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ORIGINAL ARTICLE

Long term experience in high grade glial tumors with temozolomide

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Summary

Purpose: *Temozolomide is used concurrently with radiotherapy (RT) and as consolidation therapy in high grade gliomas (HGGs). In the present study we present our experience of long-term efficacy and toxicity of temozolomide in HGGs.*

Methods: *After surgery, temozolomide was administered at 75 mg/m^2 daily concurrently with RT, followed by 6 courses of consolidation therapy (150-200 mg/m^2 for 5 days every 28 days).*

Results: *A total of 172 patients with either glioblastoma multiforme (GBM) (n= 142; 82.6%) or anaplastic astrocytoma (AA) (n= 30; 17.4%) were studied. The objective response rate (ORR) was 42.5%, including 12 (7%) complete responses (CRs) and 61 (35.5%) partial responses (PRs). In the GBM group, median progression free survival (PFS) and overall survival (OS) were 9 and 16 months, respectively. In the AA group, median PFS and OS were 16 and 24 months, respectively. Three-year OS was 18.2% for GBM, and 39.4% for AA. In elderly patients (14.5%), median PFS and OS were 8 and 11 months respectively for both HGGs. Serious toxicities were mainly hematologic.*

Conclusion: *Temozolomide is an effective agent in HGGs with favorable outcome and low toxicity profile even in advanced age.*

Key words: elderly, malignant glioma, radiation, temozolomide

Introduction

HGG, also known as malignant gliomas (grades III and IV glial tumors) are the most common and aggressive forms of malignant primary brain tumors in adults [1,2]. The majority of HGGs are GBM (60-70%), AA (10-15%) and anaplastic oligodendroglioma/ oligoastrocytoma (AO; 10%) [3]. Median OS for GBM and AA is 12-16 months and 2 years, respectively [4]. Standard care for GBM and AA is maximal surgery and RT concurrently with temozolomide and consolidation temozolomide for GBM. However, consolidation therapy with temozolomide for AA remains a controversial issue [5-8].

Chemotherapy prolongs survival in many patients with HGGs. Temozolomide (Temodal®, Temodar®) is an oral alkylator that penetrates into the blood brain barrier and spontaneously converts to 5-(3-methyltriazene-1-yl) imidazole-4-carboxamide (MTIC) at physiologic pH, requiring no hepatic or renal metabolism [9,10]. MTIC acts by methylating DNA at the O6 position of guanine and arrests of cells in the G_2-M phase of the cell cycle [11,12]. Currently, temozolomide is used in the treatment of HGGs regardless of O6-methylguanine DNA methyltransferase (MGMT) promoter methylation status [13].

In this study we present our experience of long-term results over the efficacy and toxicity of temozolomide administered concurrently with RT, and followed by consolidation treatment.

Methods

Between March 2005 and June 2010, a total of 172 patients with HGGs were retrospectively studied and analysed at the Gazi University Faculty of Medicine, Department of Medical Oncology.

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They had either histologically confirmed GBM or AA and their performance status was assessed according to World Health Organization (WHO) scale. Surgical procedures performed were gross total resection, subtotal resection and stereotactic biopsy.

Radiotherapy

RT was delivered at 2 Gy daily fractions, 5 days per week. RT was planned according to the preoperative cranial magnetic resonance imaging (MRI). The clinical target volume included the gross tumor volume plus the peritumoral edema with a margin of 2-2.5 cm. After 50 Gy, the treatment volume was reduced for boosting. The median total dose of RT was 60 Gy (range 50-66) and the mean boost dose 10.5 Gy (range 10-16).

Chemotherapy

Temozolomide was administered at 75 mg/m^2 daily concurrently with RT. Consolidation treatment included temozolomide given at 150-200 mg/m^2 for 5 days every 28 days for at least 6 cycles. If response had been achieved after 6 cycles of treatment, temozolomide was continued until disease progression in patients with residual disease. Postoperatively, neurological examination and MRI were performed every 2 months.

Response evaluation

The evaluation of treatment response was assessed by both clinical and radiological criteria using RECIST (Response Evaluation Criteria in Solid Tumors) [14]. Pseudoprogression was defined the condition where a patient with early progression had at least 50% decrease in follow-up imaging and remained clinically stable during the consolidation therapy.

The primary study endpoints were PFS, OS, while the secondary endpoint was toxicity. Safety and tolerability were measured using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) [15].

Statistical considerations

PFS was defined as the time period from the first day of chemoradiotherapy to the date of first disease progression. OS was defined as the time period from the first day of chemoradiotherapy to the date of death or lost to follow-up.

Survival analyses were estimated using the Kaplan-Meier method. Mann-Whitney U test was used to compare survival according to several prognostic factors such as age, gender, tumor grade type of surgery, and salvage treatments. A multivariate Cox proportional hazards regression model was used to test the effect of prognostic factors. P-values < 0.05 were accepted as significant. All analyses were done on an intention-to-treat basis using the SPSS, version 13.00.

Results

Patient characteristics

Of a total of 172 patients with HGGs, 142 (82.6%) had GBM and 30 (17.4%) AA. One hundred and three patients were male (59.9%) and 69 (40.1%) female, with median age of 51 years (range 16-80). Twenty-five (14.5%) patients were over 65 years old. Gross total resection was achieved in 110 (64%) patients, subtotal resection in 47 (27.3%), and stereotactic biopsy in 15 (8.7%) (Table 1).

Treatment administration, response and survival

After chemoradiotherapy, 29 patients discontinued consolidation temozolomide because of progressive disease (n=9), hematotoxicity (n=7), poor performance status (n=8), and patient decision or lost to follow-up (n=9). One hundred and thirty-nine patients who completed 6 months of treatment, received a median of 6 chemotherapy cycles (range 1-10). ORR was 42.5%, including 12 (7%) CRs and 61 (35.5%) PRs. In the GBM group ORR was 40.1%, including 10 (7.3%) CRs and 45 (32.8%) PRs. In the AA group ORR was 54.6%, including 3 (9.1%) CRs and 15 (45.5%) PRs. In the GBM group, median PFS and OS were 9 (95% CI 7.96-10.04) and 16 (95% CI 13.94-18.06) months, respectively. In the AA group, median PFS and OS were 16 (95% CI 11.76-20.38) and 24 (95% CI 12.29-35.70) months, respectively (Figures 1,2). In elderly patients (over 65 years; n= 25; 23 GBM and 2 AA), median PFS and OS were 8 (95% CI 5.60-10.40) and 11 (95% CI 3.19-18.80) months for all grades of HGGs, respectively. Pseudoprogression was detected in 4 patients and radionecrosis in one. Second operation was performed in 29 patients, second-line RT in 6 and salvage radiosurgery in 11. After progression, 15 (8.7%) patients were administered bevacizumab-irinotecan,

Table 1. Patient, disease and operation characteristics

Characteristics	*N (%)*
Age (years), median (range)	51 (16-80)
<65	147 (85.5)
≥65	25 (14.5)
Sex	
Male	109 (59.9)
Female	63 (40.1)
ECOG performance status	
0-1	132 (76.7)
2	40 (23.3)
HGG	
GBM	142 (82.6)
AA	30 (17.4)
Surgery	
Gross total resection	110 (64)
Subtotal resection	47 (27.3)
Stereotactic biopsy	15 (8.7)

HGG: high grade gliomas, GBM: glioblastoma multiforme, AA: anaplastic astrocytoma

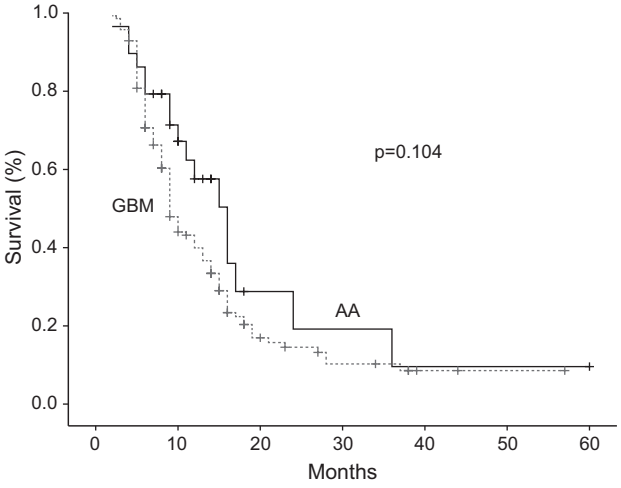

Figure 1. Kaplan-Meier estimates of progression free survival by disease groups. GBM: glioblastoma multiforme, AA: anaplastic astrocytoma.

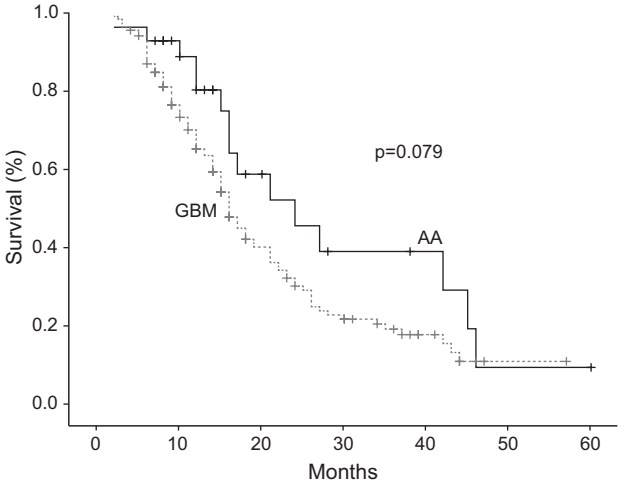

Figure 2. Kaplan-Meier estimates of overall survival by disease groups, GBM: glioblastoma multiforme, AA: anaplastic astrocytoma.

45 (26.2%) carboplatin-cyclophosphamide, and in 16 (9.3%) temozolomide was readministered (Table 2). Three-year OS was 18.2% for GBM and 39.4% for AA. Four-year OS was 11.4% for GBM and 9.8% for AA. Age (p=0.02), type of surgery (p=0.042) and temozolomide readministration (p=0.001) were independent prognostic factors; on the contrary, gender, second operation, repeat irradiation, and radiosurgery were not (Tables 3 and 4).

Toxicity

While asthenia, nausea and vomiting were the most common non hematologic toxicities, serious toxicity (grade 3/4) was mainly hematologic: thrombocytopenia (n= 22; 12.8%) and neutropenia (n=16; 9.3%). Febrile neutropenia developed in 5 patients; in 2 of them during concomitant RT and temozolomide and in 3 during consolidation temozolomide. Two patients died of toxic death: one of aspiration pneumonia complicated with acute respiratory distress syndrome (ARDS) and the other one of febrile neutropenia. Deep venous thrombosis was detected in 20 (11.6%) patients. Elevated gamma glutamyltransferase (γGT) levels were seen frequently. In 6 patients (3.4%) various forms of skin toxicity, from erythematous papulae to vesicular rash, were seen (Table 5).

Table 2. Salvage treatment

*Salvage treatment**	*N (%)*
Second surgery	29 (16.8)
Repeat irradiation	6 (3.5)
Radiosurgery	11 (6.4)
Salvage chemotherapy	
Re-temozolomide	16 (9.3)
Bevacizumab-irinotecan	15 (8.7)
Carboplatin-cyclophosphamide	45 (26.2)

*Some patients had more than one salvage treatment

Discussion

Table 3. Univariate analysis (Mann-Whitney U test) of several prognostic factors in relation to PFS and OS

Factors	*PFS p-value*	*OS p-value*
Age (years)	0.000	0.001
<60		
>60		
Sex	0.94	0.686
Male		
Female		
Grade	0.12	0.79
III		
IV		
Surgery	0.005	0.062
No		
Yes		
Re-administration of temozolomide	0.018	0.001
No		
Yes		
Re-operation	0.782	0.21
No		
Yes		
Re-irradiation	0.566	0.576
No		
Yes		
Radiosurgery	0.923	0.329
No		
Yes		

PFS: progression free survival, OS: overall survival

Table 4. Multivariate Cox regression analysis of several prognostic factors in relation to PFS and OS

Factors	*PFS*		*OS*	
	p-value	*HR (95% CI)*	*p value*	*HR (95% Cl)*
Age (years)				
(<65 vs >65)	0.003	2.010 (1.269-3.184)	0.44	1.637 (1.013-2.644)
Sex				
(Male vs female)	0.350	1.196 (0.872-1.790)	0.415	1.185 (0.768-1.783)
Grade (III vs IV)	0.124	0.660 (0.389-1.121)	0.107	0.624 (0.351-1.108)
Surgery				
(GTE vs STR-Bx)	0.018	1.558 (1.081-2.246)	0.05	1.474 (0.988-2.177)
Re-administration of temozolomide	0.008	2.406 (1.252-4.623)	0.001	3.430 (1.654-7.110)
Second surgery	0.157	0.703 (0.431-1.146)	0.168	1.527 (0.837-2.787)
Re-irradiation	0.378	0.910 (0.359-2.310)	0.843	0.624 (0.219-1.781)
Radiosurgery	0.703	1.159 (0.543-2.473)	0.314	1.533 (0.667-3.522)

PFS: progression free survival, OS: overall survival, HR: hazard ratio, GTE: gross total resection, STR: subtotal resection, Bx: biopsy

Table 5. Toxicities

Toxicities	*N (%)*
Toxic death	
Febrile neutropenia	1 (0.58)
Aspiration pneumonia (ARDS)	1 (0.58)
Hematologic (grade 3-4)	
Thrombocytopenia	22 (12.8)
Neutropenia	16 (9.3)
Febrile neutropenia	5 (2.9)
Nausea and vomiting (grade 3-4)	3 (1.7)
Asthenia (grade 3-4)	10 (5.8)
Deep venous thrombosis	20 (11.6)
Skin toxicity	6 (3.4)

In the present study, GBM (82.6%) was the most frequently diagnosed HGG and AA was diagnosed in only 17.4% of the patients. Our data showed obvious predominance of HGGs in males, (103 men vs. 69 women), in concordance with the literature [3]. At diagnosis, while our GBM patients were younger than in the literature (median 54 vs. 64 years), AA patients had age similar with the literature (median 45 years) [3,16] (Figure 1).

Surgery and RT are both the cornerstone of HGGs treatment. The addition of RT to surgery increases GBM patient survival by 7-12 months [17,18]. After standard RT, 90% of the tumors recur at the original site [8]. A meta-analysis showed significant prolongation of survival associated with postoperative chemotherapy [19]. The pivotal EORTC study [17] evaluated concomitant and adjuvant temozolomide with RT in comparison with RT alone in the primary therapy for GBM. Temozolomide-treated patients showed improved median OS survival (14.6 vs. 12.1 months, $p< 0.001$) and 2-year OS survival (26.5 vs. 10.4%; $p<0.001$) than those treated with RT alone. In our previous study [7], while median PFS and OS were 10 and 19 months for patients with GBM, median PFS and OS was not reached for AA. ORR was similar (38.7%) to recent studies, ranging from 20 to 52% for GBM [11,20,21]. Although different temozolomide regimens (dose-dense, metronomic) have been tested, standard regimen was used in the current study. There were 139 patients that completed 6 months of treatment whose objective response rate was 42.5%, including 12 CRs (7%) and 61 PRs (35.5%). We registered similar outcome for all HGGs with median PFS of 10 months and median OS of 16 months. Median PFS and OS in the GBM group were 9 (95% CI 7.96-10.04) and 16 (95% CI 13.94-18.06) months respectively, while median PFS and OS in the AA group were 16 (95% CI 11.76-20.38) and 24 (95% CI 12.29-35.70) months, respectively. While cure is not possible, chances for long-term survival are limited in patients with HGGs. Four-year OS was 11.4% for GBM and 9.8% for AA, very similar for both conditions.

In the current study, there were 25 (14.4%) patients (23 GBM, 2 AA) aged over 65 years, with median PFS and OS 8 (95% CI 5.60-10.40) and 11 (95% CI 3.19-18.80) months, respectively. These results are consistent with previous studies in elderly patients [22-24] and very similar with a recently published study which revealed a median PFS of 7 months and a median OS of 10.6 months [25].

The most important adverse prognostic factors in patients with HGGs are advanced age, histological features of HGG, poor performance status, and type of surgery [26,27]. In the present study, age ($p= 0.02$), type of surgery ($p= 0.042$) and readministration of temozolomide ($p= 0.001$) were independent prognostic factors.

Treatment options for recurrent HGGs are limited. Patients with progressive HGGs are considered for salvage therapy if their performance status is adequate. We readministered temozolomide if long-term response (over a year) was achieved with temozolomide and/or short-course of temozolomide was previously used. Although we performed repeat surgery, radiosurgery, reirradiation or salvage chemotherapy for progressive

disease, none of them showed prognostic significance.

If progression is detected by MRI early after RT concomitant with temozolomide in clinically stable patients, decision of new treatment should be postponed after 2 or 3 cycles of consolidation therapy. We observed 4 pseudoprogressions and 1 radionecrosis. Our results compared with similar literature studies [28] indicate low incidence rate of pseudoprogression (3 vs. 9-21%). This might be due to our lack of awareness of the pseudoprogression.

Our study showed that serious (grade 3/4) toxicities were hematological (thrombocytopenia, n= 22; 12.8% and neutropenia, n= 16; 9.3%), higher than those published in other studies (3.5-30%) [6, 25]. Febrile neutropenia was seen in 5 patients with one patient dying of septicemia. While severe and sustained thrombocytopenia and neutropenia occurred during concomitant chemoradiotherapy, lower hematologic toxicity was seen with adjuvant temozolomide. More investigations are needed to clarify the pathogenesis of hematotoxicity of temozolomide. Non-hematologic toxicities were asthenia, nausea and vomiting, occurring with low incidence and grade. Patients who present with seizures should be treated with antiepileptic drugs. These drugs and temozolomide can cause skin toxicities and serum γGT elevation. Patients with HGGs are at increased risk for venous thromboembolism [29,30]. In the present study 20 (11.6%) patients developed deep venous thrombosis; these patients did not receive bevacizumab-based regimen after progression. Temozolomide can cause several opportunistic infections [31]. Although a recent meta-analysis [32] did not show any benefit, prophylactic antibiotic therapy against to *Pneumocystis jiroveci* should be considered for patients with HGGs who receive steroids. We didn't see *P. jiroveci* pneumonia; however, one of our patients with aspiration pneumonia died as a result of ARDS.

We conclude that temozolomide is an effective agent in HGGs with favorable outcome and low toxicity profile, even in advanced age patients.

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