start of diagnosis to death. The baseline data and adverse reaction data of patients were analyzed through the direct counting method; the measurement data were expressed by a median, and the χ^2 test was used for comparison. GraphPad Prism 8 (GraphPad Software, La Jolla, CA, USA) and SPSS 23.0 statistical software were used for all statistical analyses. OS was analyzed using Kaplan-Meier survival curves, and the difference in survival between the 2 groups was analyzed using the log-rank test; $P < .05$ was considered statistically significant. Cox proportional hazards model was used for multivariate analysis influencing PFS and OS.

Results

Patient Characteristics

A total of 56 newly diagnosed GBM patients in our hospital were enrolled between March 2018 and November 2020. EGFR immunohistochemistry revealed positive staining on the cell membrane of slices in all patients. In total, 39 patients were in the RT + TMZ + nimotuzumab group, including 28 males and 11 females with an average age of 52 years (range 22-69 years). KPS at treatment initiation was 70 (range 70-80). GTR was performed in 34 patients, STR in 5 patients, IDH wild-type in 38 patients, and IDH mutant in 1 patient; 14 patients showed methylation of the MGMT promoter, whereas 25 were unmethylated. Among the 17 patients in the RT + TMZ group, 12 were male and 5 were female with an average age of 58 years (range 33-71 years). KPS at treatment initiation was 70 (range 60-90). GTR was performed in 15 patients, STR in 2 patients, IDH wild-type in 16 patients, and IDH mutant in 1 patient; 4 patients showed MGMT promoter methylation, whereas 13 were unmethylated. No significant differences were noted in gender, age, degree of surgical resection, IDH status, or MGMT promoter status between the 2 groups ($P > .05$). Table 1 shows the comprehensive characteristics of GBM patients.

Efficacy and Survival

As of 21 February 2022, the follow-up period was 27.9 months (95% confidence interval [CI], 25.1-30.8). Among the 39 patients in the RT + TMZ + nimotuzumab group, 33

Table 1. Patient characteristics

Characteristics	With nituzumab ($n = 39$)	Without nituzumab ($n = 17$)	χ^2	*P*
Median age (year)				
≤50	15	4	1.178	.278
>50	24	13		
Sex				
Male	28	12	0.000	1.000
Female	11	5		
KPS at initial diagnosis				
>70	16	5	0.681	.409
≤70	23	12		
Extent of surgery				
GTR	34	15	0.000	1.000
STR	5	2		
MGMT methylation status				
Methylated	14	4	0.830	.362
Unmethylated	25	13		
IDH mutation status				
Mutated	1	1		.519
Wild type	38	16		

Abbreviations: KPS, Karnofsky performance status; GTR, gross total resection; STR, subtotal resection; MGMT, O6-methylguanine-DNA methyltransferase; IDH, isocitrate dehydrogenase; RT, radiotherapy.

(84.6%) yielded the complete response as the best based on the RANO criteria, 1 (2.6%) had partial response, 4 (10.3%) had stable disease, and 1 (2.6%) had progressive disease. During follow-up, 31 patients (79.5%) demonstrated progressive disease, including 23 in situ recurrences, 5 ectopic recurrences, and 3 both in situ and ectopic recurrences. A total of 21 (53.8%) patients died. The estimated PFS rate was 53.8% at first year, and 19.6% at second year. The estimated OS rate was 89.7% at the first year, and 54.1% at the second year. For patients in the RT + TMZ group, the best response as per the RANO assessment was complete response in 15 patients (88.2%), partial response in 1 patient (5.9%), and stable disease in 1 patient (5.9%). During follow-up, 16 patients (94.1%) displayed progressive disease, including 10 in situ recurrences, 3 ectopic recurrences, and 3 both in situ and ectopic recurrences; 13 (76.5%) patients succumbed. The estimated PFS rate was 23.5% at the first year and 11.8% at the second year. The estimated OS rate was 70.6% at the first year, and 20.2% at the second year. The median PFS was 12.4 months (95% CI, 7.8-17.0) and 8.2 months (95% CI, 6.1-10.3) in the 2 groups, respectively, $P = .052$. The median OS was 27.3 months (95% CI, 19.0-35.6) and 16.7 months (95% CI, 11.1-22.2) in the 2 groups, respectively, $P = .018$ (Figs. 1-2). Fig. 3 shows the MRI changes in the patient.

Univariate analysis of known clinical prognostic factors showed that patients with GTR of the tumor at the time of surgery had a better PFS than those with STR ($P < .001$). Notably, MGMT promoter methylation improved PFS and OS ($P = .002$; $P = .028$). In addition, the use of nimotuzumab improved PFS and OS ($P = .052$; $P = .018$). Multivariate analyses were performed for PFS and OS to adjust all factors listed in Table 2. GTR was identified as an independent prognostic factor for PFS ($P < .001$). Also, MGMT promoters methylation and the use of nimotuzumab were considered independent prognostic factors for PFS and OS ($P = .003$, $P = .016$; $P = .027$, $P = .008$).

Analysis of MGMT promoter methylation status in the 2 groups revealed that 14 patients in the nimotuzumab + and methylated groups experienced a median PFS of 17.6 months (95% CI, 15.8-19.5) as well as a median OS of 28.9 months (95% CI, 26.7-31.1). The 25 patients in the nimotuzumab + and unmethylated groups had a median PFS of 10.3 months (95% CI, 6.1-14.5) and a median OS of 21.3 months (95% CI, 17.9—24.7). The 4 patients in the nimotuzumab- and methylated groups had a median PFS of 19.3 months (95% CI, 8.5-30.1) and a median OS of 20.2 months. The 13 patients in the nimotuzumab- and unmethylated groups had a median PFS of 6.7 months (95% CI, 4.4-9.0) and a median OS of 13.8 months (95% CI, 10.2-17.5). In the group without nimotuzumab, patients with methylated MGMT promoter had significantly better PFS and OS than those with unmethylated MGMT promoters ($P = .001$; $P = .026$). Nevertheless, in the group using nimotuzumab, no significant difference in PFS and OS was found between patients with and without MGMT promoter methylation ($P = .077$; $P = .278$). The comparison of patients with MGMT promoter methylation showed no significant difference in PFS and OS between patients with and without nimotuzumab ($P = .772$; $P = .779$). In patients with unmethylated MGMT promoter, PFS and OS were significantly better with nimotuzumab than in those without nimotuzumab ($P = .001$; $P = .001$) (Fig. 4).

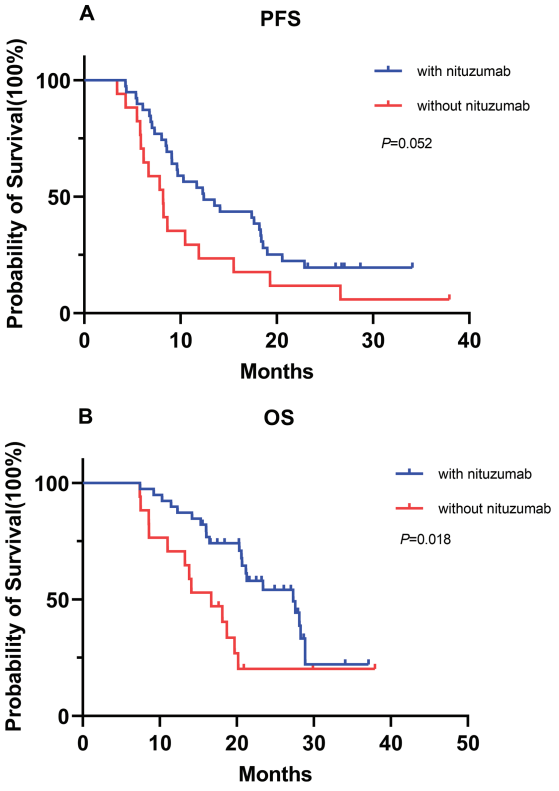

Figure 1. Progression-free survival (PFS) (**A**) and overall survival (OS) (**B**) of glioblastomas in 2 groups.

Adverse Events

During the treatment period, no statistically significant difference in toxicity was detected between the 2 groups. Nimotuzumab combined with standard TMZ + RT was safe and well-tolerated by patients. No grade 3 or higher toxicities were detected. Table 3 summarizes toxicity data for all patients. The most frequent toxicities during treatment were hematotoxicities, such as grades 1-2 neutropenia and grades 1-2 thrombocytopenia. The remainder also had vomiting, constipation, fatigue, dizziness, and increased liver transaminase. After symptomatic treatment, the above toxicities were improved. Four patients developed a rash, which was associated with nimotuzumab. After the first treatment with nimotuzumab, the body temperature of one patient was 39.1 °C; this was considered an infusion reaction which was completely alleviated after symptomatic treatment.

Discussion

Patients with GBM have a poor prognosis despite the successful application of surgery and standard chemoradiotherapy.[19] Gene amplification and protein overexpression of EGFR has been detected in several GBM patients.[20-22] Activation of EGFR signaling causes uncontrolled tumor proliferation. However, targeted therapy against EGFR amplification has emerged as one of the therapeutic options for gliomas. Notably, nimotuzumab is a humanized monoclonal antibody that detects the extracellular domain of EGFR and competitively binds to EGFR, thereby inhibiting signaling pathways. Reports have shown that the distribution of nimotuzumab is tumor-specific.[23] Also, previous preclinical studies indicate that nimotuzumab improves radiosensitivity and chemosensitivity of

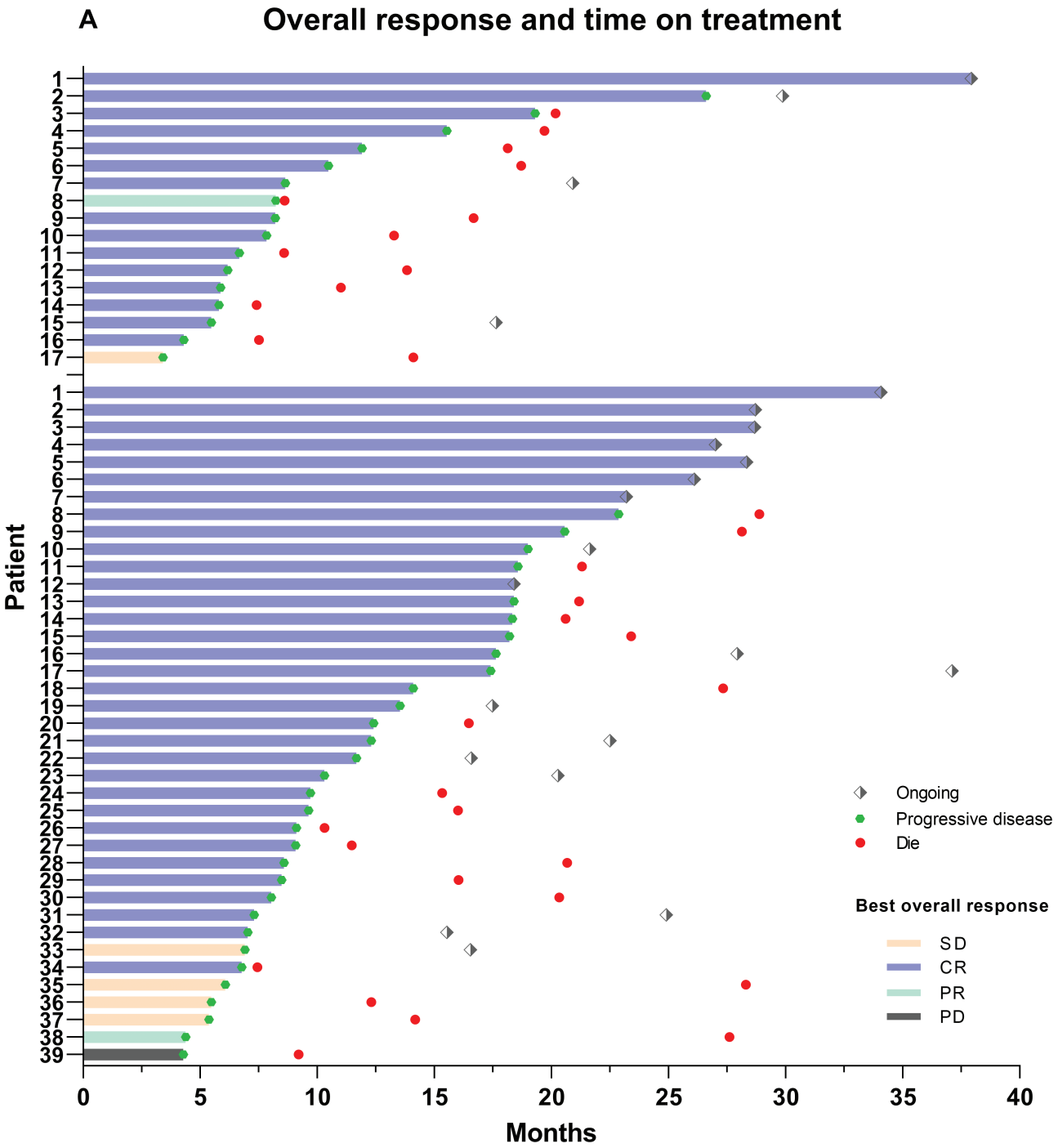

Figure 2. Follow-up of glioblastomas in 2 groups.

brain tumors that overexpress EGFR.[11,12,24] Nevertheless, its efficacy combined with CCRT against GBM remains controversial, yet researchers have unanimously affirmed the high safety and tolerability of this combinational therapy.[13,15]

Studies suggest that GBM patients with EGFR amplification have a worse prognosis.[25] Those with positive EGFR expression could benefit from nimotuzumab treatment.[26,27] Thus, our study recruited treatment-naïve GBM patients with positive EGFR expression. Of note, this is arguably the first cohort study in China that targets patients with EGFR-positive GBM. In total, we enrolled 56 patients for analysis. By February 2022, the PFS and OS of patients in the group that used nimotuzumab were superior to those that did not use nimotuzumab (12.4 vs. 8.2 months, $P = .052$; 27.3 vs. 16.7 months, $P = .018$). Through multivariate analysis, we identified that the use of nimotuzumab is an independent prognostic factor for PFS and OS in patients with EGFR-positive GBM ($P = .027$ and .008, respectively). Notably, the prognosis of patients with EGFR-positive GBM treated with the combination of nimotuzumab in our study exceeds that of all previous studies. A study by Du enrolled 36 patients with EGFR-positive GBM. All patients received TMZ and nimotuzumab based on postoperative RT. Their PFS was 11.9 months (95% CI, 5.5-18.2) and OS was 24.5 months (95%

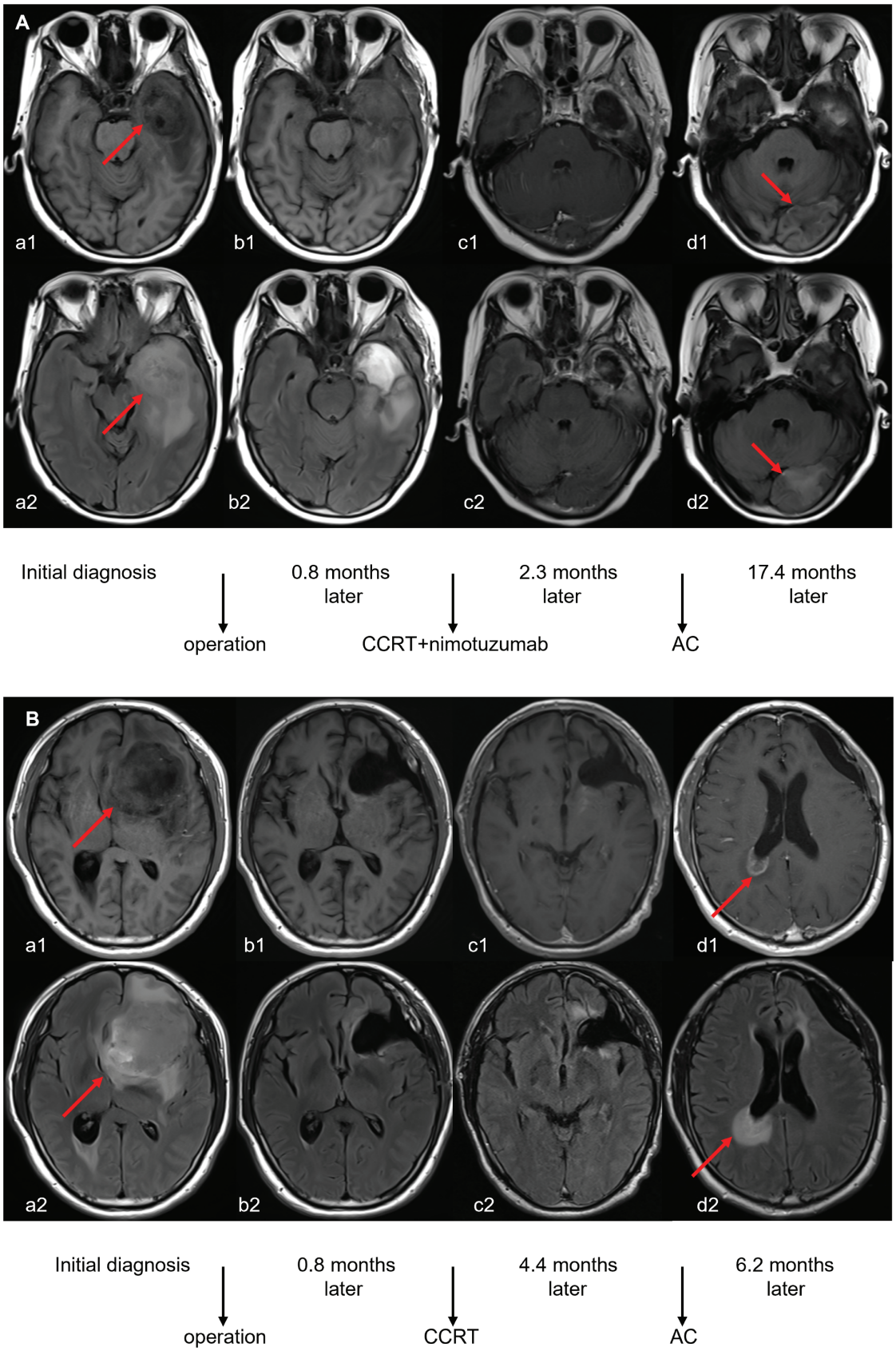

Figure 3. Magnetic resonance imaging (MRI) changes of glioblastoma (GBM) treated with nimotuzumab (**A**). MRI changes of GBM treated without nimotuzumab (**B**). Figures a-d represent pre-operation, post-operation, post-radiotherapy, and recurrence, respectively. (a1-d1) T1 enhanced MRI; (a2-d2) T2 fluid enhanced MRI. The arrow indicates the tumor area.

Table 2. Univariate and multivariate analyses for PFS and OS.

Variable	PFS			OS		
	Univariate analysis	Multivariate analysis		Univariate analysis	Multivariate analysis	
	P value (log-rank)	Hazard ratio (95% CI)	*P* value	*P* value (log-rank)	Hazard ratio (95% CI)	*P* value
Age, years: ≤50 vs. >50	.851			.976		
Sex: male vs. female	.152			.154		
KPS: >70 vs. ≤70	.320			.519		
Extent of surgery: GTR vs. STR	**<.001**	0.165 (0.064-0.427)	**<.001**	.133		
MGMT: meth vs. unmeth	**.002**	0.337 (0.164-0.692)	**.003**	**.028**	0.364 (0.161-0.826)	**.016**
Nituzumab: with vs. without	.052	0.478 (0.248-0.918)	**.027**	**.018**	0.374 (0.180-0.777)	**.008**

Abbreviations: PFS, progression-free survival; OS, overall survival; KPS, Karnofsky performance status; GTR, gross total resection; STR, subtotal resection; MGMT, O6-methylguanine-DNA methyltransferase; 95% CI, 95% confidence interval.

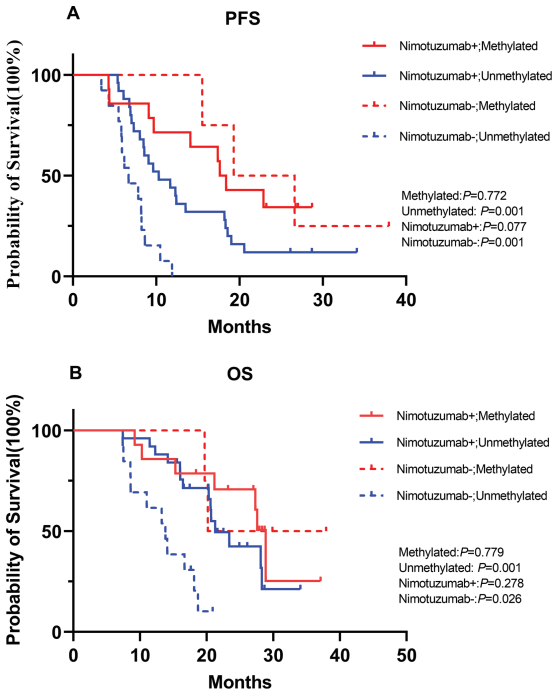

Figure 4. Progression-free survival (PFS) (**A**) and overall survival (OS) (**B**) of glioblastomas in 4 groups.

CI, 15.7-33.3).[15] The survival of patients in our study with the addition of nimotuzumab was slightly better than that of those in Du research; this may be attributed to the increased rate of GTR in our patients, which reached 87.2% compared to only 41.7% in Du research. Because many studies have shown that GTR can improve GBM prognosis. According to Wang et al, all GBM patients were treated with nimotuzumab, and in 50.0% (13/26) of EGFR-positive patients, PFS was 11 months and OS was only 13 months.[13] Among them, the GTR rate was only 34.6%, and no pathological molecular markers influencing prognosis, including MGMT promoter methylation status and IDH mutation status were mentioned in the text. Westphal et al enrolled 20 patients with EGFR amplification and administered them with nimotuzumab; they found superior PFS and OS of 8.9 and 21.2 months, respectively, compared to that in patients without EGFR amplification.[14] This was also lower than that in our study. However, they did not provide comprehensive baseline data in the analysis of EGFR amplification, hence it was difficult to analyze the reason for the difference between our study and the results of this study. Furthermore, the choice of salvage treatment after relapse also influenced OS.

Du et al enrolled 36 patients with EGFR-positive GBM and treated them with nimotuzumab. Based on the analysis of MGMT promoter methylation status, no significant difference in OS (24.5 vs. 22.9 months, $P = .527$) and PFS (9.1 vs. 11.9 months, $P = .752$) was found between methylated and unmethylated patients.[15] Westphal reported that patients with unmethylated MGMT promoter had a 4-month improvement in OS after treatment with nimotuzumab: 19.5 months (95% CI, 14.7-25.6) in the experimental group vs. 15.5 months (95% CI, 13.8-24.0) in the control group, $P = .4578$. However, the authors concluded that nimotuzumab demonstrated a clear trend of efficacy and excellent safety in patients with MGMT promoter unmethylated glioblastoma.[14] Our findings are similar to that of Westphal. Patients with unmethylated MGMT promoters were analyzed based on the application of nimotuzumab. Consequently, we found that patients who used nimotuzumab had significantly better PFS and OS than those who did not use nimotuzumab (10.3 vs. 6.7 months, $P = .001$; 21.3 vs. 13.8, $P = .001$). At the same time, a Chi-square test was performed for baseline data in these 2 groups, and no differences were noted in age, gender, KPS score, degree of tumor resection, or IDH mutation status. Thus, we believe that the combination of nimotuzumab + RT + TMZ has an advantage over RT + TMZ in patients with unmethylated MGMT promoters.

Many previous studies indicate that MGMT promoter methylation is a good prognostic factor in glioblastoma.[28,29] Here, both univariate and multivariate analyses revealed that MGMT promoter methylation could significantly influence PFS and OS. In the group without nimotuzumab, patients with methylated MGMT promoter had significantly better PFS and OS than those with unmethylated MGMT promoter (19.3 vs. 6.7 months, $P = .001$; 20.2 vs. 13.8 months, $P = .026$). This is also consistent with the findings of previous studies. Nevertheless, in the group that was administered with nimotuzumab, we found no significant difference in PFS and OS between MGMT methylated and unmethylated patients (median PFS: 17.6 vs. 10.3 months, $P = .077$; median OS: 28.9 vs. 21.3 months, $P = .278$). This may be attributed to the fact that nimotuzumab significantly improves the survival of patients with unmethylated MGMT promoters, hence the difference between patients

Table 3. Analysis of adverse events.

Adverse events	With nituzumab (n = 39)	Without nituzumab (n = 17)	χ^2	P
	Grades 1-2 (n, %)	Grades 1-2 (n, %)		
Leukopenia	20(51.3)	8(47.1)	0.084	.771
Neutropenia	13(33.3)	5(29.4)	0.083	.773
Thrombocytopenia	9(23.1)	4(23.5)	0.000	1.000
Fever	1(2.6)	0(0)		1.000
Dizziness	1(2.6)	0(0)		1.000
Vomiting	4(10.3)	5(29.4)	1.957	.162
Rash	4(10.3)	0(0)	0.650	.420
Fatigue	2(5.1)	0(0)	0.044	.834
Constipation	2(5.1)	0(0)	0.044	.834
ALT/AST elevation	1(2.6)	1(5.9)	0.000	1.000

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

with methylated and unmethylated MGMT promoters was reduced.

Furthermore, research indicates that the extent of resection is an important prognostic factor in GBM, with GTR having a better prognosis than biopsy or STR.[30-32] Both univariate and multivariate analyses showed that GTR is an independent prognostic factor for PFS ($P < .001$; $P < .001$). Nonetheless, GTR did not show a significant advantage in OS. This could be associated with the aggressive treatment of our patient after recurrence. Moreover, only 7 patients in our study were STR, and the small sample size can potentially introduce bias in the results. Therefore, our findings require further validation by subsequent studies with large samples.

No difference in toxicity was noted between patients who took nimotuzumab and those who did not. After the combination of nimotuzumab and chemoradiotherapy, the treatment-related AEs were small, and mostly grades I-II, there was no grade III or higher adverse reactions. This is because nimotuzumab binds more to tumor cells with high EGFR expression, whereas EGFR expression levels are low in normal tissues, hence fewer adverse effects.

Of course, our study also has certain limitations. Our study was a retrospective study with a small sample size. The determination of EGFR positivity in this study was based on immunohistochemical analysis and could not distinguish between mutations and amplifications. In the future, we need to consider these factors comprehensively, expand the sample size, and conduct prospective randomized controlled studies to verify these preliminary survival results.

Conclusion

According to this single-center, retrospective, cohort study in China, nimotuzumab combined with CCRT displayed superior efficacy in patients with newly diagnosed EGFR-positive GBM, particularly those with unmethylated MGMT promoter. And this combination therapy is safe and tolerable. However, a larger sample size and prospective randomized controlled studies are necessary to validate these preliminary survival results.

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Conflict of Interest

The authors indicated no financial relationships.

Author Contributions

Conception/design: C.L., L.S., X.G. Collection and/or assembly of data: C.L., L.S., X.G., L.S. Data analysis and interpretation: L.S., L.S. Manuscript writing: L.S., X.G. Final approval of manuscript: C.L.

Data Availability

The data underlying this article are not publicly available due to privacy. The data will be shared on reasonable request to the corresponding author.

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