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Survival analysis of patients with glioblastoma treated by long-term administration of temozolomide

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Abstract

This analysis aimed to investigate whether the long-term administration of temozolomide (TMZ) claimed a survival advantage for patients with glioblastoma in China.

A total of 75 patients with newly diagnosed glioblastoma at the Department of Radiation Oncology, Shenzhen People's Hospital between August 2008 and August 2016 were retrospectively evaluated during analysis. A propensity-matched analysis was performed to balance the basic characteristics of patients between compared groups. Kaplan–Meier method and Cox proportional hazards model were used to assess progression-free survival (PFS) and overall survival (OS) of patients receiving 6 adjuvant TMZ cycles compared with patients treated with more than 6 cycles.

Twenty of 75 patients received more than 6 cycles of TMZ, and the other 55 patients were treated with a median of 6 cycles ranging from 1 to 6. The patients with long-term administration of TMZ had better OS (47.0 months, 95% CI 20.0–73.9 vs 20.6 months, 95% CI 17.9–23.2, $P = .014$) but not PFS (17.0 months, 95% CI 10.1–24.5 vs 14.2 months, 95% CI 11.8–16.6, $P = .133$). Balancing the clinical factors with a propensity-matched analysis also showed the significant advantage of prolonged TMZ application in terms of OS but not PFS.

Prolonged administration of TMZ beyond 6 cycles did demonstrate survival benefits for patients with initially diagnosed glioblastoma.

Abbreviations: GTR = gross total resection, MGMT = methylguanine methyltransferase, OS = overall survival, PFS = progression-free survival, STR = subtotal resection, TMZ = temozolomide.

Keywords: glioblastoma, long-term administration, overall survival, progression-free survival, temozolomide

1. Introduction

Glioblastoma is the most common and aggressive form of primary brain tumors with a median survival of fewer than 2 years.[1–3] According to the Central Brain Tumor Registry of the United States Statistical Report, glioma accounts for about 27% of all tumors in the central nervous system and 80% of malignant tumors. Among the primary malignant tumors of the central nervous system, the incidence of glioblastoma is 3.20 per 100,000 populations uppermost, followed by the diffuse astrocytoma with the incidence of 0.53 per 100,000 populations. The incidence increases with age, among the predilection age ranging 75 to 84 years and the median age of 64 years.[4] The incidence of glioblastoma in the People's Republic of China is 1 to 4 per 100,000 populations.[5] The safe and feasible extent of resection followed by radiotherapy with concomitant and adjuvant temozolomide (TMZ, 6 cycles) is the landmark treatment protocol for the ones with newly diagnosed glioblastoma.[1,3]

TMZ converts to the active metabolite 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide by nonenzymatic chemical conversion, which causes cell cycle arrest and ultimately cell death by breaking the DNA double strands.[6,7] TMZ is well tolerated even in elderly patients with glioblastoma.[8] The fatality rate is less than 10% due to toxicity.[3,8] The common toxicities include mild hematotoxicity, fatigue, and nausea.

The mainstay of TMZ in glioblastoma has been consistently admitted, and 6 cycles of adjuvant TMZ is pervasive treatment. However, the most suitable cycles of TMZ still remain controversial. Some retrospective studies and a meta-analysis conferred the prolonged progression-free survival (PFS) and overall survival (OS) of patients with glioblastoma treated with long-term administration of more than 6 cycles of TMZ.[9–14] The OS of patients receiving fewer than 7 cycles of TMZ ranging from 8 to 20 months compared with that of patients receiving at least 7 cycles ranging from 21 to 30 months, while PFS ranged from 4 to 18 months compared with 17 to 28 months, respectively, in the aforementioned 2 groups.[9,14] However,

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some other studies queried the improvement in extended adjuvant TMZ in glioblastoma.[15,16] They considered that neither OS nor PFS of patients with newly diagnosed glioblastoma was superior, albeit they received more than 6 cycles of TMZ. Moreover, a secondary analysis of EORTC and NRG Oncology/RTOG deemed that the number of TMZ cycles contributed to somewhat improved PFS but not OS.[17,18]

In the United States, patients commonly receive up to 12 or even more cycles of maintenance TMZ following chemoradiation, but the role of extending TMZ use is still controversial.[19] It is worth mentioning that the extended administration of TMZ has been universally accepted as safe and feasible.[18] In China, glioma occurs at a younger age with a median age less than 50 years according to the large sample analysis, and the treatment of TMZ in glioblastoma is not standardized.[20,21]

Therefore, this analysis was performed to investigate whether the long-term administration of TMZ claimed a survival advantage for patients with glioblastoma in China.

2. Patients and methods

2.1. Patients

This is a retrospective study and the ethical approval was not necessary. Patients firstly diagnosed with World Health Organization grade IV glioblastoma[22] between August 1, 2008, and August 1, 2016, were selected. Only patients initially diagnosed with glioblastoma received radiation and without other kinds of malignant tumors were eligible. All patients were followed up telephonically until they died or lost to follow-up, or till August 1, 2018. The characteristics of these patients were reviewed from the records in Shenzhen People's Hospital. All patients received intracranial surgery. The extent of resection was determined by the magnetic resonance imaging (MRI) scans after the surgery and operation records. The conventional, fractionated, and conformal radiations at a daily dose of 2 Gy mostly began within 6 weeks after surgery. Treatment was carried out 5 days a week within 6 weeks to a total dose of 60 Gy with concomitant TMZ [patients received a daily dose of 75 mg/(m^2 day) for 7 days a week in the entire duration of radiotherapy]. After 1 month's interval from the end of concomitant TMZ, the patients began adjuvant TMZ of the standard regimen [150–200 mg/(m^2 day) for 5 consecutive days in each 28-day cycle] until disease progression or were unwilling to continued chemotherapy. The patients received TMZ at a starting dose of 150 mg/m^2 for 5 consecutive days of a 28-day cycle, and TMZ was increased for subsequent cycles to 200 mg/m^2 if no unacceptable treatment-related adverse events were noted. The dose, schedule, and maintenance cycles of TMZ in patients with glioblastoma were ensured from the records and their prescribing physicians. Response was evaluated by computed tomography or MRI using the standardized McDonald criteria. The patients were identified into 2 groups according to their cycles of adjuvant of TMZ.

2.2. Statistical analysis

This study aimed to evaluate the OS and PFS of patients in the 2 groups. A propensity-matched analysis was performed between the groups to balance the 4 known independent prognostic factors listed in Table 1. To balance selection biases and other confounding items, we used 1:1 matching on propensity scores and logistic regression and nearest neighbor algorithm within caliper width of 0.01. The absolute standardized differences were used to assess the imbalance of each of the variables. Briefly, the software automatically calculated the propensity score of each value and completed the matching by logistic regression analysis between 2 groups.[23–26] The Student *t* test and normality test were performed to evaluate quantitative variables. The chi-square and Fisher exact tests were performed for analyzing nominal variables. All statistical tests were 2 tailed. OS was calculated from the surgery date to death or loss of follow-up. PFS was defined from the day of surgery to progression, death, or

Table 1

Characteristics of patients.

	Before matching			After matching		
	Group A (n=55)	Group B (n=20)	*P* value	Group A (n=20)	Group B (n=20)	*P* value
Age (yr)						
Median (range)	47 (18–70)	45 (29–66)	0.279	49 (23–68)	45 (29–66)	.211
Age, *n* (%)			0.143			.102
<50 yr	31 (56.4)	15 (75.0)		10 (50.0)	15 (75.0)	
≥50 yr	24 (43.6)	5 (25.0)		10 (50.0)	5 (25.0)	
Gender, *n* (%)			0.834			1.000
Female	26 (47.3)	10 (50.0)		10 (50.0)	10 (50.0)	
Male	29 (52.7)	10 (50.0)		10 (50.0)	10 (50.0)	
Type of surgery, *n* (%)			0.600			.429
GTR	43 (80.0)	17 (85.0)		15 (75.0)	17 (85.0)	
STR	11 (20.0)	3 (15.0)		5 (25.0)	3 (15.0)	
Unknown	1	–		–	–	
MGMT status, *n* (%)			0.001			.558
Methylated	5 (9.1)	8 (40.0)		5 (25.0)	8 (40.0)	
Unmethylated	17 (30.9)	8 (40.0)		11 (55.0)	8 (40.0)	
Unknown	33 (60.0)	4 (20.0)		4 (20.0)	4 (20.0)	
TMZ cycles, *n* (%)						
Median (range)	6 (1–6)	12 (7–30)	0.000	6 (1–6)	12 (7–30)	.000
Interval time						
	4.4 (1–10)	3.8 (1.1–8.9)	0.468	3.9 (1–10)	3.8 (1.1–8.9)	.986

GTR = gross total resection, interval time = the time between postoperation and radiation, MGMT = methylguanine methyltransferase, STR = subtotal resection, TMZ = temozolomide.

deadline of follow-up. OS and PFS curves were depicted by the Kaplan–Meier method. Univariate and multivariable analyses were compared using the log-rank test and Cox proportional hazards model. A value of $P < .05$ was defined as statistically significant. All statistical analyses were performed with SPSS Statistics version 22.0 (IBM, NY).

3. Results

3.1. Patient characteristics

Altogether 75 patients with initially diagnosed glioblastoma were identified. Their characteristics are summarized in Table 1. The patients were divided into 2 groups according to different cycles of TMZ: fewer than 7 cycles (group A = TMZ for less than or equal to 6 cycles, $n = 55$) and beyond 6 cycles (group B = TMZ more than 6 cycles, $n = 20$). The median age was 47 years (range 18–70) and 45 years (range 29–66), respectively ($P = .279$). Table 1 shows that both groups were balanced for age ($P = .143$), sex ($P = .834$), type of surgery ($P = .600$), but not methylguanine methyltransferase (MGMT) status ($P = .001$). After matching by propensity analysis, the MGMT promoter methylation status of tumor was balanced ($P = .558$). In the case of more than 6 cycles of TMZ, patients received median TMZ cycles of 12 (range 7–30). In the case of 6 cycles of TMZ, 43 patients (78.2%) experienced gross total resection; 15 patients (85.0%) received more than 6 cycles of TMZ.

3.2. OS and PFS

The last time of follow-up was on August 1, 2018. Forty-three patients (78.2%) demised and 47 patients (85.5%) relapsed in group A. Ten patients (50.0%) demised and 15 patients (75.0%) relapsed in group B. The median OS was 22.0 months (95% CI 18.8–25.2), and the median PFS was 14.8 months (95% CI 11.5–18.1) in the overall population. The median OS was 20.6 months (95% CI 17.9–23.2) in group A compared with 47.0 months (95% CI 20.0–24.5) in group B ($P = .014$). The median PFS was 14.2 months (95% CI 11.8–16.6) in group A compared with 17.0 months (95% CI 10.1–24.5) in group B ($P = .133$). After propensity analysis, the median OS was 20.0 months ($P = .024$) and the median PFS was 13.0 months ($P = .086$) in groups A and B. These data demonstrated that the superior OS derived from the different therapy rather than the number of people (Fig. 1).

Univariate analysis was performed to evaluate the clinical factors including age, sex, type of surgery, MGMT status, and TMZ cycles. The model identified the MGMT promoter methylation status, and the number of TMZ cycles was associated with OS (Table 2). The prolonged number of TMZ cycles was a positive factor for OS (HR = 0.43, 95% CI 0.22–0.86, $P = .017$). The MGMT unmethylated status was a significant risk factor for disease progression and OS (HR = 2.84, 95% CI 1.30–6.20, $P = .009$ and HR = 4.65, 95% CI 1.57–13.76, $P = .005$, respectively). The prolonged cycles of TMZ, whether before or after matching, were favorable factors for OS but not PFS (Table 2). In particular, the multivariate analysis also supported that the methylation of MGMT status (HR = 4.17, 95% CI 1.34–12.90, $P = .014$) improved the OS of patients. The multivariate analysis revealed that extended TMZ treatment for more than 6 cycles (HR = 0.67, 95% CI 0.32–1.39, $P = .277$) might not be an independent factor associated with survival when adjusted for known prognostic factors in glioblastoma (age, sex, MGMT promoter methylated, and type of surgery).

4. Discussion

The number of adjuvant TMZ cycles in patients with glioblastoma was generally recognized as 6, followed by RT/TMZ–TMZ treatment since 2005.[1] Some researches attempted to improve the benefits by prolonging the adjuvant TMZ cycles or using dose-dense TMZ therapy.[2,27] Although the role of prolonging the adjuvant TMZ cycles still remains controversial, it has become a common practice not only in the United States but also in China, especially among the population well tolerant to TMZ.

In the present study, 75 Chinese patients diagnosed with glioblastoma who received adjuvant TMZ therapy were identified. Patient characteristics in both groups were well balanced (Table 1). The patients receiving more than 6 cycles of TMZ seemed to be superior survivors with median OS reaching to 47.0 months (95% CI 20.0–24.5, $P = .014$). The prolonged OS was worth noting. Gloria B[11] also supported that patients in whom adjuvant chemotherapy was stopped at cycle 6 experienced a median survival of 16.5 months, whereas, those who received more than 6 cycles survived for 24.6 months ($P = .031$). Extended adjuvant therapy was not associated with increased toxicity. Prolonged administration of TMZ after radio-chemotherapy in patients with GBM was feasible and seemed to be well-tolerated. There is a growing number of data, including the present study, which suggests a benefit of this strategy on PFS and OS.[12,14] The extended TMZ treatment failed to show the survival improvement in multivariate analyses may associate the limit object and observe time.

The univariate and multivariate analyses of PFS and OS showed that MGMT promoter methylation was a strong and predictive biomarker when patients diagnosed with glioblastoma received TMZ treatment. In patients with a methylated MGMT promoter status, the prolonged administration of TMZ was associated with increasing PFS and OS (Tables 2 and 3). This was similar to the preliminary analysis.[15,16] Though the present study did not demonstrate that the PFS of patients in group B was superior to that of in group A, which was contrary to other studies.[17,18] We had observed an interesting thing some patients obtained survival benefit from prolonged TMZ treatment even they suffered from progression during the treatment. Maybe this could help to understand the OS improvement. The superior OS might be also due to the median age of participants in this study, who were younger than those in Gramatzki's study.[15] Valduvieco demonstrated the impact of delay in initiation of RT on the survival of patients with glioblastoma, indicating that the initiation of radiation therapy within 6 weeks after surgery was a favorable and independent prognostic factor for survival.[28] Most of the patients in this study received radiation therapy within 6 weeks after the surgery. However, the proportion of MGMT status was significantly lower than that in Gramatzki's study, which was 40.0% vs 56.7%, leading to inferior PFS.

Nowadays the effect of extended maintenance of TMZ varies. Some studies hypothesize that the extended treatment of TMZ may confer resistance to tumor cells and be detrimental. Prolonged exposure to TMZ therapy results in mutational changes, which may portend resistance to oral alkylating medicine and aggravate the cumulative toxicities, whereas no obvious mechanism of resistance was identified in glioblastoma cells.[29,30] Hence, the potential possibility that prolonged administration of TMZ accelerated the development of alkylating drug resistance and generated counterproductive result was

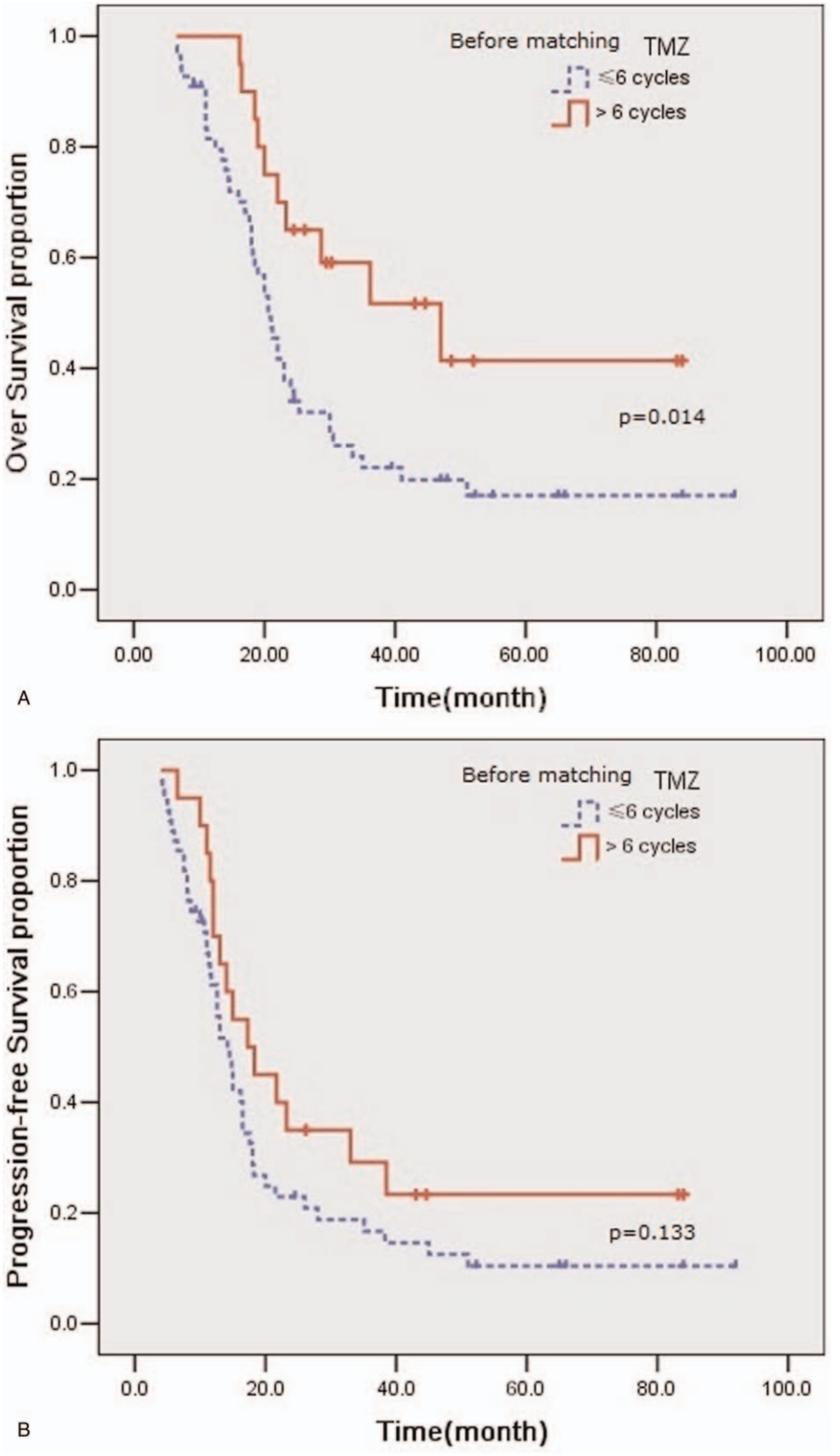

Figure 1. Association of TMZ exposure with the outcome. Overall survival and progression-free survival in patients with initially diagnosed glioblastoma by the number of TMZ cycles (A and B) Before matching: ≤6 cycles ($n=55$) and >6 cycles ($n=20$). (C and D) After matching: ≤6 cycles ($n=20$) and >6 cycles ($n=20$). TMZ = temozolomide.

Table 2

Univariate analysis of PFS and OS in 75 patients.

		PFS		OS	
	No.	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Before matching					
Age (yr)					
<50	46	1		1	
≥50	29	1.41 (0.85–2.37)	.184	1.44 (0.83–2.48)	.190
Gender					
Female	36	1		1	
Male	39	1.20 (0.73–1.99)	.474	1.140 (0.67–1.96)	.629
Type of surgery					
GTR	60	1		1	
STR	14	1.49 (0.78–2.84)	.228	1.49 (0.78–2.84)	.228
Unknown	1	–	–	–	–
MGMT status					
Methylated	13	1		1	
Unmethylated	25	2.84 (1.30–6.20)	.009	4.65 (1.57–13.76)	.005
Unknown	37	1.89 (0.89–3.99)	.096	4.36 (1.53–12.41)	.006
Number of TMZ					
≤6 cycles	55	1			
>6 cycles	20	0.64 (0.36–1.15)	.139	0.43 (0.22–0.86)	.017
After matching					
Number of TMZ					
≤6 cycles	20	1			
>6 cycles	20	0.55 (0.28–1.11)	.094	0.42 (0.19–0.92)	.031

GTR = gross total resection, MGMT = methylguanine methyltransferase, OS = overall survival, PFS = progression-free survival, STR = subtotal resection, TMZ = temozolomide.

inconclusive but the patients benefited from treatment was obvious. Parallelly, recent studies had showed that maintenance chemotherapy with pemetrexed chemotherapy or maintenance treatment with fluoropyrimidine plus bevacizumab after first-line therapy demonstrated prolonged survival advantages only in patients with non-small cell lung cancer and those with metastatic colorectal cancer.[31–33] Furthermore, a phase II rescue study suggested that conventional adjuvant TMZ doses or a treatment-free interval might benefit from salvage TMZ therapy.[34]

Since this was a retrospective study, some limitations were unavoidable including nonrandom nature, small size of population, and some missing data of characteristics including the

Table 3

Multivariate analysis of PFS and OS.

		PFS		OS	
	No.	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Before matching					
Age (yr)					
<50	46	1		1	
≥50	29	1.48 (0.87–2.53)	.148	1.39 (0.79–2.45)	.257
Gender					
Female	36	1		1	
Male	39	1.34 (0.79–2.27)	.269	1.38 (0.79–2.42)	.255
Type of surgery					
GTR	60	1		1	
STR	14	1.49 (0.78–2.84)	.228	1.49 (0.78–2.84)	.228
Unknown	1	–	–	–	–
MGMT status					
Methylated	13	1		1	
Unmethylated	25	2.70 (1.14–6.41)	.024	4.17 (1.34–12.90)	.014
Unknown	37	1.76 (0.77–4.02)	.179	3.63 (1.20–11.02)	.023
Number of TMZ					
≤6 cycles	55	1			
>6 cycles	20	0.85 (0.44–1.62)	.614	0.67 (0.32–1.39)	.277
After matching					
Number of TMZ					
≤6 cycles	20	1			
>6 cycles	20	0.68 (0.29–1.57)	.371	0.49 (0.20–1.18)	.109

GTR = gross total resection, MGMT = methylguanine methyltransferase, OS = overall survival, PFS = progression-free survival, STR = subtotal resection, TMZ = temozolomide.

MGMT status of patients, which is an important prognostic factor of survival. However, the study still suggested physicians to consider prescribing the long-term administration of TMZ for Chinese patients.

Author contributions

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