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ORIGINAL ARTICLE

Prognostic factors in glioblastoma patients managed with radiotherapy combined with temozolomide

Evangelia Peponi[1], Ioannis Tourkantonis[2], Ifigeneia Tasiou[1], Nicholas Pavlidis[2], George Pentheroudakis[2], Periklis Tsekeris[1]

[1]*Department of Radiation Oncology and* [2]*Department of Medical Oncology, University Hospital of Ioannina, Ioannina, Greece*

Summary

Purpose: *No consensus on clinicopathologic prognostic factors that predict the outcome of patients with newly diagnosed glioblastoma multiforme (GBM) managed with resection, postoperative radiotherapy (RT) and adjuvant temozolomide (TMZ) exists today. The purpose of this study was to assess the outcome, compliance and toxicity in GBM patients treated with TMZ at our Center, as well as to evaluate factors with prognostic significance.*

Methods: *91 GBM patients were enrolled in this retrospective study (2004-2012). 3D-conformal RT was given to a median total dose of 60Gy (daily dose 2Gy). Eighty nine (98%) of the patients received concurrent TMZ (75mg/m²) and 74 (81%) received adjuvant TMZ (150-200mg/m² for 5 days every 28 days) up to 12 cycles.*

Results: *At a mean follow up of 18.6 months, the median overall survival (OS) was 15.1 months. Grade 3/4 haematologic toxicity was observed in 19.8% of the patients while 4 patients (4.4%) experienced grade 3/4 non haematologic toxicity. In univariate analysis, significant correlation was found between OS and no/minor neurologic deficit at diagnosis (p=0.02), acute onset of symptoms (p=0.04) and 6 cycles of adjuvant TMZ (p<0.001). The addition of more than 6 cycles of TMZ did not offer any statistically significant survival benefit. In multivariate analysis, only the absence of major neurologic deficit remained associated with overall survival (p=0.016).*

Conclusion: *3D conformal RT with TMZ achieved acceptable disease control with satisfactory compliance and toxicity. Intact neurologic function was associated with superior outcome, as a surrogate of low tumor burden, early treatment start and/or indolent tumor biology.*

Key words: *glioblastoma, prognostic factors, radiotherapy, survival, temozolomide*

Introduction

GBM is the most common malignant primary brain tumor in adults accounting for approximately 12–15% of all intracranial neoplasms and 60-75% of astrocytic tumors [1]. Until recently median survival was generally less than one year from the time of diagnosis, with less than 15% of patients being alive two years post-diagnosis [2,3]. The randomized EORTC 26981/22981-NCIC CE3 trial in 2005 established that the addition of concomitant TMZ to standard postoperative RT followed by 6 monthly cycles of adjuvant TMZ significantly improved patient outcomes compared to postoperative RT alone [4]. It remains uncertain, however, whether concomitant TMZ, adjuvant TMZ, or both are important for this survival advantage. Moreover, no consensus was reached on standard clinicopathologic parameters with predictive significance for patients treated with modern TMZ-based chemoradiation.

The aim of this retrospective study was to assess the toxicity, compliance, and outcome of 91 GBM patients treated at a single center with postoperative 3D-conformal RT combined with concomitant and adjuvant TMZ. Furthermore, we sought to evaluate factors with prognostic value in this single-center population.

Correspondence to: Evangelia Peponi, MD, PhD. University Hospital of Ioannina, Department of Radiation Oncology, Stavrou Niarchou Ave. 1, 45500 Ioannina, Greece. Tel: +30 26510 99474, Fax: +30 26510 46617, E-mail: vagelita@yahoo.com
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Methods

Patient and tumor characteristics

Between September 2004 and July 2012, 91 patients with newly diagnosed GBM were treated postoperatively with 3D-conformal RT combined with concomitant and/or adjuvant TMZ at the University Hospital of Ioannina. Preoperatively, all patients had brain computed tomography (CT) scan and/or magnetic resonance imaging (MRI) performed. Laboratory tests were also performed to evaluate haematologic, renal, and hepatic function.

As determined by the surgical report and postoperative imaging, in 36 (40%) patients macroscopically complete resection was achieved, while 43 (47%) patients underwent partial/subtotal tumor resection. Biopsy only was performed in 8 (9%) patients. In 3 (4%) patients, no biopsy was performed and the diagnosis was based on MR spectroscopy. The O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status was not routinely obtained.

RT was delivered within 4 weeks after surgery, using 3D-conformal techniques, with 6 MV photons to a total dose of 60 Gy, delivered in a once-daily schedule of 2.0 Gy per fraction. The median total RT dose was 60 Gy (range 38-64). Patients were immobilized with commercially available thermoplastic masks in supine position. Brain CT images (5mm slice thickness) were acquired without contrast agent infusion. Regarding RT volume, a shrinking field approach was used. The initial Planning Target Volume (PTV) encompassed the enhancing lesion and surrounding edema with a 1-2 cm margin, while after 40 Gy the PTV was reduced to include only the preoperative enhancing lesion with a 2.5cm margin. The radiation dose was prescribed to the PTV covered by the 95% isodose line.

During RT, TMZ was administered at a daily dose of 75 mg/m^2, given 7 days per week from the first to the last day of RT. After a 4-week break, patients received an average of 6 cycles (range 1-12) of adjuvant oral TMZ (150–200 mg/m^2 daily) for 5 days every 28 days. Since 2007, the institutional policy was amended to allow extended adjuvant therapy up to 12 cycles of TMZ. Antiemetics, anticonvulsants and corticosteroids were prescribed, if needed. Prophylactic antibiotic treatment against *Pneumonocystis carinii* was routinely given. During chemoradiation, clinical evaluation and weekly laboratory tests were performed.

Follow-up

Institutional standards for patient assessment included physical and neurologic examination, laboratory monitoring, and imaging (CT/MRI) approximately 1 month after the end of concurrent chemoradiation and at 3-month intervals thereafter or earlier if indicated. Tumor progression was defined as a new lesion or an increase in tumor size by at least 25% according to the McDonald's criteria [5]. Toxicity was graded according to common terminology criteria for adverse events (CTCAE) of the National Cancer Institute (NCI), version 3.0.

Prognostic factors

Patient age, gender, Karnofsky performance status (KPS), presence of preoperative neurologic deficits, acute onset of symptoms, secondary GBM, tumor diameter, tumor location, extent of resection, number of adjuvant cycles of TMZ, treatment delay or interruption due to toxicity, and antiepileptic drug use were analysed as potential prognostic factors.

Statistics

Overall survival was defined as the period from the first day of RT to the date of death or last follow-up.

Statistical calculations of Kaplan Meier curves were performed using StatView® program (Abacus Concepts Inc., Berkeley, CA) and differences between groups were evaluated with log-rank test. For multivariate analysis the Cox proportional hazard regression model was used. A p-value ≤0.05 was considered as statistically significant.

Results

Patients/Treatment

The median patient age was 61 years (range 20-83) and the median KPS before RT was 80 (range 40-100). The male:female ratio was 1.9:1. The median tumor diameter at diagnosis was 4.2cm (range 1.8-8.2). Tumor location was parietal in 33%, temporal in 31%, frontal in 22%, occipital in 5% and other location in 9%. Ninety eight percent (89/91) of the patients received concurrent TMZ, while in 74/91 (81%) of the patients, adjuvant TMZ was administered. Post-diagnosis, 30 (33%) patients received any enzyme-inducing antiepileptic drug, while 56 (62%) patients received non enzyme-inducing antiepileptic drugs.

Regarding adjuvant treatment, 74 (81%) patients started the adjuvant TMZ cycles 4 weeks after the end of RT. Sixty seven percent of the patients completed 4 cycles of adjuvant TMZ, while 47% ultimately completed 6 cycles. Patients' clinical and tumor characteristics and treatment details are outlined in Table 1.

Treatment response and disease outcomes

With a mean follow up of 18.6 months (range 3-96), the actuarial 1- and 2-year OS rates were 65.7 and 33.5%, respectively (April 2013). At the time of analysis, 57 patients had died. The median OS was 15.1 months (range 1-96).

Table 1. Patient, disease and treatment characteristics (N = 91)

Characteristics	*N*	*%*
Patients		
Gender		
Male	60	66
Female	31	34
Median age, years (range)	61.2 (20-83)	
KPS		
<70	19	21
≥70	72	79
Tumor diameter (cm)		
<5	60	66
≥5	31	34
Extent of resection		
Complete	36	40
Partial	43	47
Biopsy	8	9
None	3	4
Concomitant RT/TMZ	89	98
Week 3 RT concomitant	89	98
Week 5 RT concomitant	87	96
Total concomitant period	82	90
Adjuvant TMZ (cycles)		
<6	32	35
=6	42	46
>6	14	15

KPS: Karnofsky performance status, RT: radiotherapy, TMZ: temozolomide

Grade 3/4 toxicity

Nine (10%) patients had any type of grade 3 or 4 haematologic toxicity; one of these patients died due to thrombocytopenia. Seven (8%) patients discontinued or interrupted RT due to toxicity, while 8 (9%) patients transiently interrupted concomitant chemotherapy.

Among the 89 patients who started chemoradiation, 82 completed the concomitant phase with both RT and TMZ. Six (6.7%) patients discontinued therapy because of haematologic toxicity and one (1.1%) patient due to colon perforation. In the adjuvant setting, 16 (18%) patients delayed and/or received lower dose of TMZ. The main reason for not completing adjuvant TMZ in our study was disease progression (30 patients/33%), while in only 9 (10%) patients adjuvant TMZ was stopped due to treatment toxicity. One case of histologically confirmed radiation-associated necrosis was reported 12 months post-treatment. The incidence of grade 3/4 toxicity is outlined in Table 2.

Table 2. Grade 3/4 heamatologic and non-heamatologic toxicity (N = 91)

Variable		*Patients*	
	Number of events	*N*	*%*
Overall heamatologic toxicity	23	18	19.8
Concurrent RT/TMZ			
Neutropenia	4		4
Febrile neutropenia	1		1
Thrombocytopenia	7		8
Adjuvant TMZ	11	9	10
Neutropenia	4		4
Thrombocytopenia	6		7
Liver enzymes elevation	1		1
Overall non heamatologic toxicity	4	4	4.4
Concurrent RT/TMZ	2	2	2
Pneumonia	1		1
Colon perforation	1		1
Late toxicity	2	2	2
Pneumonia	1		1
CNS necrosis	1		1

RT: radiotherapy, TMZ: temozolomide

Potential prognostic factors

Uni- and multivariate analyses were performed to examine the impact of various prognostic factors on OS. In univariate analysis, significant correlation was found between OS and no/minor neurologic dysfunction at diagnosis (p=0.02). Statistical significance was also observed for the correlation of OS with administration of 6 cycles of adjuvant TMZ (p<0.001). The addition of more than 6 cycles of TMZ did not retain any statistically significant difference. Patients presented with an acute onset of symptoms, such as a new onset seizure, showed a statistically significant improvement in OS (p=0.04) (Figure 1).

There was a trend towards inferior OS in cases where RT was interrupted (p=0.09). The addition of anticonvulsants that enhance TMZ metabolism through the P450 cytochrome system also showed a trend toward inferior OS (p=0.09). A trend towards superior OS was observed in patients with frontal tumor location (p=0.057).

Neither statistically significant difference nor a trend for significance were observed regarding the association of OS with KPS, extent of resection, age, sex, baseline tumor diameter, secondary GBM and TMZ delay or interruption.

In a stepwise multivariate Cox regression model considering KPS, extent of resection, acute onset of symptoms, tumor diameter (>5cm), anti-

Table 3. Univariate and multivariate analyses for prognostic factors

Variable	*Univariate analysis*	*Multivariate analysis*	
	p-value	*HR (95%CI)*	*p-value*
Neurologic dysfunction	0.020	0.52 (0.31-0.88)	0.016
None/minor			
Moderate/severe			
Acute symptoms	0.040	1.01 (0.42-2.89)	0.95
Yes			
No			
Adjuvant TMZ (cycles)	<0.001	1.59 (0.85-2.98)	0.15
6			
<6			
RT interruption	0.09	0.65 (0.21-2.10)	0.47
Yes			
No			
Anticonsulvants	0.09	0.73 (0.34-1.35)	0.32
Enzyme inducing			
Non-enzyme inducing			

TMZ: temozolomide, RT: radiotherapy, HR: hazard ratio, CI: confidence interval

convulsants, RT delay/interruption and TMZ delay/interruption either in the concomitant or in the adjuvant setting, only absence of neurologic dysfunction at diagnosis remained statistically associated with OS (hazard ratio 0.52 for the risk of death compared to patients with neurologic deficits, 95% CI 0.31-0.88, p=0.016) (Table 3).

Discussion

Since the publication of the European and Canadian randomized trials (EORTC 26981/22981-NCIC) in 2005 [4], surgery followed by RT plus concomitant TMZ and 6 cycles of adjuvant TMZ has been considered the standard of care for adult patients with GBM. As randomized controlled trials need to be confirmed in routine clinical practice, taking into account differences in treatment and tumor characteristics between the trial population and unselected patients, the objective of this analysis was to assess the compliance, toxicity, prognostic factors and outcome of 91 GBM patients treated at a single center. Our study showed that chemoradiation and adjuvant TMZ is indeed effective regarding outcome and toxicity in routine clinical practice.

The results of our patient cohort demonstrated a median OS of 15.1 months, which compares

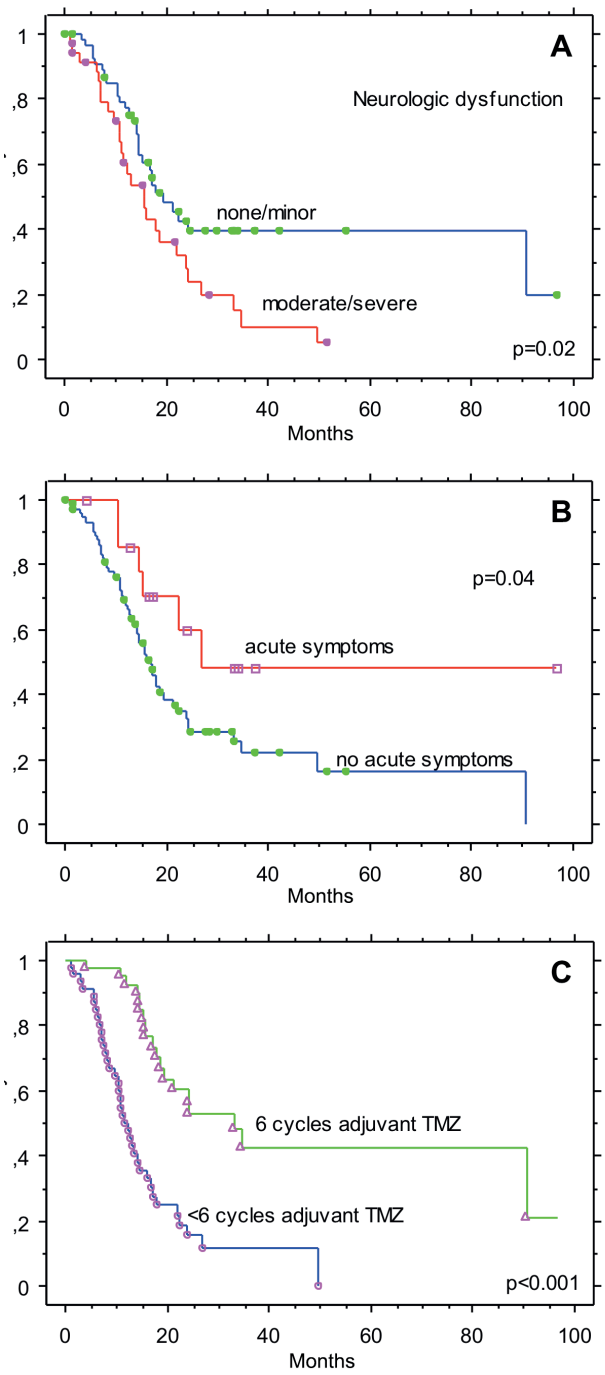

Figure 1. Kaplan-Meier overall survival of patients by (A) neurologic status at diagnosis, (B) acute onset of symptoms and (C) completion of 6 cycles of adjuvant TMZ.

favorably to other studies [4,6-8]. It has been proposed that outcome results are quite dependent upon pre-treatment prognostic factors such as age, performance status, and extent of surgical resection [2,9-11]. In our patient cohort, the median age was 61.2 years, which was slightly higher than the age of 56 years reported by Stupp et al. [4]. Eighty-seven percent of our patients underwent major debulking, with 40% having complete

tumor excision, a result comparable to that reported by Stupp et al., where 83% of the patients underwent major debulking, with 40% having complete tumor excision. In our study, 46% of the patients completed the concomitant and 6 cycles of adjuvant TMZ treatment, and compliance was the same as in the study by Stupp et al. Moroever, RT with concomitant TMZ was well tolerated by the majority of patients. Regarding grade 3/4 toxicity, the incidence in our patients was comparable to that reported by Stupp et al.

Although it has recently been suggested that extensive surgical resection lengthens OS [12-14], our study failed to confirm this, perhaps due to factors like modest patient sample size, tumor location and tumor size. Nevertheless, surgery to the greatest possible extent should always be attempted when feasible.

The performance status of the patient at diagnosis is widely accepted to affect survival [2,6,15]. In our analysis, although the KPS was not significantly associated with improved OS, the absence of neurologic deficits preoperatively emerged as a prognostic factor, the statistical significance persisting in multivariate analysis. This could indicate that intact neurologic function may act as a prognostic factor or actually be a surrogate marker of low tumor burden, and/or indolent tumor biology.

One question arising from our analysis is the contribution of the concurrent and adjuvant TMZ administration to the OS benefit. The fact that completion of 6 cycles of adjuvant TMZ was associated with improved OS in univariate analysis confirms previously reported data [7,16], that administering adjuvant TMZ is superior to any policy of close follow-up and salvage treatment in case of disease progression. Patients in the EORTC-NCIC phase 3 study [4] discontinued adjuvant TMZ after 6 monthly cycles, mainly because of concerns regarding the fact that prolonged chemotherapy with alkylating agents has been associated with myelodysplastic syndromes and secondary leukemia [17]. Some studies have suggested improved progression-free and OS with the administration of prolonged adjuvant treatment with more than 6 cycles of TMZ [18], with acceptable toxicity [19]. Nonetheless, we failed to demonstrate the prolonged treatment as an independent prognostic factor favoring OS, perhaps due to the small number of patients (15%) receiving more than 6 adjuvant cycles of TMZ. Of note, enzyme-inducing anticonvulsants induce a number of enzymes of the cytochrome P450 system and may influence of TMZ [20,21].

Some studies have postulated that patients with GBM who present with an acute onset of symptoms or with symptoms that are particularly disabling may show a trend to improved survival [13,22]. In our patient cohort, 15 (16%) patients presented with an acute onset of seizures, which is a proportion relatively consistent with other seizure incidence reports [13]. In univariate analysis, our results demonstrated a statistically significant improvement in OS among patients who presented with an acute onset of symptoms when compared to those with more subtle symptoms. This seemed to be independent of other variables such as location or tumor size. Our finding suggests that a history of seizure in the first disease onset may indicate a positive prognostic factor. It seems that patients presenting with acute symptoms may have earlier disease diagnosis and thereby better prognosis, since they have immediate scans and are referred earlier for therapeutic intervention.

The results of this study are subjected to limitations arising from the retrospective nature of the analysis, the modest patient sample size and the absence of molecular tumor stratification. MGMT methylation status and quality of life measurements were also not available. Nevertheless, patients were treated relatively consistently and data were collected with meticulous follow-up.

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