Effects of Dimethyl Fumarate on the Karnofsky Performance Status and Serum S100β Level in Newly Glioblastoma Patients: A Randomized, Phase-II, Placebo, Triple Blinded, Controlled Trial

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Abstract

Background: Glioblastoma (GBM) is the most common primary central nervous system malignancy with a low survival without extra logistics. Currently, there is no definitive chemotherapy among the studied options. This study aims to evaluate the neuroprotective effects of dimethyl fumarate (DMF) on surgical brain injuries in patients treated for GBM.

Materials and Methods: This randomized, phase II, placebo, triple-blinded, controlled trial was performed on 36 patients with a diagnosis of GBM. All the patients received DMF (240 mg, three-times per day) or placebo (with the same shape and administration route) one week before surgery. Also, patients in both groups after the operation received standard treatments (radiotherapy plus chemotherapy). In addition, Kanofsky's performance status (KPS) score was evaluated at baseline and one month later. Also, serum S100β was measured 48 hours before and after surgery.

Results: There was no significant difference among DMF and control groups with regard to age, gender, and the extent of resections (P>0.05). The most adverse event in both groups was a headache. Although the serum S100β level was not markedly changed after surgery, the mean KPS in the DMF group was higher than in the control group after surgery.

Conclusion: The DMF could be a possible good regime for the treatment of GBM; however, questions are raised regarding its efficacy and application for the addition to standard treatment.

Keywords: Glioblastoma; Kanofsky's Performance Status; Dimethyl Fumarate; S100β; Surgical Brain Injury
Introduction

Glioblastoma multiforme (GBM) is the most common primary central nervous system (CNS) cancer among adult populations worldwide [1]. The estimated incidence rate of GBM is 3.19 per 100,000 in the USA [1, 2]. GBM, yet, remains amongst cancers with the worst prognosis, with only a small proportion of patients achieving long-term remission. Several studies have shown that only 2.2% of patients survive three years or more after diagnosis, a figure that should increase in the near future with recent therapeutic advances [3, 4]. Currently, the European society for medical oncology recommends concomitant chemo-radiotherapy and radiotherapy (a total of 60 Gy) along with daily intravenous temozolomide (TMZ) with maintenance TMZ implemented for 6–12 cycles (every 28 days) as the standard of care (SoC) for GBM after surgery [5].

Despite recent therapeutic advances, the survival rate of GBM patients has not increased significantly, making the development of new therapeutic approaches a top priority for researchers. Due to the rapidly evolving nature of GBM and the high risk of resistance to new drugs, the development of new drugs is not considered efficient [6, 7]. Therefore, identifying new applications for existing drugs with known pharmacokinetics and safety characteristics has gained a lot of interest [8, 9]. One previously used drug with a good efficacy profile is dimethyl fumarate (DMF). The DMF, a fumaric acid methyl ester, has been used in several clinical trials for its anti-inflammatory properties and is currently used to treat relapsing multiple sclerosis and psoriasis [10, 11]. The potential benefits of DMF as an anti-cancer agent have been shown in preclinical models of melanoma [12], breast cancer [13], cervical cancer [14], colon cancer [15], GBM [16], ovarian cancers [17], and lung cancers [17].

In addition to the anti-cancer features, DMF has been shown to have neuroprotective effects, which is of special interest in the surgical management of CNS cancers. Since even with the highest precision, number of surgeries, matter to the surgeon’s experience, injuries to the brain tissue and lead to cerebral edema, ischemia, etc. [18]. Studies have shown that cerebral edema following a blood-brain barrier (BBB) disruption plays a mainstay role in the pathophysiology of surgical brain injury (SBI). Therefore, treatments that can reduce BBB damage can reduce cerebral edema after surgery and, ultimately, SBI [19, 20]. Since the serum level of S100β—a protein found in the cytoplasm and nucleus of many cells in the body—rises with disruption of the BBB integrity, it is considered a good indicator for measuring the effect of drugs on the integrity of the BBB during brain injury [19]. Phase-I clinical trial of using DMF with TMZ and radiotherapy in patients with GBM was performed in 2017, which revealed the safety of this drug in these patients [21]. We hypothesize that due to DMF’s anti-inflammatory feature and its effects on BBB, it might have a positive effect on the outcome of surgical treatment in patients with GBM [21, 22]. Hence, in this phase-II clinical trial, we aimed to evaluate and compare the efficacy of DMF comparison with SoC in individuals suffering from GBM.

Materials and Methods

Sample Size
To calculate the sample size, PASS 11 software (NCSS, LLC Kaysville, Utah, USA) was used to compare the Karnofsky performance scale (KPS) score using the non-inferiority test of the difference between the two means. The information used to determine the sample size was the mean of the KPS score (73) in the placebo group obtained from previous studies [21]. The new treatment was expected to increase KPS mean score by about 10 points to an average of 83. Therefore, to determine the sample size according to these hypotheses and at the 95% confidence interval (CI) and statistical powers of 80%, the sample size was calculated to be 18 individuals for each group.

Trial Design and Participants
This study was a phase-II, randomized, triple-blinded, placebo, controlled trial on the patients who were selected from those re-
ferred to Shariati Hospital of Tehran University of Medical Sciences (a tertiary academic hospital) located in Tehran, Iran. In the active sampling phase for lasting 40 months (from 2018 to 2021), eligible patients were enrolled in the study. All of the patients were candidates for surgery for the first time based on the initial radiological diagnosis of GBM. Two researchers evaluated all patients in terms of inclusion and exclusion criteria (Table-1). In addition to pre-operative imaging, post-operative pathology was also evaluated by an experienced neuropathologist. To better assess the KPS change, individuals with new neurological deficits after surgery were excluded from the study.

Randomization and Blinding
Randomization was done using the block randomization technique, and patients were assigned in a 1:1 ratio to receive dimethyl fumarate or a placebo. The list of random allocations of individuals in groups was based on 4, 6, and 8 random blocks and was done by the person in charge of randomization with concealment. The person performing randomization did not have information about the type of intervention. Surgeons, patients, and statistical analysts were blinded in all steps, capsule content, and each patients’ allocation group and remained so until trial closure.

Interventions
All of the surgeries were done by a single surgical team (under the supervision of A.K). After surgery, all patients were referred to the same radiotherapy and chemotherapy center to receive up-to-date SoC. This treatment for newly diagnosed glioblastomas includes maximum safe surgical resection, radiotherapy (60 Gy, 2 Gy per day, five days a week for six weeks), and concomitant intravenous chemotherapy (TMZ; 75mg/m²/day, for six weeks), and then oral chemotherapy with TMZ (150-200mg/ m² day, 1-5 days per 28 days, six cycles).

Table 1. Inclusion and Exclusion Criteria.

| Inclusion | Exclusion |
|-----------|-----------|
| 1. Newly diagnosed GBM based on T1-weighted MRI with contrast | 1. History of acute or chronic diseases with poor prognosis, autoimmune diseases, immunodeficiency with a history of previous cancer |
| 2. Age ≥ 18 years | 2. Any infection in the last two weeks |
| 3. Taking contraceptive medication | 3. Drug allergies to TMZ, DMF |
| 4. History of coagulation disorder or hemorrhagic diseases | 4. History of coagulation disorder or hemorrhagic diseases |
| 5. Previous history of GBM | 5. Previous history of GBM |
| 6. Pregnancy or breastfeeding | 6. Pregnancy or breastfeeding |
| 7. High liver enzymes (above twice normal) and proteinuria (more than 150 mg per day) | 7. High liver enzymes (above twice normal) and proteinuria (more than 150 mg per day) |
| 8. Primary WBC count less than 3500 and/or lymphopenia below 500 | 8. Primary WBC count less than 3500 and/or lymphopenia below 500 |
| 9. History of any immunologic disorders during less than six months | 9. History of any immunologic disorders during less than six months |
| 10. Existence of tumor metastasis | 10. Existence of tumor metastasis |
| 11. Other malignancies | 11. Other malignancies |
| 12. A history of obvious head trauma in the last three months | 12. A history of obvious head trauma in the last three months |
| 13. Psychosis and cognitive impairment | 13. Psychosis and cognitive impairment |
| 14. History of disability due to other neurological diseases such as CVA and hemiparesis | 14. History of disability due to other neurological diseases such as CVA and hemiparesis |
| 15. Contraindications for MRI | 15. Contraindications for MRI |

GBM: Glioblastoma; MRI: Magnetic resonance imaging; TMZ: Temozolomide; DMF: Dimethyl fumarate; WBC: White blood cells; CVA: Cerebrovascular accident
Patients in both groups underwent their routine medication as before. Patients in the DMF group received 240 mg capsules (three times a day) from one week before surgery until the day of surgery, in addition to the usual treatments. The control group went through all the steps similar to the treatment group, and instead of DMF, a placebo capsule with the same shape and substance other than the main drug, such as the same preservatives, was administered. A schematic figure of the trial is presented in Figure-1.

**Outcomes**

Electronic information of each patient, including clinical information, radiological findings, and surgical information were recorded. Baseline information of patients, symptoms, the extent of tumor removal with surgery, imaging details, and histology were prepared and recorded. Also, all the adverse events regarding treatment were recorded.

Tumor resection was performed as gross total resection (GTR; > 99% of enhancement), near-total resection (NTR; 90-99% enhancement), and subtotal resection (STR; <90% of enhancement). The extent of resection was defined by a neuroradiologist based on 48-hours post-operative magnetic resonance imaging (MRI; the Siemens MAGNETOM Avanto 1.5T) of each patient. Lesion biopsy was also recorded based on the surgeon’s opinion.

In order to evaluate the level of S100β, blood samples were taken from all patients 48 hours before and after surgery by the method of enzyme-linked immunosorbent assay using the commercially kit (Roche diagnostics Corp., Basel, Switzerland). The KPS questionnaire was obtained from all patients before surgery by one of the researchers, and all of them were re-evaluated by the same researcher one month later in the outpatient clinic.

**Ethical Considerations**

This study was approved by the Research Ethics Committees of the School of Medicine, Tehran University of Medical Sciences (code: IR.TUMS.MEDICINE.REC.1398.344). Also, this study was registered in the Iranian Registry of Clinical Trials under the number IRCT20200226046624N1 (available at https://fa.irct.ir/trial/46358).

All patients were informed verbally as well as in writing with a pre-designed consent form including possible complications, allocation strategies, the implication of the study and its objectives. All patients received contact information from the relevant researcher and were advised to contact him if they had any questions and/or concerns. All patient information in this study was recorded confidentially, and when using the information, personal information from which patients could be identified was removed. Also, the research team covered all costs in addition to the standard treatment process for the patients, and no additional costs were imposed on the patients.

**Data Analysis**

All data were recorded on electronic forms using SPSS V22 (IBM, Armonk, NY, USA) software. The normal distribution of data was examined, and based on the data distribution, independent t-test and chi-square tests were used. In comparison with baseline measurements, to control for baseline value, analysis of covariance test was used. For non-parametric variables, the Mann-Whitney U test was used. P-value<0.05 was considered significant.

**Results**

A total of 41 patients with GBM who met the eligibility criteria were enrolled.

Figure 1. A: schematic representation of the trial process. I: specific to intervention group; C: specific to control group; B: both groups.
A CONSORT flowchart of the study is presented in Figure-2. Five patients (2 intervention and 3 control) were excluded from the study as their neurological condition deteriorated after the surgery; hence, they could not be evaluated using the KPS score. Histopathological examination of retrieved specimens during surgery for all of the participants confirmed the diagnosis of GBM. The mean age of patients in the placebo and DMF groups were 48 ±16.55 years and 47.7 ± 11.57 years, respectively (Table-2). The statistical test showed no significant difference between the mean age of patients in the DMF and placebo groups (P=0.9). In the placebo group, 13 patients (48.1%) and in the DMF group (51.9%) were male patients (P=0.07). The baseline characteristics of patients are presented in Table-2. There were no marked differences among baseline characteristics of patients. Overall, 31 (86.1%), 3 (8.3%), and 2 (5.6%) patients underwent GTR, NTR, and STR, respectively. There were no statistically significant differences in the extent of resection among the studied groups (P>0.05).

**Outcomes**

The most common complication in all patients was headache (25%). Also, 14 patients (38.9%) did not report any adverse effects. The most common adverse events were headaches (n=5) in the control group and headaches and vomiting (n=4) in the DMF group. The chi-square test showed that the frequency of adverse events was not significantly different between the two groups (P=0.95).

**Figure 2.** CONSORT flow diagram of the study.
The highest and lowest KPS score of patients before surgery was 80 and 70 in both groups, respectively. The mean KPS score of patients before surgery in the control group was 72.22 ±4.27, and the mean KPS score of patients before surgery in the DMF group was 73.94±5.09. The KPS score of patients before surgery was not significantly different between groups (Figure-3A, P=0.406).

The mean KPS score of patients after surgery in the control group was 71.11±8.32. The mean KPS score of patients after surgery in the DMF group was 81.22±7.58. The statistical test showed that the KPS score after surgery, when corrected for baseline KPS score, was higher in the DMF group, and the KPS after surgery was significantly different between the two groups when assessed by the Mann-Whitney U test (Figure-3B, P=0.001).

The mean pre-operative serum concentration of S100β in the control group patients was 0.6±0.18 μg/l. At the same time, this concentration before surgery in the DMF group was 0.48±0.19 μg/l (Figure-4A). However, the mean serum concentration of S100β after surgery among patients in the control and DMF groups were 0.59±0.26 μg/l and 0.51±0.2 μg/l, respectively (Figure-4B). The present study showed that the mean serum concentration of S100β in patients before (95% CI: -0.005 to 0.25, P=0.06) and after (95% CI: -0.08 to 0.24, P= 0.31) surgery was not statistically significant between the two groups (Figure-4).

Discussion

Neurosurgical procedures are invasive, whether elective or emergency. Due to the unique nature of the nervous system, iatrogenic brain injury, to some extent, is inevitable. Surgeries performed on sensitive areas, no matter the surgeon’s experience and accuracy, are linked to post-operative neurological deficits. The brain tissue in the periphery of the surgical site is extremely susceptible to injury caused by surgical procedures. Therefore, it is crucial to monitor and manage these changes postoperatively to minimize long-term neurological sequelae.
by essential surgical techniques such as incision, retraction, and electrocauterization. The most commonly observed complications are brain edema and hemorrhage following SBI [23]. Despite many advances in endoscopic techniques, unavoidable SBI can eventually lead to neurological damage and adverse outcomes for the patients [24].

In this study, 36 patients with GBM were studied. Mean age and gender distribution did not differ between the control and DMF groups. The most complaint of patients in both groups was a headache. The KPS score before surgery was not significantly different between the control and DMF groups. The KPS score after surgery was significantly increased compared to the control group. * P≥0.01 vs. Control.

The KPS score is a broad scale for classifying patient prognosis and determining appropriate management in GBM [25]. The low pre-operative KPS score is associated with shorter overall survival [26]. However, surgery can have a significant effect on the patient’s functional status, which in turn changes their KPS score [27]. Previous studies have shown that although patients’ KPS scores can decrease significantly in the short term (one to five days after surgery), it returns to baseline and are higher after about two weeks [25, 26]. In the present study, the mean KPS score in the control group before surgery was 72, and after surgery was 71. Therefore, it seems that the KPS score of patients did not differ in the short term. However, the pre-operative mean KPS score in the DMF group increased from about 73 to about 81.
Considering that the extent of tumor resection and the initial manifestations were not statistically significant between the two groups, DMF could benefit patients regarding their performance. Also, in line with the results of the study of Patel et al. [25], although KPS one month after surgery was generally at least equal to that before surgery, the relative increase and improvement in functional status in the DMF group may have been due to the effects of DMF.

The study by Chambless et al. [27] also showed that the mean KPS scores before and after surgery were 70 and 80, respectively, and 57% of patients experienced an improvement in their KPS score after surgery. In the present study, this rate was significantly higher in the DMF group than in the control group. On the other hand, the surgical resection rate is an independent factor in the prognosis and functional status of patients [28].

In the present study, almost all patients in both groups underwent GTR. Also, the KPS score and age of patients in the two groups before surgery were not significantly different from each other. Therefore, it seems that due to the lack of significant differences in age, gender, and KPS score before surgery between the two groups, KPS improvement in the intervention group can be one of the effects of DMF.

The present study showed that the amount of S100β before and after surgery was not significantly different between the DMF and control groups. It was expected that, the S100β should increase relative due to trauma and tissue damage from surgery. In contrast, this was not observed in any of the groups. Therefore, one of the reasons for this could be GTR with minimum damage to healthy tissues.

On the other hand, although the DMF in this study did not significant change on the S100β level, it improved the KPS score of the patients. Therefore, considering that the duration of DMF administration was about one week before surgery, its ineffectiveness might be due to the short time of drug administration. We may also indicate that DMF might not lead to neuroprotection through prevention of BBB integrity disruption but through other means.

The present study results showed that headache was the most common complication after surgery with no significant difference between the two groups. Therefore, DMF seems to be a safe drug, and its possible adverse effects are mild.

**Limitations**

Our study has some limitations. First, the DMF administration period, as well as the follow-up, were short. Also, we cannot examine overall and progression-free survival among the studied patients. However, based on our short-term results and considering controlling several confounding factors, such as the extent of resection and pre-functional status, a relative improvement in KPS score could be due to the possible effect of the DMF. In contrast, there may be a lack of effectiveness in a longer follow-up by eliminating other confounding factors. In future studies, overall survival and disease progression should be evaluated in GBM patients using DMF. Also, a bigger sample size is required with longer administration period of the drug to assess its effectiveness.

**Conclusion**

The present study results showed that the administration of DMF in patients with GBM might cause a relative improvement in the functional status of patients in the short term. However, it did not have a significant effect on the serum S100β level. In addition, DMF administration has no serious adverse effects, and due to its limited and possible efficacy, as well as its high cost, it is recommended that this drug could be used as a neoadjuvant treatment only in certain groups of patients, and selectively depending on the patient’s condition so that it may be effective in short-term among patients with poor prognosis.

**Conflict of Interest**

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest. Also, one of the authors of the article (Ehsan Jangholi) is the “deputy editor” of the journal. Based on the journal policy, this author was completely excluded from any review process of this article.
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