Original Article

The efficacy and safety of low-dose temozolomide maintenance therapy in elderly patients with glioblastoma: a retrospective cohort study

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Background: Radiotherapy combined with temozolomide chemotherapy (STUPP regimen) is the standard treatment regimen for newly diagnosed glioblastoma (GBM). It is considered feasible to prolong the treatment cycle of temozolomide (TMZ), however, the efficacy and safety of prolonging the treatment cycle of TMZ are still lacking in elderly patients with glioblastoma. This study observed the efficacy and safety of low dose TMZ maintenance therapy in elderly patients with glioblastoma after receiving standard STUPP regimen.

Methods: The clinical data were retrospectively analyzed in 34 patients with glioblastoma aged ≥65 years from April 2017 to April 2021 in Ningbo First Hospital. The patients received conventional radiotherapy (59.4 Gy/28 F/5.5 weeks) and TMZ (75 mg/m^2·d) concurrent chemotherapy, followed by sequential TMZ (150–200 mg/m^2·d, d1–5, q28d) adjuvant treatment for 6 cycles, and patients with no disease progress or intolerable side effects received low dose TMZ (100 mg/m^2·d, d1–5, q28d) maintenance treatment. The patient's progression free survival time (PFS), total survival time (OS) and adverse reactions were observed by telephone, outpatient reexamination and other follow-up methods. Kaplan-Meier method was used to calculate and draw the survival curve for survival analysis.

Results: Twenty-four of 34 patients were finally included in the analysis, including 13 males and 11 females (65–74 years old), with a median of 14 cycles (8–38 cycles) of adjuvant TMZ chemotherapy. The median PFS was 11.0 months [95% confidence interval (CI): 8.67–13.33 months] and the median OS was 17.4 months (95% CI: 12.49–22.31 months). The main adverse reactions were digestive tract reactions and hematological toxicity. Three cases of grade III granulocytopenia occurred during the adjuvant treatment, while no grade III or above related adverse reactions occurred during the follow-up TMZ reduction maintenance treatment: leukopenia (5/24), anemia (2/24), decreased blood platelets (2/24), asthenia (5/24), nausea (4/24), and abnormal liver function (3/24).

Conclusions: In general, for elderly patients with good Karnofsky Performance Scale (KPS) scores, further reducing TMZ to maintain chemotherapy after the standard STUPP regimen may improve the PFS and OS to a certain extent, with tolerable adverse reactions and reduced cost. However, prospective randomized grouping study is still needed to determine whether clinical benefits will be achieved.

Keywords: Elderly patients; glioblastoma; radiotherapy; temozolomide maintenance

Submitted Oct 25, 2022. Accepted for publication Nov 15, 2022.
doi: 10.21037/apm-22-1255
View this article at: https://dx.doi.org/10.21037/apm-22-1255

Introduction

Glioblastoma multiforme [GBM; World Health Organization (WHO) Grade IV] is a highly invasive and malignant intracranial tumor, which has the highest incidence among primary malignant central nervous tumors, with males being affected more than females (1). In patients ≥65 years old, the incidence is 2.63 times that of the general adult population (2), and the prognosis becomes less favorable as the age of the patient increases (3). At present, the main therapy to treat GBM is surgical resection for safe removal within the maximum range. After surgery, patients are required to undergo the STUPP regimen: synchronous radiotherapy and chemotherapy followed by 6 cycles temozolomide (TMZ) chemotherapy (4,5). The STUPP regimen is considered the standard treatment scheme for newly diagnosed GBM. Evidence has shown that the long-term TMZ course based on the STUPP scheme is safe and feasible, with no significant increase in adverse reactions (6,7). However, due to the degeneration of organ function, the weakening of physiological adaptability, and the decline of immune function in elderly patients, their tolerance and sensitivity to treatment will be weakened. Therefore, long-term treatment with conventional dose of TMZ may increase the risk of adverse reactions and complications in elderly patients. In this study, a retrospective analysis was made to observe the effectiveness and safety of a lower dose of TMZ maintenance treatment. We present the following article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1255/rc).

Highlight box

Key findings

- Reduced TMZ to maintain chemotherapy after the standard STUPP regimen may improve the PFS and OS for elderly GBM patients, with tolerable adverse reactions and reduced cost.

What is known and what is new?

- Sustained low dose TMZ is safe for elderly GBM patients and could ameliorate prognosis with better PFS and OS.
- This study adds new evidence for the safety and efficacy of TMZ maintenance chemotherapy after standard STUPP regimen for elderly GBM patients.

What is the implication, and what should change now?

- Prospective randomized grouping study is still needed to determine whether clinical benefits of reduced TMZ maintenance chemotherapy will be achieved.

Methods

Patients

A total of 34 elderly GBM patients were admitted to the Radiochemotherapy Center of Ningbo First Hospital from April 2017 to April 2021. According to the inclusion criteria, 24 patients were finally included in the study. The inclusion criteria were as follows: (I) age ≥65 years; (II) initial diagnosis of GBM had been made upon admission; (III) pathological diagnosis of GBM; (IV) all patients underwent total/subtotal resection; (V) Karnofsky Performance Scale (KPS) score ≥80 (8); (VI) after surgery, all patients completed the treatment of STUPP regimen, without intolerable toxicity, and the condition was stable within 1 month after treatment, without tumor recurrence; (VII) there was no abnormal function of important organs such as heart, liver, and kidney. This study was approved by the Ethics Committee of Ningbo First Hospital (No. 2021RS002) and conducted according to the Declaration of Helsinki (as revised in 2013). All participants gave informed consent before taking part. The clinical research design of this study was to collect the treatment information of these 24 patients according to the follow-up data. Then the progression-free survival (PFS), overall survival (OS), and adverse drug reactions were analyzed. The baseline clinical characteristics of patients are shown in *Table 1*.

Treatment

(I) All patients underwent craniotomy under general anesthesia to remove tumors, and the KPS scores were performed before and after surgery. (II) Brain magnetic resonance imaging (MRI) was performed in all patients within 72 hours after operation. (III) Radiotherapy regimen: (i) target area delineation (9): gross tumor volume (GTV) included the visible lesions after operation and abnormal signal area of MRI T2/fluid-attenuated inversion recovery (FLAIR), and clinical target volume 1 (CTV1) was defined as GTV extended by 2 cm; CTV2 was the expansion of GTV by 1 cm. For the skull, ventricle, cerebral falx, tentorium cerebellum, visual organ, brain stem, and other natural barrier areas, the expansion was 0–0.5 cm. CTV1 expanded 0.3 cm to form planning target volume 1 (PTV1), and CTV2 was expanded 0.3 cm to form PTV2. (ii) Radiotherapy dose: PTV1 50.4 Gy/28 F, PTV2 59.92 Gy/28 F. (IV) Within 4–6 weeks after operation, patients underwent the STUPP regimen, that is, from the first day to the last day of radiotherapy, TMZ 75 mg/(m^2·d)

Table 1 The clinical characteristics of patients

Clinical characteristics	Number (n)
Sex	
Male	13
Female	11
Age (year), median [range]	68 [65–74]
Tumor location	
Frontal lobe	10
Temporal lobe	5
Parietal lobe	3
Occipital lobe	3
Other	3
Tumor size (cm)	
<4	8
4–6	10
>6	6
Degree of surgical resection	
Full cut	19
Subtotal cut	5

was orally administered for 42 days. Adjuvant TMZ oral administration started 28 days after the end of concurrent radiotherapy and chemotherapy: 150–200 mg/(m^2·d), repeated every 4 weeks from the first to the fifth day, to a total of 6 cycles. (V) Maintenance chemotherapy: after 6 cycles of TMZ adjuvant treatment, if the disease had no progression or intolerable side effects, it was changed to TMZ 100 mg/(m^2·d), repeated every 4 weeks from the first to the fifth day, until the disease progressed or intolerable side effects occurred. (VI) The imaging evaluation after treatment referred to the response assessment in neuro-oncology (RANO) standard.

Observation indicators

A total of 24 patients were followed-up (telephone follow-up, outpatient reexamination, etc.). The observation indicators included progression-free survival (PFS), overall survival (OS), and adverse drug reactions. The PFS was defined as the final follow-up deadline from the end of surgery to the determination of disease progression, or in the absence of disease progression; OS was defined as the deadline from the end of surgery to death or final follow-up, and the last follow-up was up to December 2021. The end point event was that the patient died of GBM, and the censored data included patient loss, death from other causes, and survival at the end of follow-up. The adverse drug reactions referred to the WHO grading standard for common adverse drug reactions of chemotherapy.

Statistics

The software SPSS 24.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Kaplan-Meier method was used to calculate and draw the survival curve for survival analysis. The continuous variables of non-normal distribution were represented by the median and range, and the counting data were represented by the number of cases and percentage.

Results

The clinical characteristics of patients

A total of 24 elderly patients with GBM were recruited, including 13 males and 11 females. The age range of patients was 65–74 years old. The location of brain tumors was 10 cases in frontal lobe, 5 cases in temporal lobe, 3 cases in parietal lobe, 3 cases in occipital lobe, and 3 cases in other parts. The tumor size and surgical resection degree are shown in *Table 1*. The median time of adjuvant TMZ chemotherapy was 14 cycles (8–38 cycles).

Patients' adverse reactions during different treatment phases

The main adverse reactions for patients receiving TMZ chemotherapy were digestive tract reactions and hematological toxicity (*Table 2*). Only 3 patients had grade III granulocytopenia, which occurred during the adjuvant treatment. However, no grade III or above related adverse reactions occurred during the follow-up maintenance treatment of TMZ reduction. Other symptoms, such as fatigue, nausea, vomiting, and abnormal liver function, were all of grade I–II.

The survival rates of patients

The median PFS period was 11.0 months [95% confidence

Table 2 Patients' adverse reactions during different treatment phases

Adverse reactions	Adjuvant treatment		Maintenance treatment	
	Level I–II	Level III–IV	Level I–II	Level III–IV
Leukopenia	8	3	5	0
Anemia	4	0	2	0
Thrombocytopenia	5	0	2	0
Abnormal liver function	3	0	3	0
Nausea	17	0	4	0
Vomiting	7	0	0	0
Fatigue	14	0	5	0

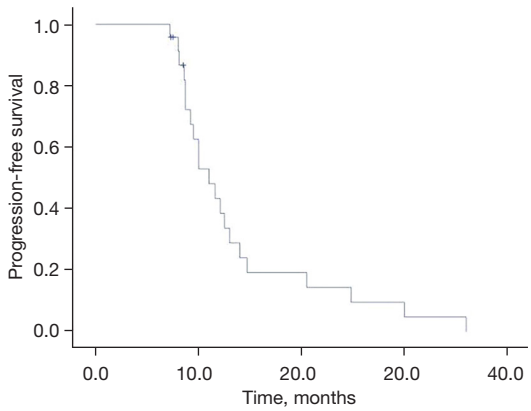

Figure 1 Kaplan-Meier analysis of progression-free survival.

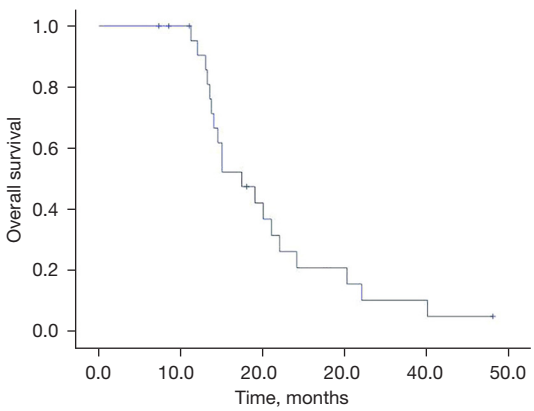

Figure 2 Kaplan-Meier analysis of overall survival.

interval (CI): 8.67–13.33 months] (*Figure 1*), and the median OS period was 17.4 months (95% CI: 12.49–22.31 months) (*Figure 2*).

Discussion

Glioma originates from glial cells and is the most common primary intracranial tumor. In the past 30 years, the incidence of primary malignant brain tumors has increased annually, especially in the elderly (10). According to statistics, glioma accounts for 27% of all central nervous system (CNS) tumors. Among primary malignant CNS tumors, GBM has the highest incidence (46.1%), which increases with age, with the highest incidence at 75–84 years old, and the median age of new diagnosis of 64 years old (11). GBM is characterized by high malignancy, invasive growth, easy recurrence and metastasis, and poor prognosis. The treatment is mainly surgical resection combined with radiotherapy and chemotherapy. A large-scale phase III clinical study (5) by the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) established STUPP as the standard treatment scheme for newly diagnosed high-grade glioma.

TMZ is an oral alkylating agent, which exerts alkylation damage on cell DNA to form a cross-linking interference mismatch repair system, contributing to cell death and achieving the effect of inhibiting tumor progression (12). TMZ is characterized by little toxicity and side effects, good tolerance for long-term use, and no cumulative effect (13). Furthermore, several studies have analyzed the efficacy and safety of its long-term use (>6 cycles) (6,7,14,15). The results showed that the treatment group with TMZ >6 cycles could significantly prolong the PFS and OS of GBM, and the prolonged TMZ course did not markedly increase the toxicity. Therefore, for patients with continuous improvement and tolerable toxicity in TMZ treatment, a long treatment cycle of adjuvant chemotherapy should be

considered (9).

It has been reported that advanced age and low KPS score are independent risk factors for short survival of patients with GBM (16-18). In terms of the overall population, the incidence of GBM will increase with age, and patients over 65 years old are 2.63 times more represented among patients with GBM than the general adult population (2). At present, no uniform international standard has been proposed for the definition of "elderly". The WHO defines 60–74 years as younger elderly, that is, ≥60 years old can be defined as elderly. The National Comprehensive Cancer Network (NCCN) defines 65–75 years as the early elderly, that is, ≥65 years old can be defined as elderly (19). At present, the age limit of elderly in China is 65 years old (9). Due to the degeneration of organ functions, the impairment of physiological adaptability, and the decline of immune function in elderly patients, their tolerance and sensitivity to treatment will be weakened, which will increase the risk of adverse reactions and complications in elderly patients. Therefore, both doctors and patients tend to be conservative in the choice of treatment and the adequate treatment sometimes is neglected. However, for the elderly patients with GBM, some studies have pointed out that TMZ is also beneficial. The prospective randomized phase III clinical study of German NOA-8 showed that the efficacy of TMZ alone was not inferior to radiotherapy in GBM patients >65 years old, and the median OS was 8.6 months and 9.6 months, respectively (20). The clinical trial of the Nordic Brain Tumor Research Group included 342 newly diagnosed elderly GBM patients (≥65 years old). The results showed that the OS of the TMZ group was significantly longer than that of the standard radiotherapy group (8.3 *vs.* 6 months) (21). The results of a global multicenter phase III clinical study showed that for the elderly GBM patients ≥65 years old, the total survival period of patients receiving short-term radiotherapy combined with TMZ maintained chemotherapy was significantly longer than that of those receiving short-term radiotherapy alone (22). Therefore, the guidelines recommend that the standard STUPP protocol (9) is accessible to elderly patients with good physical condition. In general, there is no consensus on the treatment plan for elderly patients with glioma and little is known about the standardization of diagnosis and treatment guidelines for elderly GBM.

In this study, 24 elderly GBM patients with KPS score ≥80 were treated with standard STUPP regimen after surgery. After treatment, patients with stable disease were given long-term TMZ oral chemotherapy. However, considering the tolerance of elderly patients, a reduced dose of TMZ was utilized in the maintenance treatment. In terms of adverse reactions, only 3 patients had grade III granulocytopenia, which occurred during adjuvant treatment. However, during the follow-up maintenance treatment, no grade III or above related adverse reactions occurred, and the remaining adverse reactions, such as fatigue, nausea, vomiting, and abnormal liver function, were all grade I-II, showing good safety. In terms of long-term efficacy, the median PFS was 11.0 months (95% CI: 8.67–13.33 months), and the median OS was 17.4 months (95% CI: 12.49–22.31 months). Compared with the results in NOA-8 study and the clinical trial of the Nordic Brain Tumor Research Group, the OS was longer in our study. However, considering that the data in this study were drawn from a retrospective analysis in a single center without a control group, the PFS and OS analysis may have been biased. In addition, due to the small number of cases, subgroup analysis of molecular pathological phenotype such as MGMT methylation and IDH1/2 mutation could not be conducted, and thus more cases should be added to improve the data accuracy.

Taken together, our retrospective data analysis showed that for elderly patients with good KPS score, further low-dose TMZ maintenance chemotherapy after standard STUPP regimen may improve PFS and OS of these patients to a certain extent, without increasing adverse reactions. The low-dose TMZ maintenance therapy could also reduce the treatment cost, which is in line with the principle of high therapeutic efficacy, low toxicity, and low cost of elderly oncology treatment. With the accumulation of clinical data, we intend to further identify the targeted patients who would really benefit from the low-dose TMZ maintenance chemotherapy with molecular pathological phenotype.

Conclusions

Our results suggest that for elderly patients with good KPS scores, further reducing TMZ to maintain chemotherapy after the standard STUPP regimen may improve the PFS and OS to a certain extent, with tolerable adverse reactions and reduced cost.

Acknowledgments

We thank Ruishuang Ma (Department of Radiotherapy and Chemotherapy, Ningbo First Hospital, Ningbo, China) for

excellent assistance.
Funding: This work was supported by grants from the Zhejiang Medical and Health Science & Technology Project (No. 2020KY826 to QT).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-1255/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-22-1255/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1255/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. This study was approved by the Ethics Committee of Ningbo First Hospital (No. 2021RS002) and conducted according to the Declaration of Helsinki (as revised in 2013). All participants gave informed consent before taking part.

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(English Language Editor: J. Jones)

Cite this article as: Tao Q, Zhu T, Ge X, Gong S, Guo J. The efficacy and safety of low-dose temozolomide maintenance therapy in elderly patients with glioblastoma: a retrospective cohort study. Ann Palliat Med 2022;11(11):3513-3519. doi: 10.21037/apm-22-1255

