Does Early Postsurgical Temozolomide Plus Concomitant Radiochemotherapy Regimen Have Any Benefit in Newly-diagnosed Glioblastoma Patients? A Multi-center, Randomized, Parallel, Open-label, Phase II Clinical Trial

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Abstract

Background: The radiochemotherapy regimen concomitantly employing temozolomide (TMZ) chemotherapy and radiotherapy (RT) 4 weeks after surgery, followed by 6 cycles of TMZ is a common treatment for glioblastoma (GBM). However, its median overall survival (OS) is only 14.6 months. This study was to explore the effectiveness and safety of early TMZ chemotherapy between surgery and chemoradiotherapy plus the standard concomitant radiochemotherapy regimen.

Methods: A randomized, parallel group, open-label study of 99 newly diagnosed GBM patients was conducted at 10 independent Chinese neurosurgical departments from June 2008 to June 2012. Patients were treated with concomitant radiochemotherapy regimen plus early postsurgical temozolomide (early TMZ group) or standard concomitant radiochemotherapy regimen (control group). Overall response was assessed based on objective tumor assessments, administration of corticosteroid and neurological status test. Hematological, biochemical, laboratory, adverse event (AE), and neurological condition were measured for 24 months of follow-up. The primary efficacy endpoint of this study was overall survival (OS). The secondary endpoint was progression free survival (PFS).

Results: The median OS time in the early TMZ group was 17.6 months, compared with 13.2 months in the control group (log-rank test \( P = 0.021 \)). In addition, the OS rate in the early TMZ group was higher at 6, 12, and 18 months than in the control group, respectively \( (P < 0.05) \). The median PFS time was 8.7 months in the early TMZ group and 10.4 months in the control group (log-rank test \( P = 0.695 \)). AEs occurred in 29 (55.8%) and 31 (73.8%) patients respectively in early and control groups, including nausea (15.4% vs. 33.3%), vomiting (7.7% vs. 28.6%), fever (7.7% vs. 11.9%), and headache (3.8% vs. 23.8%). Only 30.8% and 33.3% were drug-related, respectively.

Conclusions: Addition of TMZ chemotherapy in the early break of the standard concomitant radiochemotherapy regimen was well tolerated and significantly improved the OS of the GBM patients, compared with standard concomitant radiochemotherapy regimen. However, a larger randomized trial is warranted to verify these results.

Key words: Chemoradiotherapy; Chemotherapy; Glioblastoma; Malignant Glioma; Temozolomide

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**INTRODUCTION**

Glioblastoma (GBM) is the most common and lethal form of malignant glioma. It accounts for the majority of gliomas, while astrocytoma and GBM account for about 75% of all gliomas.\(^1\)\(^,\)\(^2\) Despite the increasing prevalence of GBM, only a few clinical strategies for treatment optimization have been developed due to presumed poor prognosis, comorbidities, poor physiological responses, and increased risk.\(^3\)\(^,\)\(^4\) Thus, there is an urgent need for novel treatment options to improve the survival for GBM patients.

Before the regimen proposed by Stupp et al.\(^5\) (concomitant radiochemotherapy followed by adjuvant chemotherapy), there were no prospective controlled randomized, phase 3 clinical trials demonstrating a significant survival benefit with single-agent or multi-agent chemotherapy for GBM.\(^7\) Stupp et al.\(^8\)\(^,\)\(^9\) demonstrated that adding temozolomide (TMZ), a clinically approved cytotoxic alkylating agent, to radiotherapy (RT) regimens in newly-diagnosed GBM patients resulted in a clinically meaningful and statistically significant survival benefit with only a minimal increase in toxicity. Stupp et al. recommended daily TMZ (75 mg/m\(^2\)) administration from the first to last day of RT treatment (2 Gy given 5 days/week for 6 weeks, totaling 60 Gy). Thereafter, 6 cycles of adjuvant TMZ (150–200 mg/m\(^2\)) should be administered for 5 days during each 28-day cycle. In practice, however, treatment strategies remain highly variable in clinical settings,\(^9\) though several large clinical trials are currently being conducted with the aim of optimizing treatment of GBM.\(^3\)

Although the concomitant radiochemotherapy regimen treatment employing TMZ alone with conventional RT is a well-accepted strategy for improving survival in GBM patients, the median survival improved by this regimen (from 12.1 months with RT alone to 14.6 months with RT plus TMZ) was not satisfactorily substantial. According to the concomitant radiochemotherapy regimen, TMZ is initiated 4–5 weeks after surgery; however, the length of this time interval between surgery and chemo-RT (CRT) lacks substantiation from research and there may be an opportunity to achieve improved results by administering TMZ in this early period. Some researchers found that new contrast enhancement indicative tumor growth appeared in 53% of the GBM patients in the interim between surgery and CRT.\(^9\) This suggests that reducing the time between surgery and adjuvant therapy may be beneficial for GBM patients. The early use of TMZ aims to minimize or eliminate malignant growth during the immediate period following surgery. Thus, the current study examined patients treated with the concomitant radiochemotherapy regimen with the addition of early TMZ chemotherapy to evaluate the safety and efficacy of this modified regimen.

**METHODS**

**Study design**

A prospective randomized, parallel group, open-label study of newly-diagnosed GBM patients in 10 independent Neurosurgical Departments across China was conducted to compare the efficacy and safety of the concomitant radiochemotherapy regimen plus early postsurgical TMZ chemotherapy (early TMZ group) with standard postsurgical concomitant radiochemotherapy regimen (control group) between June 2008 and June 2012. The patients were followed for 24 months after surgery. The study protocol was approved by the Independent Ethics Committee/Institutional Review Board of each participating center, and the study was designed in accordance with all local guidelines. All patients provided written informed consent for participation prior to treatment and were allowed to voluntarily withdraw for any reason.

**Patients**

The patients who met all of the following criteria were included: (1) Histologically confirmed newly-diagnosed primary GBM in the supratentorial cerebral hemisphere; (2) gross total resection or large resection of >70% in imaging studies; (3) capable of providing paraffin-embedded tissue specimens during surgery for O'-methylguanine DNA methyltransferase (MGMT) staining analysis; (4) currently aged 18–70 years at study onset; Eastern Cooperative Oncology Group performance status of 0–2; (5) life expectancy ≥9 months; (6) clinical findings of absolute neutrophil count (ANC) ≥1.5 × 10\(^9\)/L, platelet count ≥100 × 10\(^9\)/L, blood urea nitrogen (BUN), and creatinine (Cr) <1.5 × the upper limit of normal (ULN); total bilirubin (TBil) and direct bilirubin (DBil) <1.5 × ULN, alanine transaminase (ALT) and aspartate transaminase (AST) <3 × ULN, and alkaline phosphatase (AKP) <2 × ULN. Furthermore, all female patients of child-bearing age and their partners consented to undergo effective contraceptive treatment throughout the study. All male patients were recommended to use contraception and freeze sperm due to the risk of infertility or other reproductive abnormality.

The patients were excluded according to the exclusion criteria: (1) Current diagnosis or history of malignancies within the 3-year period preceding enrollment; (2) presurgical treatment with chemotherapy, RT, or other anti-tumor medications or treatment with sensitizers; (3) recurrent or multiple malignant gliomas, including gliomatosis cerebri, or metastatic extracalvarial or subtentorial lesions; (4) overlapping RT domains in the head or neck; (5) acute infections requiring intravenous antibiotics; (6) frequent vomiting or other medical conditions that could interfere with oral medication intake or produce partial bowel obstruction; (7) confirmed human immunodeficiency virus infection or symptomatic acquired immune deficiency syndrome; (8) current pregnancy or breastfeeding; (9) history of hypersensitivity to TMZ or other analogic alkylating agents; and (10) other indications of poor compliance or study completion, as determined by the investigators.

After surgery, eligible patients were randomly assigned to either early TMZ group or control group on a 1:1
basis. The randomization code was prepared by the trial statistician using computer-based random number table. The randomized allocation and instructions were prepared in double-enclosed, opaque, sealed, and sequentially numbered envelopes. The randomization was done at each site according to the randomization code with envelop concealment. Due to the nature of the treatment, participants were aware of the treatment allocation.

**Data collection and validation**

Data were collected in the Department of Neurosurgery at 10 independent centers across China, including (1) Huashan Hospital, Fudan University, (2) Beijing Tiantan Hospital, Capital Medical University, (3) Changzheng Hospital, Second Military Medical University, (4) Sun Yat-Sen University Cancer Center, (5) The Second Affiliated Hospital of Zhejiang University School of Medicine, (6) Nanfang Hospital, Southern Medical University, (7) West China Hospital of Sichuan University, (8) Peking Union Medical College Hospital, (9) General Hospital, Tianjin Medical University, and (10) Xijing Hospital, The Fourth Military Medical University. Clinical research personnel reviewed data from case report forms for omissions and errors, and all data were archived in central computer databases according to standard procedures.

**Clinical assessments**

**Neuroimaging**

Objective tumor assessments were made from magnetic resonance imaging (MRI) scan according to Macdonald’s criteria. For measurable lesions, the product of the largest perpendicular diameters of enhancement was recorded. Tumor size was measured using the sum of the products of the largest perpendicular tumor diameters. Nonmeasurable lesions were assessed by approximate definitions of measurable lesions. In screening period, enhanced MRI (tumor assessments/measurements) was performed within 3 days after surgery. Moreover, during the study, MRI assessment was performed in below periods: The end of early chemotherapy, the end of post-CRT, the end of cycle 3 and cycle 6 of adjuvant chemotherapy, month 12 in the follow-up period and at the end of the study of month 24, at the time when progressive disease (PD) or relapse develops, and as medical need requires.

**Clinical laboratory characteristics**

Hematological characteristics of red blood cell count, hemoglobin, white blood cell count (WBC) and differentials, ANC, and platelet count were measured for each patient. Blood biochemical parameters of total protein, albumin, ALT, AST, AKP, TBil, Dbil, BUN, Cr, blood glucose, K+, Na+, and Cl− were measured for each patient. Each patient also underwent physical examinations, including vital signs and weight. MGMT testing was conducted through immunohistochemistry (IHC) staining (n = 90). The percentage of stained tumor cells was scored as “−” (0–10%) and “+” (>10%). For statistical analysis, scores of “−” were defined as a negative staining group and scores of “+” was defined as positive staining group.

**Postsurgical chemotherapy with TMZ**

Treatments of 20 mg and 100 mg TMZ (Temodal®) (Merck Sharp and Dohme Ltd, United Kingdom) in oral capsule form were used for all administrations. The patients were administered medications on an empty stomach at least 1 h before meals, with antiemetic therapy if necessary. Patient treatment in the two groups is detailed in Figure 1.

Both patient groups underwent routine surgery (day 0) and were screened from postsurgical day 1 to day 14. In the early TMZ group, 14 days after surgery, TMZ was administered orally at 75 mg·m⁻²·d⁻¹ for 14 days. From day 29, patients were treated with a standard therapy regimen (Stupp) as in control group. Briefly, 4 weeks after surgery, patients were administered a total daily dose of 60 Gy in 30 fractions of conventional RT 5 days a week over the course of 6 weeks. These patients simultaneously underwent 75 mg/m² oral TMZ administration for 42 days. After a 4-week break, TMZ was administered to all patients for 6 cycles on days 1–5 of every cycle (28 days/cycle). Dosage in cycle 1 was 150 mg/m² once daily for 5 days followed by 23 days without treatment. At the start of cycle 2, if nonhematologic toxicity for cycle 1 was Grade 2 or less (except for alopecia, nausea, and vomiting), ANC ≥1.5 × 10⁹/L, and platelet count ≥100 × 10⁹/L, the dose was escalated to 200 mg·m⁻²·d⁻¹. If not escalated at cycle 2, the dose was not escalated in subsequent cycles. The dose remained at 200 mg·m⁻²·d⁻¹ in all following cycles except in the case of toxicity [Figure 1]. During the study, dose adjustment would be made for subjects if toxicity occurred. The detailed dose of TMZ was recorded.

**Efficacy and safety determination**

The primary efficacy endpoint was overall survival (OS), and the secondary efficacy endpoint was progression-free survival (PFS) and the objective tumor assessment after surgery. Adverse event (AE) occurrence, severe AEs (SAEs), and life-threatening AE occurrences; clinical laboratory findings; physical examinations (including vital signs/weight); and neurological condition at each follow-up examination, were used to determine safety of treatment.

**Statistical analysis**

The study was exploratory and planned to enroll a total of 100 subjects in 10 sites in China. A sample size of 50 patients/arm was to detect a lower bound of 95% confidence interval (CI) of 10% for the actual 2-year OS rate at 26.5% (point estimate) in arm A or arm B. This was in the consideration of a yearly discontinuation rate at 20% and the threshold of clinical efficacy being not <10% for OS within 2 years.

Efficacy analyses were primarily based on the intent-to-treatment (ITT) population including all the randomized subjects. Safety analyses were performed on the safety population including all randomized and treated subjects.

All data were analyzed with SAS® software package version 9.1.3 (SAS, Cary, NC, USA). All data were summarized with descriptive statistics for continuous
variables and/or frequency or percentages for categorical variables. OS was measured from the date of diagnosis to the date of death or last follow-up. PFS was measured from the date of diagnosis to the date of disease progression, recurrence, death, or last follow-up. Kaplan–Meier method was used to estimate the distribution of OS and PFS. The proportion of surviving and progression-free patients at 2 years was determined with a 95% CI for both OS and PFS. The log-rank test was used to compare the difference between the two treatment groups. For objective assessment of neuroimaging and overall tumor response, response rates and 95% CI were reported, and between-group differences were evaluated by Fisher’s exact test. Cochran–Mantel–Haenszel test was used to determine the relationship between MGMT status and objective response. Fisher’s exact test was used to compare the incidence of AEs between two treatment groups. Statistical tests and CIs were two-sided. A P value of <0.05 was considered statistically significant.

**RESULTS**

**Patient demographic and clinical characteristics**

A total of 99 subjects were randomized in the study, of whom 52 received the standard TMZ regimen plus early postsurgery TMZ chemotherapy (early TMZ group) and 47 received the standard TMZ regimen (control group). The characteristics of the patients in the two groups were well balanced at baseline [Table 1]. Eighty-eight patients discontinued the study. One patient (1.9%) in the control group and one patient (2.4%) in the early TMZ group discontinued due to AEs. Seventeen patients (36.2%) in the control group and 23 patients (44.2%) in the early TMZ group discontinued due to PD. Forty-five patients (47.8%) completed the 6 cycles TMZ adjuvant chemotherapy (50.0% [n = 26] in early TMZ group and 45.2% [n = 19] in the control group).

### Table 1: Demographic and baseline characteristics in the ITT population

| Characteristics          | Early TMZ group (n = 52) | Control group (n = 47) | Total (n = 99) | P     |
|--------------------------|--------------------------|------------------------|----------------|-------|
| Age (years) Mean (SD)    | 48.5 (13.0)              | 52.1 (10.1)            | 50.2 (11.8)    | 0.130 |
| Median                   | 50.0                     | 53.0                   | 51.0           |       |
| Range                    | 20–69                    | 22–70                  | 20–70          |       |
| Gender, n (%)            |                          |                        |                |       |
| Male                     | 32 (62)                  | 34 (72)                | 66 (67)        | 0.250 |
| Female                   | 20 (38)                  | 13 (28)                | 33 (33)        |       |
| Race, n (%)              |                          |                        |                |       |
| Chinese                  | 52 (100)                 | 47 (100)               | 99 (100)       | NA    |
|Extent of surgical resection, n (%) |                     |                        |                |       |
| Complete                 | 42 (81)                  | 35 (74)                | 77 (78)        | 0.45  |
| Large (>70%)             | 10 (19)                  | 12 (26)                | 22 (22)        |       |
| ECOG status, n (%)       |                          |                        |                |       |
| 0                        | 19 (37)                  | 8 (17)                 | 27 (27)        | 0.800 |
| 1                        | 23 (44)                  | 29 (62)                | 52 (53)        |       |
| 2                        | 10 (19)                  | 10 (21)                | 20 (20)        |       |
| MGMT staining, n (%)     |                          |                        |                |       |
| Positive                 | 20 (42)                  | 15 (36)                | 35 (39)        | 0.560 |
| Negative                 | 28 (58)                  | 27 (64)                | 55 (61)        |       |

SD: Standard deviation; MGMT: O–6-methylguanine DNA methyltransferase; ECOG: Eastern Cooperative Oncology Group; TMZ: Temozolomide; ITT: Intent-to-treatment; NA: Not available.

**Figure 1:** Treatment regimens in the early chemotherapy and control groups.
excluded from the safety population (n = 94). Furthermore, no statistically significant differences were detected between the two treatment groups for the tumor objective assessments or clinical characteristics and baseline demographics of any population (P > 0.05 for all).

**Efficacy outcomes**

Median OS time was 17.6 months in the early TMZ group and 13.2 months in the control group. The difference between the two treatment groups was statistically significant [log-rank test P = 0.021, Figure 2]. The OS rate in the early TMZ group was significantly longer than that in the control group at 6, 12, and 18 months follow-up assessments. The 2-year OS rate in the early TMZ group was 24.0% (95% CI: 9%, 43%) [Table 2]. The median PFS time was 8.7 months in the early TMZ group and 10.4 months in the control group. There was no statistically significant difference between the two treatment groups [log-rank test P = 0.695, Figure 2 and Table 2]. Furthermore, we performed the survival analysis based on the results of IHC for MGMT in the two cohorts (early TMZ group and control group), and revealed no statistical significance between the groups.

**Nonhematologic and hematologic adverse event occurrences**

Twenty-nine patients (55.8%) in the early TMZ group and 31 patients (73.8%) in the control group had at least one AE. The most commonly reported nonhematologic AEs (≥10% in any treatment group) were nausea (15.4% vs. 33.3%), vomiting (7.7% vs. 28.6%), headache (3.8% vs. 23.8%), and fever (7.7% vs. 11.9%) in the early TMZ and control groups, respectively [Table 3]. Most AEs were mild to moderate.

No significant changes in laboratory blood biochemistry values were observed between the two groups (P > 0.05). Only minor, nonsignificant changes in physical examination results and vital signs were observed between the two treatment groups (P > 0.05) (data not shown). The most common hematologic AEs were WBC decrease, neutrophil count decrease, and platelet count decrease. The incidence and grading of these AEs were listed in Table 4.

**Discussion**

Conventional use of TMZ following resection of GBM (concomitant radiochemotherapy regimen) has been proven effective in improving OS rates in GBM, and the Stupp protocol is currently considered the standard of care for newly-diagnosed GBM. However, this protocol has been modified to optimize treatment and improve outcome. In the present study, median OS of early TMZ group was 17.6 months, compared to 13.2 months in the

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**Table 2: Analysis of OS and PFS in the ITT population**

| Items                        | OS                          | PFS                          |
|------------------------------|-----------------------------|------------------------------|
|                              | Early TMZ group (n = 52)    | Control group (n = 47)       | Early TMZ group (n = 52)    | Control group (n = 47)       |
| Median survival time, months (95% CI) | 17.6 (15.2–23.0)            | 13.2 (11.1–18.8)             | 8.74 (6.4–14.8)             | 10.4 (8.2–15.4)              |
| Survival rate, months, % (95% CI) | 93.6 (81.4–97.9)            | 86.9 (71.3–94.3)             | 64.1 (49.2–75.7)            | 72.2 (55.4–83.6)             |
| 6                            | 83.4 (68.1–91.7)            | 60.4 (41.1–75.1)             | 49.2 (34.5–62.2)            | 45.8 (29.0–61.1)             |
| 12                           | 48.5 (31.3–63.8)            | 38.6 (20.1–56.9)             | 28.7 (16.5–42.1)            | 26.2 (11.7–43.4)             |
| 24                           | 24.0 (8.8–43.2)             | –                            | 20.9 (10.3–34.0)            | –                            |
| Treatment effect             | Log-rank P 0.021            | 0.695                        |

OS: Overall survival; PFS: Progression-free Survival; CI: Confidence interval; ITT: Intent-to-treatment; TMZ: Temozolomide.
control group. These data suggest that employing additional administrations of TMZ during the immediate 3–4-week period following surgery may further improve the survival of GBM patients.

A systematic review of 6 recent randomly controlled trials demonstrated that postoperative radiation therapy was effective for management of GBM following surgery (pooled risk ratio, 0.81; 95% CI, 0.74–0.88; \( P < 0.00001 \)).[10] Furthermore, treatment with 60 Gy, as applied in the concomitant radiochemotherapy regimen in the current study, has been demonstrated to be the optimal RT dose in multiple-modality therapies, with doses >60 Gy and confocal RT showing no further benefits.[11] Thus, the RT dosage used in the current study was optimal, as demonstrated by these previous studies.

The 5 years analysis of EORTC-NCIC 26981 trial demonstrated the benefit of adjuvant TMZ with RT lasted throughout 5 years of follow-up. OS was 27.2% at 2 years and median OS was 14.6 months with TMZ in the combined-treatment group, versus 4.4% at 2 years and median OS of 12.1 months with RT alone.[3] Comparatively, the current modified approach employing early TMZ plus standard concomitant radiochemotherapy regimen produced an OS of 17.6 months and a survival rate of 24.0% at the 24-month follow-up. These results demonstrate that survival rate is similar and OS may be increased by early application of TMZ. Some patients underwent only biopsy and partial resection in EORTC 26981 trial.[4] However, the extent of surgical resection in our inclusion criteria is >70%. Hence, the rate of complete resection in our study is higher than EORTC 26981, which may contribute to the longer survival of patients in our study. There are several possible benefits for early application of TMZ in addition to concomitant radiochemotherapy regimen. First, despite surgery, infiltrating cancer cells that reside away from the main tumor mass are thought to be responsible for tumor recurrence, as well as radiation and chemotherapy resistance.[12,13] Pirzkall et al. examined the imaging of 32 patients with newly-diagnosed GBM who underwent MR examinations prior to surgery, after surgery, and prior to RT/TMZ CRT.[5] They found that new contrast enhancement indicative of tumor growth was appeared in 17 patients (53%) in the interim between surgery and CRT. This suggested that reducing the time between surgery and adjuvant therapy may be important, and early application of TMZ can be a way to address this problem. Second, there were studies providing supporting evidences for the existence of cancer stem-like cells (CSCs) and the efficacy of TMZ may be enhanced.

Recently, a number of specialized early postsurgical treatments for GBM patients have become available, including surgical medication implants, such as Gliadel® wafers which release carmustine slowly over a period of 2–4 weeks after placement.[21] Like the strategy employed in the current study, these drugs aim to minimize or eliminate malignant growth during the immediate period following surgery in order to improve GBM patient survival. A recent study, however, reported that over one third of patients eligible for such contemporary treatments, including wafer placement during surgical debulking of GBM tumors, were not treated due to surgeon preference, expense, or unavailability of the medication at the time of surgery.[22] Because TMZ is regularly available in most oncological clinics, it is highly likely that this early treatment is simple and practical. While further research will be required to compare the efficacy and safety of early postsurgical TMZ

### Table 3: Most common nonhematologic AEs* in the safety population

| Items                                      | Early TMZ group (n = 52, %) | Control group (n = 42, %) | \( P \) |
|--------------------------------------------|-----------------------------|---------------------------|-------|
| Gastrointestinal disorders                 |                             |                           |       |
| Nausea                                     | 8 (15.4)                    | 14 (33.3)                 | 0.041 |
| Vomiting                                   | 4 (7.7)                     | 12 (28.6)                 | 0.012 |
| Nervous system disorders                   |                             |                           |       |
| Headache                                   | 2 (3.8)                     | 10 (23.8)                 | 0.004 |
| General disorders and administration site conditions |                             |                           |       |
| Fever                                      | 4 (7.7)                     | 5 (11.9)                  | 0.507 |

*Incidence ≥10% in at least one treatment group. TMZ: Temozolomide; AEs: Adverse events.

### Table 4: Hematologic AEs in the safety population

| Blood and lymphatic system disorders        | Early TMZ group (n = 52, %) | Control group (n = 42, %) |
|--------------------------------------------|-----------------------------|---------------------------|
|                                           | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| White blood cell count decreased (leukopenia) | 16 (31) | 14 (27) | 2 (4)   | 0 (0)   | 14 (33) | 2 (5)   | 3 (7)   | 0 (0)   |
| Neutrophil count decreased (neutropenia)   | 4 (8)   | 12 (23) | 2 (4)   | 1 (2)   | 3 (7)   | 2 (5)   | 1 (2)   | 0 (0)   |
| Platelet count decreased (thrombocytopenia) | 4 (8)   | 8 (15)  | 0 (0)   | 0 (0)   | 8 (19)  | 3 (7)   | 3 (7)   | 0 (0)   |

TMZ: Temozolomide; AEs: Adverse events.
treatment plus concomitant radiochemotherapy regimen with other, more modern, early postsurgical treatment strategies, considering the current findings that this strategy could improve patient outcomes with minimal additional risk. This study has several limitations. First, a statistical difference was only found in OS rate, but not in PFS rate, between two treatment groups. The statistical difference in OS was hypothesis generating for primary endpoint and this finding warrants further investigations by a comparative randomized controlled trial design in Chinese diseased population. Second, accurate measurement of PFS was hard because there were no diagnostic criteria for disease progression or recurrence, and differentiating of disease progression/recurrence, pseudo-progression, and RT effects are difficult. While accurate OS can be measured easily because it was measured from the date of diagnosis to the date of death or last follow-up in both treatment arms. This may explain why OS was significantly longer in the early TMZ group, while PFS did not differ significantly between the groups. Furthermore, the entire study group was Chinese, and it is possible that some differences may exist between various populations in response to this treatment. Additionally, the MGMT expression in this study was only tested by IHC, which could not indicate the MGMT promoter methylation status, thus the correlation between MGMT promoter methylation status and this modified early TMZ regimen needs to be further investigated. There is a growing concern about the potential drug-related effects of TMZ chemotherapies. Among alkylating drugs used in chemotherapy, the occurrence of the AE aplastic anemia appears unique to TMZ treatments and can even occur following short exposure, warranting disclosure to patients in many modern clinical settings. In addition, TMZ may increase the risk of alkylator-induced acute myeloid leukemia. In a recent analysis of 5127 reports on 3490 patients, 76 aplastic anemia and aplasia cases, as well as 17 leukemia cases were identified to be possible drug-related following TMZ therapy. Thus, further studies using larger cohorts will be required to fully assess the risk of alkylator-induced acute myeloid leukemia and aplastic anemia associated with prolongation of TMZ treatments for GBM.

In conclusion, cumulatively, these preliminary findings indicate that addition of 2 weeks TMZ treatments starting from 14th day after surgery to the concomitant radiochemotherapy regimen can improve OS in GBM patients. Compared to concomitant radiochemotherapy regimen alone, similar AE and SAE occurrences were observed, and no differences in physical, clinical, or biochemical parameters were observed between the two treatment groups. Further study, however, will be required to fully assess the safety profile of prolongation of TMZ chemotheraphy in consideration of very rare SAEs, such as aplastic anemia and alkylator-induced acute myeloid leukemia that have been suggested to be associated with TMZ exposure. Due to the wide availability of TMZ, this modified concomitant radiochemotherapy regimen may allow notable improvements in OS for GBM patient with minimal additional risks and expense.

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Conflicts of interest
There are no conflicts of interest.

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