Effect of Concomitant and Adjuvant Temozolomide on Prognosis and Survival in Glioblastoma Multiforme

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Abstract

Aim: Glioblastoma multiforme (GBM) is the most common malignant primary brain tumor in adults. The most common problem in the follow-up after GBM treatment is the lack of local control. This study aims to evaluate the efficacy and safety of Temozolomide (TMZ) in cases who received post-surgical radiotherapy and TMZ treatment in GBM compared to cases who received only radiotherapy treatment after surgery.

Methods: The cases diagnosed with GBM were divided into two groups. The first group was divided into cases that received only radiotherapy after surgery, and the second group (combined treatment group) was divided into cases that received post-surgical radiotherapy and TMZ treatment. 28 cases who received radiotherapy and TMZ treatment after surgery and 26 cases who received only radiotherapy after surgery were included in the study. Local fractionated radiotherapy (60 Gy total dose: 2 Gyx5 days/week for 6 weeks) was applied to all cases. Only in the second group, 75 mg/m^2/day 7 days/week orally, 200 mg/m^2/day 5 days as monotherapy for 6 weeks, and six cycles of TMZ every 28 days were administered concomitantly. In addition to the effect of TMZ on prognosis and survival, the effects of age, gender, and resection size on progression-free survival (PSS) and overall survival (GSS) were evaluated in both groups.

Results: There was no statistically significant benefit in terms of both PFS and OS in both groups for age and gender, a statistically significant benefit was found for resection size (total-subtotal). At the end of the study, PFS was 14 months in the combined treatment group and 6 months in the radiotherapy alone group (P<0.0001). OS was 16 months in the combined treatment group and 12.5 months in the radiotherapy alone group (P=0.0354).

Conclusion: Combined (RT + TMZ) treatment after total surgical treatment was found to be more effective on prognosis and survival than radiotherapy alone.

Keywords: *Glioblastoma multiforme, temozolomide, radiotherapy, surgery*

1. Introduction

According to the World Health Organization, one of the top three causes of death in both developed and developing countries after the first 5 years of age is cancer-related deaths.

Glioblastoma multiforme (GBM) is the most common primary brain tumor in adults and is one of the most rapidly progressing and deadly tumors known[1]. GBM is the most common primary brain tumor that can be seen at any age. The median survival after diagnosis is less than one year. In the most appropriate treatment conditions, this period can be extended to two years. Intracranial tumors account for 14% of all tumors and 48% of malignant central nervous system tumors. It is responsible for approximately 1.5% of all cancers and 2% of all cancer-related deaths. It ranks fourth in cancer-related deaths[2-4].

Despite improvements in treatment modalities, there has been no significant change in GBM treatment outcomes. Therefore, preclinical and clinical studies are increasingly continuing to develop other treatment strategies that may be beneficial when combined with RT in malignant gliomas[5].

Temozolomide (TMZ) is an alkylating agent that converts alkyl

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groups to guanine bases in the cell, causing DNA damage and causing apoptosis6. It can be taken orally due to its small molecular structure (194.151 g/mol) and lipophilicity. The plasma half-life is about 2 hours. However, crossing the blood-brain barrier has only 20% bioavailability[6].

Standard treatment in cases with GBM; surgery (CER) + radiotherapy (RT) ± chemotherapy (CT). Since the beginning of the 2000s, TMZ has taken its place in standard treatment as a chemotherapeutic agent in cases with GBM. Despite these advances, KT has a limited role in the adjuvant treatment of primary disease or after relapse[7]. Different multimodal treatment approaches have been developed to prolong survival. High-dose RT, adjuvant CT, alternative fractionation regimens in radiotherapy, heavy particle therapy, use of radiosensitizers together with RT, interstitial brachytherapy, radiosurgery, stereotactic fractionated RT, and intensity modulated RT are some of the treatment modalities that are being developed[8-10]. In this study, we aimed to determine the effect of TMZ, which we use as a chemotherapeutic agent following post-surgical radiotherapy in standard treatment protocols, on prognosis and survival, by comparing it with the cases in which we gave only radiotherapy after surgical treatment in previous years.

2. Materials and methods

Twenty-eight patients who received post-surgical radiotherapy and chemotherapy treatment at Çukurova University Faculty of Medicine Neurosurgery Clinic between May 2006 and March 2010 were randomized to this study. Between 2000 and 2005, 26 patients who received only radiotherapy after surgery were randomly selected.

Cases with histological diagnosis of glioblastoma were divided into two groups. The first group was divided into cases that received only radiotherapy after surgery, and the second group was divided into cases that received post-surgical radiotherapy and TMZ treatment. Radiotherapy consists of administering a dose of 2 Gy/fraction five days a week (Monday to Friday), once a day for a total of 45 days over 6 weeks, with an additional dose of 46 Gy to the whole brain and 20 Gy to the tumor bed, giving a total dose of 66 Gy, we applied conventional fractionated irradiation. Preoperative CT or MRI was used to determine the target volume while applying an additional dose to the tumor site. Since the target volume is whole brain irradiation; It was determined as an area of 2 cm from the tumor border. According to tumor location, different field entrances were used to distribute the dose; supplemental dose areas vary. Chemotherapy with TMZ was administered at a dose of 75 mg/m^2/day, 7 days a week, for a total of 49 days from the first day to the last day of radiotherapy. After a 4-week break, patients received adjuvant TMZ therapy at a dose of 150 mg/m^2/day for 5 days every 28 days, the standard regimen for six cycles (Figure 13). The anti-edema treatment, which was started parenterally from the beginning of the treatment, was discontinued by reducing the dose within 1-2 months after radiotherapy. Anti-epileptic therapy was continued uninterrupted. As anti-emetic prophylaxis, selective 5-HT3 (5-hydroxytryptamine) receptor antagonists have been used at initial doses of concomitant TMZ therapy and during 5-day adjuvant TMZ administration. Side effects during post-surgical radiotherapy (with or without concomitant TMZ), during the adjuvant treatment period, and throughout the study period (from enrollment to disease progression or final follow-up) were evaluated separately.

Observation and Follow-up During radiotherapy (with or without TMZ), patients were checked every week. During the controls, the neurological status of the patients along with their complaints was examined and complete blood counts were checked. The patients were called for their first controls 4 weeks after the end of radiotherapy, and their neurological and general conditions were evaluated, and the tumor response was checked with control CT or MRI. Thereafter, clinical and radiological examinations were performed at 3-month intervals as long as they were asymptomatic. During adjuvant TMZ therapy, patients were clinically evaluated monthly and subjected to a comprehensive investigation including CT or MRI at the end of cycles 3 and 6. Response criteria were evaluated based on clinical response together with the results of radiological neuroimaging studies and according to the US Medical Research Council's neurological scale and corticosteroid requirement. Responses were then grouped into four categories: 1) Complete response 2) Partial response 3) Stable disease 4) Progressive disease. Toxic effects are graded according to the National Cancer Institute General Toxicity Criteria version 2. Grade 1 indicates mild adverse effects, Grade 2 indicates moderate adverse effects, Grade 3 indicates serious adverse effects, and Grade 4 indicates life-threatening adverse effects.

Radiotherapy time frame; is defined as the time from day 1 of radiotherapy to day 28 after the last day of radiotherapy or to the first day of adjuvant TMZ therapy. The adjuvant chemotherapy segment; is defined as the period from the first day of adjuvant TMZ therapy to 35 days after the first day of the last TMZ course.

Progression-free survival (PFS); was determined as the time from the start of treatment to the date of progression of the disease, the date of the last control in patients without progression, and the date of death in patients who died without progression. Overall survival (OS); was defined as the time from the start of treatment to death.

2.1. Statistical analysis

The X-test (gender, age, type of surgery, KPS) and t-test were used when comparing patient characteristics that have an impact on prognosis. Kaplan-Meier method was used to calculate PFS and OS. The log-rank test was used when comparing the PFS and OS groups. Hazard Ratio and 95% CI (confidence interval) calculated p values were found. Statistical calculations were made using SPSS 11.0 program. $P<0.05$ was considered statistically significant.

3. Results

There was no significant difference in demographic and baseline characteristics between the two treatment groups. In the post-surgical radiotherapy-only (CER + RT) group, 14 (54%) cases were male, and 12 (46%) were female. Karnofsky performance scale values of all patients were evaluated as ≥80 before treatment (Table 1). In the group that received TMZ (CER + RT + TMZ) together with postoperative radiotherapy, 15 (53%) of the cases were male and 13 (47%) were female. In the CER + RT group, the youngest patient was 24 years old and the oldest was 71 years old; the mean age (± standard deviation) was 52.05 ± 13.02, and the median age was 50.5 ± 5. In the group receiving CER + RT + TMZ, the youngest patient was 25 years old and the oldest was 69 years old; the mean age (±standard deviation) was 49.65 ± 12.42, and the median age was 48.5 ± 4.4. Total excision was performed in 15 (57%) cases and subtotal excision was performed in 11 (43%) cases in the CER + RT group. In the group receiving CER + RT + TMZ, total excision was performed in 15 (53%) patients, and subtotal excision was performed in 13 (47%) cases. The median time from diagnosis to the start of treatment was calculated as 11.2 days in the CER + RT + TMZ group and 10.3 days in the CER + RT group. The mean duration of radiotherapy was 41.2 days in the CER + RT + TMZ group and 42.1 days in the CER + RT group (P=0.92).

Headache was the most common complaint in the study group at the time of admission to our clinic. Symptoms such as loss of

strength, epilepsy, forgetfulness, nausea-vomiting, and loss of consciousness were observed depending on factors such as the size of the mass lesion, the age of the case, and the location of the lesion. All subjects in the CER + RT group received radiotherapy at a total dose of 66 Gy (46 Gy to the whole brain + 20 Gy to the tumor bed) as planned. All patients in the CER + RT + TMZ group completed both radiotherapy and TMZ treatment as planned. The adjuvant TMZ cycle was applied to 28 cases in the CER + RT + TMZ group. Adjuvant TMZ could not be given to 1 of the cases after radiotherapy due to disease progression, 2 cases could not complete 6 cures of adjuvant TMZ treatment due to progression, and adjuvant TMZ treatment was terminated in 3 cases due to toxic effects. A total of 22 cases completed six treatment cycles as planned. Hematological side effects were not observed in the CER + RT group. CER + RT + TMZ (concomitant and sequential) was well tolerated. The main side effect was myelosuppression. In the concomitant RT + TMZ phase after surgery; Grade 3 and 4 thrombocytopenia occurred in 1 case, and Grade 2 anemia in 1 case. During adjuvant TMZ treatment; Grade 3 thrombocytopenia was found in 2 cases, grade 2 anemia in 1 case, and Grade 2 leukopenia in 1 case. No mortality due to treatment toxicity was observed.

Non-hematological toxicity was mild. In the combined treatment group, treatment-related rash was seen in 3 cases, constipation in 2 cases, and arthralgia in 1 case. No late-term neurological side effects were observed. As a non-hematological side effect in the CER + RT group; Grade 1 acute skin reaction was observed in 9 cases, grade 1 nausea and vomiting in 3 cases, and fatigue in 3 cases.

3.1. Treatment After Disease Progression

A second surgery was performed on 1 patient in the CER + RT group and 2 patients in the CER + RT + TMZ group who progressed. Rescue chemotherapy was not applied to any of the cases.

3.2. Survival Results in Patient Groups

When this study conducted in our clinic was evaluated in January 2010 during the data analysis phase, 26 (100%) of 26 patients in the CER + RT group died. Twenty-four (86%) of 28 cases in the CER + RT + TMZ group died, and 4 cases were still alive. There was progression in 3 (75%) of these 4 cases. The follow-up period of the cases in the CER + RT group; had a mean of 13.5 months (3-48 months), and a median of 13.70 (95% CI; 11.38 - 15.20) months. The follow-up period of patients in the CER + RT + TMZ group; had a mean of 14.32 (3-48 months), the median of 13.80 months.

The median PFS was 14 months in the CER + RT + TMZ group and 6 months in the CER + RT group (95% CI 0.05732 - 0.2742) **(**Figure 1). The log-rank test showed a significant PFS difference between the two groups (P < 0.0001). Median OS was 16 months in the CER + RT + TMZ group and 12.5 months in the CER + RT group (95% CI 0.3213–0.7654) **(**Figure 2). The log-rank test showed a significant difference in survival between the two groups (P= 0.0354).

3.3. Prognostic Factors

The effects of age, gender, and resection size, which are considered to be important prognostic factors, on PFS and OS were investigated as a stand-alone factors in both groups.

3.4. Survival Results in the CER + RT Group by Age

When examined by age, the median PFS in the CER + RT group was; It was found to be 5.6 months for those over 50 years of age and 7 months for those 50 years and younger (95% CI: 0.3276-2.357). This result was not statistically significant (P=0.5168). When analyzed by age, the median OS in the CER + RT group was 10 months in those over 50 years of age and 12.6 months in the group 50 years and younger (95% CI: 0.2436 - 2.251). This result was not statistically significant (P = 0.5842).

3.5. Survival Results in the CER + RT Group by Gender

When analyzed by gender, the median PFS in the CER + RT group was 6 months in female patients and 5 months in male patients (95% CI: 0.2946-2.5440). This result was not statistically significant (P=0.7568). OS was 13 months in female patients and 10.5 months in male patients (95% CI: 0.2865-2.216). This result was not statistically significant (P=0.7462).

3.6. Survival Results in the CER + RT Group by resection size

When analyzed according to resection size, the median PFS in the CER + RT group was 8 months in total resection and 5 months in subtotal resection (95% CI: 0.2567-2.867). This result was statistically significant (P=0.02). Median OS was 15 months for total resection and 8 months for subtotal resection (95% CI: 0.3257 - 3.584). This result was statistically significant (P< 0.01).

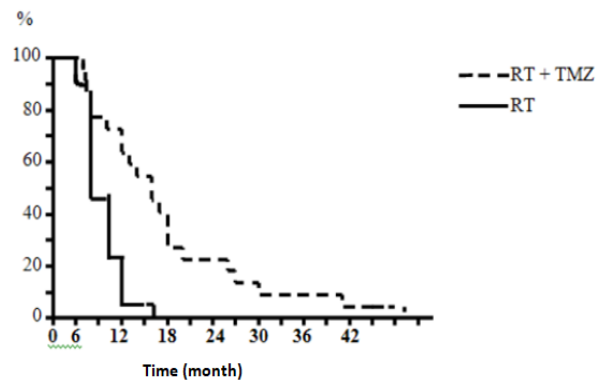

Figure 1
Progression-free survival in all patients

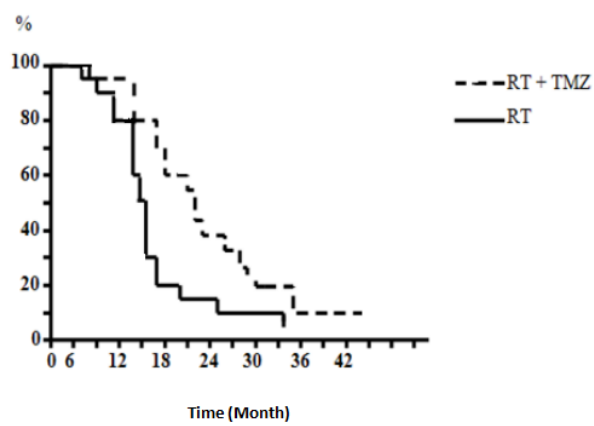

Figure 2
Overall survival in all patients

Table 1
Baseline demographic characteristics of the cases

		CER + RT	CER + RT + TMZ	P
Gender	Male	14	15	0.65
	Female	12	13	
Age	≤ 50	12	12	0.62
	> 50	14	16	
	Average ± SEM	52±13	49 ± 12.4	0.43
	Median ± CI	50,5±5	48.5 ± 4.4	
Surgery Type	Total	15	15	0.21
	Subtotal	11	13	
From diagnosis to treatment elapsed time (days) (Average)		10,3	11.2	

3.7. Survival Results in CER + RT + TMZ Group by Age

When analyzed according to age, the median PFS in the group receiving CER + RT + TMZ was found to be 9 months in those over 50 years of age and 13.5 months in those aged 50 and younger (95% CI: 0.8741–4.376). This result was not statistically significant (P =0.1363). Median OS was 16 months for those over 50 years of age and 18.6 months for those 50 years or younger (95% CI; 0.5965 vs 3.897). This result was not statistically significant (P=0.2865).

3.8. Survival Results in CER + RT + TMZ Group by Gender

When analyzed by gender, the median PFS in the group receiving CER + RT + TMZ was 12 months in female patients and 11 months in male patients (95% CI; 0.5359-3.965). This result was not statistically significant (P=0.4365). The median OS was 22 months in female patients and 20 months in male patients (95% CI; 0.3465-2.645). This result was not statistically significant (P=0.4985).

3.9. Survival Results in CER + RT + TMZ Group by Resection Size

When analyzed according to the size of the resection, the median PFS was found to be 14.5 months in the CER + RT + TMZ group, in those who underwent total resection, and 8 months in those who underwent subtotal resection (95% CI; 1.5641-2.385). Statistically significant (P = 0.012). Median OS was 18.5 months for total resection and 13 months for subtotal resection (95% CI; 0.1259 - 1.8649). This result was statistically significant (P = 0.03).

4. Discussion

GBM is the most lethal and least controllable primary CNS tumors. Despite various treatment approaches, the most important reason for failure in high-grade brain tumors is failure to achieve local control of the tumor. Despite advances in imaging, surgery, and radiotherapy techniques, patients with GBM have a poor prognosis. Therefore, the search for more effective chemotherapeutic agents is of great interest. It is important to determine the tumor size in planning the surgery and/or radiotherapy to be applied in the treatment of brain tumors, evaluating the response to treatment, and predicting the prognosis. It has been reported in the literature that tumor size before surgery + adjuvant treatment has a positive effect on survival, and the prognosis is poor if the tumor size is large enough to involve more than one lobe. Another factor that has an impact on survival is the location of the tumor. In brain tumors, the localization of the tumor, the extent of local spread, and its proximity to vital areas of the brain are important in terms of the degree of neurological damage [10-12]. In our cases, we get better results in more appropriately located cases such as the frontal and temporal lobes.

In many retrospective studies in the literature, it has been stated that aggressive tumor resection is a factor that prolongs survival in high-grade gliomas, the residual tumor size on postoperative CTs is more important than the preoperative size, and it correlates with the time of progression and prognosis of the tumor[11,12]. In brain tumors, factors such as tumor size before treatment and tumor size after surgery and/or radiotherapy, which have prognostic value, are still discussed. Post-surgical changes have a feature such as retention of contrast material in radiological examinations. Therefore, it is very difficult to distinguish between postoperative changes and residual tumors. In the studies, it was concluded that the radiological determination of the residual tumor is more appropriate in the first 3 days postoperatively. Because the postoperative changes start to hold the contrast agent as early as the 3rd day and the uptake peaks after approximately 2 weeks. This takes up to 45 days. Therefore, MRI should be performed in the first three days or 45 days after the treatment to detect the tumor size[13]. We did not evaluate our cases with MRI in the early period. We made a total-subtotal distinction only with cerebral CT. We found higher rates of PFS and OS in patients who underwent total resection in both of our study groups.

In a randomized phase III study conducted by the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC), the combined use of CER + RT and TMZ has been shown to prolong survival in patients with GBM[14]. In this study, 573 cases were randomized into two groups as only CER + RT and CER + RT with simultaneous TMZ and then adjuvant TMZ application. RT was administered 2 Gy/day x 30 fractions, a total of 60 Gy, within 6-7 weeks, excluding weekends. Simultaneous administration of TMZ at a dose of 75 mg/m^2/day from the first day to the last day of RT for a total of 49 days, including the

weekend, and adjuvant administration 4 weeks after the end of RT (150-200 mg/m^2/day) every 4 weeks 6 cycles were applied for 5 days. As a result of this study, While the median OS was 12 months in patients who received only CER + RT, it was 15 months in the arm combined with TMZ. While the 2-year OS was only 10% in the CER + RT group, this rate was 26% in the arm combined with TMZ. The median PFS was 5 months in the CER + RT arm alone, and 6.9 months in the TMZ combined arm. The 1- and 2-year PFS rates were 9% and 2% in patients who received CER + RT alone, compared to 27% and 11% in the arm combined with TMZ (P<0.0001). In this phase III study, a significant improvement in survival was demonstrated by combining CER + RT with TMZ in newly diagnosed GBM patients. Similar values were determined in our study, and we obtained similar results in our study.

Reardon et al[15] performed TMZ before post-surgical RT in patients with newly diagnosed GBM. Patients received four cycles of TMZ. At the end of the treatment, a reduction in tumor size was found in 52% of patients with GBM. 9% (3/33) of patients showed complete remission (radiologically no tumor detected), 42% (14/33) showed a partial reduction in tumor size, and only 12 (36%) of patients progressed.

In a phase II study by Athanassiou et al[16], 110 patients received 60 Gy RT after CER alone in one arm and TMZ at a dose of 75 mg/m^2/day concurrently with CER + RT in the other arm, followed by 150 mg/m^2/day 1-5 and 15 6 courses of adjuvant TMZ were applied every 28 days, between -19 days. In the results of this study, the median PFS was 5.2 months versus 10.8 months; 1-year PFS was 7.7% versus 36.6%, OS 7.7 versus 13.4 months, and 1-year OS 15.7% versus 56.3%. Toxicity was mostly hematological, and it was reported that 1 patient died due to grade IV myelotoxicity resulting in sepsis. Our PFS and OS results are in agreement with this study.

In the study of Huang et al[17], while the median PFS was 15 months in the 1st group in which 6 cycles of TMZ were given, the median PFS was 20.1 months in the 2nd group in which they gave more than 6 cycles of TMZ. The median OS in group 1 was 19.4 months. OS was 25.6 months in Group 2. Groups 1 and 2 had a 2-year survival rate of 36% and 66%, respectively (P=0.02). and 5-year survival was 7% in both. According to this study, the TMZ dose we applied to our patients seems to be sufficient.

In our study, as in other studies[14-17], toxicity was higher in the group in which adjuvant therapy was applied, but it was at acceptable levels. Nausea and vomiting, which were the most common side effects, were generally mild.

In our study, we made our subgroup analysis evaluations for age, gender, and surgical resection according to prognostic factors in both groups. Our results showed a statistically insignificant difference in both PFS and OS for age and gender. In terms of the amount of resection, a statistically significant difference was found in both groups in terms of both PFS and OS. In the first group, PFS was determined as 5 months and OS as 8 months in patients who underwent subtotal surgical treatment, while this period was 8 months and 15 months, respectively, in patients who underwent total surgical treatment. In the second group, PFS was determined as 8 months and OS as 18.5 months in patients who underwent subtotal surgical treatment, while this period was found to be 14.5 months and 3 months, respectively, in patients who underwent total surgical treatment. These results are consistent with the literature[18-20].

5. Conclusions

Although the number of cases in our study is lower than in other studies, it shows that 6 cycles of TMZ treatment following post-surgical RT combined with TMZ may be an effective agent by prolonging survival in newly diagnosed cases with GBM. It also demonstrates that it is important to start chemotherapy early in the disease to allow time for the drug to act against the rapidly growing tumor. It supports that it is superior to CER + RT therapy alone. With this treatment regimen, both PFS and OS will be improved and this beneficial effect will be achieved with a safe and tolerable chemotherapeutic agent. In these cases, this intensive and continuous treatment was generally applied without any problems. However, considering the cost of this treatment, it may be thought that the expected results would be much more acceptable (cost/benefit ratio). However, the presence of such adjuvant treatments in these tumors with a very poor prognosis gives hope for the development of other treatment modalities.

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Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by for this study the Cukurova University Institution Ethics Committee (2010-Thesis number 247902).
https://tez.yok.gov.tr/UlusalTezMerkezi/tezDetay.jsp?id=F_E_jXAckxV6q8q2gxDqXg&no=LFoKzqq7GW9ilSrzaL1JLg

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Author contributions

Collection of the data, draft: MU, SS, Writing of the article, performed the analysis, review of the literature: SY, EA, Critical review of the article, design of the study: HB,UT,EK

All authors read and approved the final manuscript.

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