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ORIGINAL ARTICLE

Benefit and outcome of using temozolomide-based chemoradiotherapy followed by temozolomide alone for glioblastoma in clinical practice

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Summary

Purpose: *Temozolomide (TEM), an oral alkylating agent, has shown promising activity in the last 10 years in the treatment of glioblastoma multiforme (GBM). Our goal was to show the benefit of concomitant therapy involving 3D conformal radiotherapy and temozolomide in clinical practice.*

Methods: *This was a retrospective/prospective study and included a total of 113 patients with GBM diagnosis. Forty-seven patients received postoperative radiotherapy and 66 received concomitant temozolomide plus 3D conformal radiotherapy.*

Results: *The mean overall survival of patients who received postoperative radiotherapy alone was 9.93±6.475 months, compared to statistically longer overall survival in the group of patients who received radiotherapy plus temozolomide (13.89±8.049 months) (p=0.006). The latter group was divided into two subgroups, one consisting of patients who received 6 complete cycles of temozolomide, and a second with patients who received incomplete treatment. Statistically significant longer overall survival was registered in the first subgroup compared to the second (p=0.006).*

Conclusion: *The concomitant usage of temozolomide and radiotherapy was beneficial, and statistically significant difference among groups and subgroups was observed regarding overall survival.*

Key words: *glioblastoma, radiotherapy, temozolomide*

Introduction

Primary malignant brain tumors commonly include astrocytomas, oligodendrogliomas, and ependymomas, with astrocytomas representing the most common type which comprises around 76% [1]. The World Health Organization (WHO) has defined 4 histological grades of astrocytomas that range from the less aggressive tumors (grade I) to highly malignant tumors (grade IV). The most malignant type of grade IV astrocytomas is GBM, which has a median survival time limited to approximately 10-15 months [2]. GBM is histologically characterized by its increased cellularity and mitotic activity, with additional necrosis or endothelial proliferation [1-4].

GBM is the most common primary brain tumor and accounts for over 51% of gliomas [5]. The average age of incidence of primary GBM is 62 years [4]. It occurs in both men and women, however, primary GBM occurs more frequently in males, while secondary GBM occurs more frequently in females [6]. Beside necrosis and endothelial proliferation, it is also characterized by very important immunohistological and molecular markers. These markers can predict overall survival, but up to date, except for O^6-methylguanine DNA (MGMT) methyltransferase methylation, no statistically significant association between biomarkers and drugs on the one hand and

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overall survival benefit on the other hand has been found.

Although there are many kinds of treatment available for GBM including surgical resection, chemotherapy, and radiation therapy, the average survival time following diagnosis of GBM patients is only 14 months [7]. Furthermore, the 5-year survival rate of GBM is very low. If complete surgical resection is impossible due to the location of the tumor, partial resection may be performed; however, partial resection is associated with significantly lower survival rates [8]. Although there are many different chemotherapeutic agents available for the treatment of GBM, the current standard chemotherapy used is temozolomide. Temozolomide is an oral alkylating agent and inhibits DNA repair mechanisms in tumor cells [9-11]. In comparison to other different chemotherapeutic agents available, temozolomide is associated with the lowest incidence of recurrent gliomas and longer survival rates. During the last decade certain advancements were made in radiotherapy of GBM as well. Advancements were done in the development of new techniques in radiotherapy and usage of MRI-CT image registration and fusion for better delineation of the target volume in GBM [12].

Despite these advancements in all three treatment modalities for GBM, there are researchers trying to develop of new target drugs, but up until today none of them has shown statistically significant increase in overall survival in newly diagnosed GBM patients [13]. Even with aggressive surgical resections using state-of-the-art preoperative and intraoperative neuroimaging, along with recent advances in radiotherapy and chemotherapy [14], no better survival of GBM patients has been reached.

The gold standard in the treatment of GBM patients is surgical resection, followed by temozolomide concomitant with 30-days radiation therapy with 60Gy. This treatment is followed by prolonged temozolomide therapy in 6 cycles [15].

The objective of the present study was to assess the effectiveness of temozolomide in addition to radiotherapy in patients with newly diagnosed GBM in the northern Serbian province Vojvodina in routine clinical practice at the Oncology Institute of Vojvodina, second largest oncological center in Serbia.

Methods

In the present study we used GBM patients data who were treated at the Oncology Institute of Vojvodina, from January 2007 to January 2015. The study was retrospective/prospective and included in total 113 patients with GBM diagnosis. Among the total number, 47 patients received postoperative radiotherapy alone (group I) and 66 received concomitant temozolomide plus 3D conformal radiotherapy (group II). Among the latter 66 patients, 37 received incomplete temozolomide treatment (1-5 cycles) (subgroup IIa) and 29 received regular 6 cycles of temozolomide after chemoradiotherapy (subgroup IIb) at a dose of 150 to 200mg/m^2. All of the patients had pathological confirmation of GBM. Both subtypes of GBM, namely giant cell and gliosarcoma, were also included. Patients with a secondary glioblastoma, based on a prior histopathological diagnosis of a lower grade astrocytoma, were excluded as well as patients with prior chemotherapy and patients with low performance status.

Group I consisted of patients treated from January 2007 and December 2011. The treatment planning of these patients was realized using Xio 4.52 software. Delineation was done on CT data. Group II consisted of patients treated with concomitant chemoradiotherapy (radiation+temolozomide) from January 2012 to January 2015 and delineation was done on mutual MRI and CT data, with help of image registration and fusion with XiO 4.52 software.

In group II each patient was scanned in the treatment position with immobilization devices. CT data were exported from CT simulator and sent to the radiotherapy treatment planning system. The MR data were obtained by a Siemens Avanto or Siemens Magnetom Trio. The patients were scanned according to the standard diagnostic protocol, and records were stored in the hospital Picture Archiving and Communications System (PACS).

The first step in correlating CT and MR images was image registration. Image registration is the process in which two image data sets are put into the common coordinate system. Registration and fusion were immediately visually evaluated. Visual inspection of all slices and cross-sections means that registration and fusion have actually passed individual quality control, i.e. verification of resulting image matching [16]. Manual correction of image registration was necessary in some cases, depending on the matching results, i.e. quality of CT and MR data in certain cases where CT set was used as a reference, and MR set was reoriented and registered to the CT coordinate system.

The next step was a delineation of target volumes, gross tumor volume (GTV), clinical target volume (CTV), planning target volume (PTV) and the organs at risk (OARs), according to recommendations in both patient groups, with the difference that delineation in group I used only CT data [12]. RTOG and NCCN recommendations have been used for delineation, depending on the patient. There are two major approaches to delineating the CTV. The recommendation of the European Organization for Research and Treatment of Cancer (EORTC) is to deliver radiotherapy in a single phase (60 Gy, 2 Gy per fraction) while the Radiotherapy and Oncology Group (RTOG) recommends two phases starting with a larger volume that receives 46 Gy before ''coning down" for the additional 14 Gy. Criteria for different recommendations were tumor location, the tumor volume, and MRI-CT fusion possibility. Besides the delineation of the target volumes, the following OARs were

delineated: cochlea, eyes, lacrimal gland, brain stem, optic chiasm, optic nerves, retina and hypophysis [17].

Concomitant chemotherapy in group II consisted of temozolomide (marketed as Temodal in Europe and Canada and Temodar in the United States; Schering-Plough) at a dose of 75 mg/m^2 per day, given 7 days per week from the first day until the last day, but for no longer than 42 days.

After a 4-week break, patients received up to 6 cycles of adjuvant temozolomide according to the standard 5-day schedule every 28 days. The dose was 150mg/m^2 for the first cycle which was increased to 200mg/m^2 beginning with the second cycle to the end of the sixth cycle, according to Stepp et al. [15].

Statistics

The obtained data were processed in SPSS v17.0 software package [18]. The mean survival time and standard deviation were calculated for all analyzed groups and subgroups, and comparison between groups was carried out by Student's t-test, one-way ANOVA and *post-hoc* Tukey HSD test. Furthermore, comparison of survival between different groups/subgroups was done and graphically represented by Kaplan-Meier curves and log rank (Mantel-Cox) test. Statistical significance was set at $p<0.05$.

Results

The mean overall survival in group I (post-operative radiotherapy alone) was 9.94 months, compared to statistically longer overall survival in the group of patients who received chemoradiotherapy (group II: 13.88 months) (p=0.006). The mean overall survival in the total patient cohort was 12.24 months (Table 1).

Subgroup IIa consisted of patients who received 6 complete cycles of temozolomide, while subgroup IIb comprised patients with incomplete temozolomide treatment. Statistically significant difference in mean survival was observed between groups I and II (p=0.004). *Post-hoc* analysis revealed statistically significant difference in mean survival between group I and subgroup IIb (p=0.001). Comparison of mean survival between subgroup IIa and IIb revealed longer mean survival in the group of patients who received complete temozolomide treatment (12.08 vs 16.17 months), but without statistically significant difference (p=0.066) (Table 2).

In order to test age as a prognostic factor, the total patient cohort, regardless of the applied therapy, was divided in the elderly group (≥65 years) and younger group (≤64 years), according to WHO classification. Statistically significant longer overall survival was noted in the younger group, with mean overall survival of 13.21 months, as compared to 9.88 months in the elderly group (p=0.035) (Table 3).

Kaplan-Meier method was used for comparison between group I and II (Figure 1) and survival after 6, 12 and 24 months (Table 4). Statistically significant difference (p=0.006) in overall survival (in months) was observed between the groups.

Table 1. Mean survival time in months in GBM patients groups

Treatment (Groups)	*n*	*Mean*	*SD*	*p value*
I (RT)	*47*	*9.94*	*6.475*	
II (RT+Temozolomide)	66	13.88	8.049	0.006
Overall	133	12.44	7.657	

Table 2. Mean survival in months in GBM patients groups and subgroups

Treatment (Groups/subgroups)	*Treatment (Groups/subgroups)*	*Mean*	*SD*	*p value*
I (RT)	*IIa (RT + Incomplete TEM)*	*12.08*	*6.475*	*0.378*
	IIb (RT + Complete TEM)	16.17	7.522	0.001
IIa (RT + Incomplete TEM)	I (RT)	9.94	8.242	0.378
	IIb (RT + Complete TEM)	16.17	7.657	0.066
IIb (RT + Complete TEM)	I (RT)	9.94	6.475	0.001
	IIa (RT + Incomplete TEM)	12.08	7.522	0.066

RT: radiotherapy, TEM: temozolomide, SD: standard deviation

Table 3. Means in months for survival in GBM patients age (WHO classification)

Age groups, years	*n*	*Mean*	*SD*	*p value*
≤ 64	*80*	*13.21*	*8.322*	*0.035*
≥ 65	33	9.88	5.110	

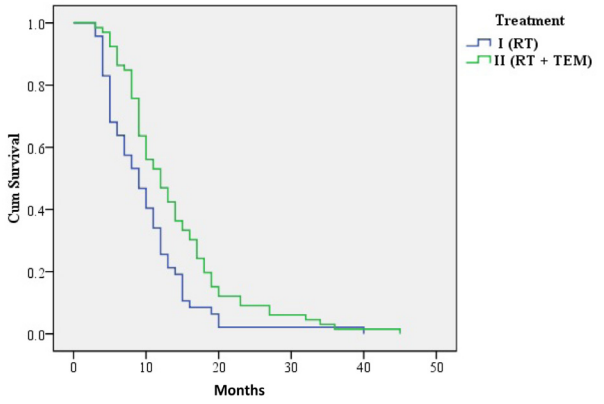

Figure 1. Kaplan-Meier survival of group I and II of GBM patients (p=0.006).

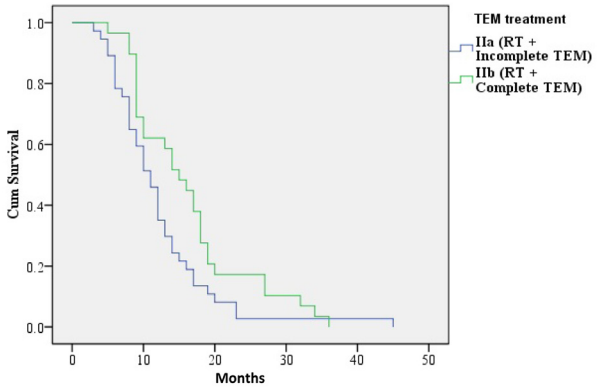

Figure 2. Kaplan-Meier survival of subgroups IIa and IIb of GBM patients (p=0.001).

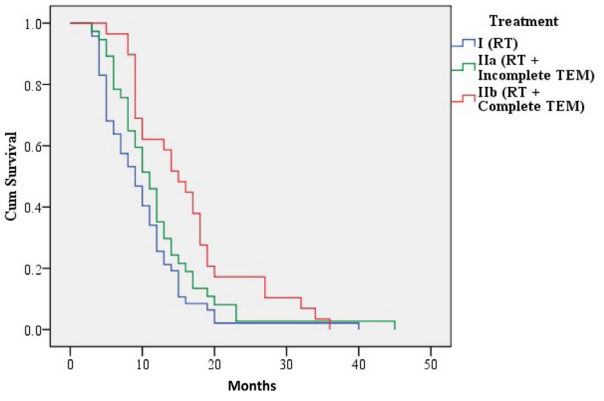

Figure 3. Kaplan-Meier survival comparing group I and subgroups IIa and IIb of GBM patients (p=0.006).

Table 4. Survival in group I and group II of GBM patients

Groups	*6 months (%)*	*12 months (%)*	*24 months (%)*
Group I (RT)	63.8	25.5	2.1
Group II (RT+TEM)	86.4	47	9.1

RT: radiotherapy, TEM: temozolomide

Table 5. Survival in subgroup IIa and IIb of GBM patients

Subgroups	*6 months (%)*	*12 months (%)*	*24 months (%)*
Subgroup IIa	96.6	58.6	17.2
Subgroup IIb	78.4	35.1	2.7

The overall survival in group II after 6, 12 and 24 months was 26.4, 4.7 and 9.2%, respectively vs 63.8,25.5 and 2.1% in group I.

Kaplan-Meier method was also used for comparison between subgroup IIa and IIb (Figure 2) and survival after 6, 12 and 24 months (Table 5). Overall survival (in months) was highly different (p=0.001) between subgroups. Overall survival in subgroup IIa in 6, 12 and 24 months was 96.6, 58.6 and 17.2%, respectively vs 78.4, 35.1 and 2.7% in subgroup IIb.

For the complete overview of the obtained data, Kaplan-Meier method was also used for comparison between group I and subgroups IIa and IIb (Figure 3). Statistically significant difference in overall survival was observed between groups I and subgroup IIb and also between subgroups IIa and IIb. However, no significant difference was found between group I and subgroup IIa.

Discussion

GBM represents the most malignant primary brain tumor. Despite extensive efforts and advancements in treatment, the 2-year survival rate is very low [15]. The treatment of GBM represents a great challenge. Until recently, prolongation of survival was attempted to be reached by chemotherapy applied prior or after radiation therapy with modest success [19].

Recently, according to the results of Stupp et al. study [15], temozolomide concomitant with radiotherapy followed by 6 cycles of adjuvant temozolomide has been applied and showed statistically significant increase in survival in GBM patients. Our study was designed based on clinical practice, not on rigorous criteria of a clinical study. The outcome of randomized controlled trials cannot be directly applied without considering differences in patient characteristics between the trial population and patient populations in routine clinical practice. In our study, we evaluated survival according to present data, for two main groups (one receiving postoperative radiotherapy alone and the second receiving radiotherapy plus temozolomide followed by adjuvant temozolomide (completed or non-completed)). The results of our study showed statistically significant prolongation of the mean survival time in the group receiving radiotherapy plus tomozolomide.

Other studies also reported benefit from chemoradiotherapy (radiotherapy plus temozolomide). Raj et al. [20] demonstrated a mean survival of 15.4 months in the group of patients receiving chemoradiotherapy, as compared to the group receiving only radiotherapy (12.4 months). Karacetin et al.

[21] detected mean survival of 19 months in patients who received radiotherapy plus temozolomide and 11.5 months in those with radiotherapy alone. Similar benefit was found by Wang et al. [22]. In a clinical study conducted by Stupp et al. [15] the mean survival time was 14.6 months in the group treated by concomitant temozolomide, as compared to 12.1 months in the group treated by postoperative radiotherapy. Results presented by van Genugten et al. [23] based on clinical practice, with a design similar to our study, revealed a mean survival time of 12.0 months in the radiotherapy plus temozolomide group, while in patients who received postoperative radiotherapy alone survival was 8 months only.

The 6-month survival after therapy in a study performed by Muni et al. [24] was 95% in patients treated by radiotherapy plus temozolomide vs 78% in patients who underwent postoperative irradiation alone. In a study by Stupp et al. overall survival was 86.3 vs 84.2%, registered in patients treated by radiotherapy plus temozolomide vs patients undergoing postoperative radiotherapy alone after 6 months [15].

One-year survival varied among different studies that examined temozolomide effects. Wick et al. [25] presented a study of one-year survival rate, which in the group of patients treated with temozolomide was 72%, whereas in our study the corresponding figure was 47%, but not lower when compared to the patients who received postoperative radiotherapy alone. Stupp et al. [15, 26] showed one-year survival rate from 61% in the temozolomide vs 50.6% in the group with radiotherapy alone. Muni et al. showed one-year survival rate of 20%, contrary to 5%, in favor of radiotherapy plus temozolomide [24].

Considering 2-year survival, Stupp et al. [15] found 26.5 and 10.4% for radiotherapy plus temozolomide and radiotherapy only, respectively. In our study, the 2-year survival was 9.1% vs 2.1%, favoring patients treated with a combination of radiotherapy plus temozolomide. Considering various studies available, it could be observed that with current treatment (temozolomide plus radiotherapy followed by temozolomide alone) approximately only 2-5% of patients with newly diagnosed GBM are expected to survive longer than 2 years [15]. In the present study, we presented results from our clinical practice, and not as a rigorously controlled trial. We have had two groups of patients treated by chemoradiation (radiotherapy plus temozolomide followed by temozolomide alone) and one subgroup (IIb) with complete adjuvant 6 cycles of temozolomide (43.9%) that underwent full 6 cycles of adjuvant temozolomide, and the portion of these patients in the study was similar to large studies presented by Stupp et al. (36.6%) [15,26]. In contrast, in a study by Athanassiou et al. complete adjuvant temozolomide (6 cycles) has got 61.4% patients after chemoradiation [27], which is higher compared with our study or the Stupp et al. study [15]. No significant difference was found in our study for the 2-year survival rate between patients receiving incomplete temozolomide treatment and receiving only postoperative radiotherapy. For 6-months and one-year survival rates, the percentages were higher in the group receiving incomplete temozolomide as compared to postoperative radiotherapy alone. One of the possible explanations for the latter might be that the total dose of adjuvant temozolomide that was administered in 6 cycles after chemoradiation, represents a cutoff that leads to a statistically significant benefit. It should be mentioned that MGMT methylation status of the patients was not investigated in the present study. So, it could be assumed that all the examined groups included also patients with negative methylation status. Furthermore, it may be assumed that more than 6 cycles of post chemoradiation temozolomide would further improve overall survival, but a major randomized phase III clinical trial performed by Gilbert et al. didn't prove this possibility (the median OS was 21.4 months for the standard arm and 20.2 months for the dose-dense arm) [28].

A statistically significant difference in survival was demonstrated in patients below or above 65 years of age. It is interesting that both age groups included a certain number of patients who were treated with postoperative radiotherapy only, which may imply that age represents an independent factor which impacts overall survival. Some of the reasons for shorter survival among elderly patients may include less favorable tumor biology, less aggressive care, treatment toxicity due to impaired physiologic reserve, and competing comorbidities that may shorten life [29]. But despite the shorter survival of elderly patients over 65 years Scott et al. [30] and Iwamoto et al. [31] propose aggressive treatment approach. The aforementioned studies showed that more aggressive approach increases overall survival. However, two recent large epidemiological reviews demonstrate that undertreatment is still the standard [31,32]. While these two studies [31,32] focused on patients with different age cutoffs (one defined "elderly" as 60 years and up and the other as 65 years and up), their results are strikingly similar to ours. In contrast to these studies, Iwamoto et al. [33] described their experience at Memorial Sloan-Kettering, demonstrating better overall survival

of elderly patients treated more aggressively over time compared to studies that reported less aggressive treatment (8.6 vs 4.5 months).

In the last two decades, statistically significant higher overall survival was shown for concomitant therapy followed by adjuvant postoperative therapy with temozolomide. Although this treatment was proved to contribute to longer overall survival in our study, there are certain disadvantages. The main disadvantage of our study may be that we could not make MGMT methylation status assessment as well as the isocitrate dehydrogenase and to determine survival in relation to these molecular markers. However, statistically significant difference among groups was observed. But, the major advantage is that these results were obtained in everyday clinical practice, beyond randomized controlled studies.

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Conflict of interests

The authors declare no confict of interests.

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