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ORIGINAL ARTICLE

Concomitant temozolomide and radiotherapy versus radiotherapy alone for treatment of newly diagnosed glioblastoma multiforme

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Summary

Purpose: *To study the efficacy and safety of radiotherapy (RT) with concomitant and subsequent temozolomide in comparison to RT alone in the treatment of patients with newly diagnosed glioblastoma multiforme (GBM) after brain surgical intervention.*

Methods: *Twenty patients received cranial fractionated RT (60 Gy total dose: 2 Gy/day, 5 days/week, for 6 weeks) with concomitant oral temozolomide (75 mg/m^2/day x 7 days/week, for 6 weeks) followed by temozolomide monotherapy (200 mg/m^2/day × 5 days every 28 days for 6 cycles). Another 20 patients received only cranial RT (Co-60 teletherapy, 60 Gy in 30 fractions).*

Results: *At the end of the study the median time to progression free survival (PFS) was 13 months in the temozolomide plus RT treatment group and 5 months in the RT-alone group (p=0.0001). Median overall survival (OS) in the temozolomide plus RT and the RT-alone group was 19 and 11.5 months, respectively (p=0.0264). The main side effect in the temozolomide plus RT group was myelosuppression. Concomitant treatment resulted in grade 3 hematologic toxicity in 6 patients.*

Conclusion: *These data show that the combination of temozolomide, concomitant and subsequent to RT seems more effective than RT alone in patients with newly diagnosed GBM and that multimodality treatment is safe and well tolerated.*

Key words: concomitant radiotherapy, glioblastoma multiforme, radiotherapy, temozolomide

Introduction

Primary brain tumors account for 2% of all malignant diseases. The most common histologic types in adults are grade 3 anaplastic astrocytoma (AA) and grade 4 GBM [1,2]. The standard therapy of malignant gliomas is surgical cytoreduction followed by RT alone or combination with adjuvant chemotherapy or chemotherapy for postoperative residual disease [3,4]. Despite this multimodal approach, the prognosis of GBM patients is still poor. Median survival ranges between 9 and 12 months and 2-year survival is only between 8 and 12% [5,6].

Temozolomide is a second generation oral alkylating agent with demonstrated efficacy in the treatment of malignant gliomas. Temozolomide has almost 100% bioavailability. It can also penetrate the blood brain barrier, and 40% of plasma concentrations reach the central nervous system [7]. Temozolomide has a good activity in the treatment of both recurrent and newly diagnosed malignant gliomas [8,9]. Resistance to temozolomide partially occurs as a result of expression of the O6-alkylguanine DNA alkyl transferase (AGT). This repair enzyme, also known as methylguanine DNA methyltransferase, is an important determinant of *in vitro* temozolomide cytotoxicity. Chronic exposure to temozolomide results in the extinction of this enzyme [9]. Studies showed that chronic administration of temozolomide at the dose of 75 mg/m^2 for 6-7 cycles was safe [10].

Concomitant administration of temozolomide and RT has been investigated both in *in vitro* and *in vivo* studies. *In vitro* studies showed that the treatment of glioma cells with temozolomide and radiotherapy may have additive and synergistic effects. In a phase II study by Stupp et al. [11] continuous daily temozolomide therapy with concomitant RT followed by adjuvant temozolomide in newly diagnosed GBM patients was well toler-

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ated and improved survival. A phase III study completed recently by European Organisation for Research and Treatment of Cancer (EORTC) has confirmed these data [12]. Depending on these data this study aimed to compare the effectiveness and safety of RT with concomitant and subsequent temozolomide in comparison to RT alone in newly diagnosed GBM patients.

Methods

Objectives

The primary endpoints of this study were PFS and OS in patients with GBM, treated postoperatively with either cranial RT alone or cranial RT concomitantly with temozolomide, and then subsequent temozolomide for 4-6 cycles. Secondary endpoints were safety and tolerability of the treatment.

Patients

Between January 2004 to December 2006, 40 patients treated at Sisli Etfal Education and Training hospital, Istanbul, were included in the study. The outcome of these patients who received the protocol-compliant treatment, was analyzed. Four to 6 weeks after histopathologic diagnosis of GBM, eligible patients were assigned to receive either RT alone or RT plus concomitant temozolomide and post-RT temozolomide. The eligibility criteria included age ≥18 years and histologically verified GBM according to World Health Organization classification. Other inclusion criteria were Karnofsky performance status (KPS) ≥80, sufficient bone marrow function (hemoglobin ≥10 g/dL, absolute neutrophil count ≥1,500/μL and platelet count ≥100,000/μL), normal renal function (serum creatinine level < 1,5 mg/dL), and normal liver function (bilirubin < 1,5 times the upper limit of normal, AST < 2,5 times the upper limit of normal, and alkaline phosphatase < 2 times the upper limit of normal). Patients with poor health due to non-malignant systemic disease or those with acute infection were excluded (Table 1).

Study design and treatment

Patients who met all the inclusion criteria were randomized to receive either cranial RT alone or cranial RT plus temozolomide (concomitant and subsequent). All patients received standard whole brain RT (2 Gy/fraction, 5 days per week), for a total of 60 Gy. The patients were treated with thermoplastic immobilization masks to ensure adequate immobilization during therapy and reproducibility. Treatment volumes were based on CT and/or MRI scans. Treatment volume was determined by adding 2-2.5 cm margin to contrast-booster tumor volume estimated by CT and/or MRI scans. Co-60 teletherapy unit was used in the treatment of all patients.

Patients randomized to the combination treatment group received temozolomide (75 mg/m^2 per day, 7 days per week) one hour before RT and also in the morning of the days that RT was not applied. Four weeks after RT completion 6 cycles of subsequent temozolomide (200 mg/m^2 for 5 days every 28 days) were given. Prophylactic antiemetics were used routinely. Intravenous bolus dexamethasone 16 mg/day was administered as anti-oedema therapy from the first day of therapy, tapered gradually to stop in 1-2 months after the end of RT. Antiepileptic therapy (phenytoin 300 mg/day p.o.) was not discontinued.

Observation and monitoring

Patients were closely monitored for toxicity during RT. Laboratory tests included monthly serum biochemistry and weekly full blood count. Neurological examination, full blood count, and serum biochemistry profile were carried out in every temozolomide cycle, and in every follow-up visit (every 3 months) of the RT-alone group. CT or MRI scans were performed with or without contrast before the first treatment cycle and then every 3 months. Disease progression was defined radiologically (25% or more increase in the largest diameter of the tumor, or a new lesion in MRI or CT), neurologically or clinically. Then, the results were categorized according to Response Evaluation Criteria in

Table 1. Patient characteristics

Characteristics	*RT*	*RT + TEM*	*p-value*
Gender			0.75
Men	10	9	
Women	10	11	
Age (years)			0.3429
Median	51.5	52.5	
Range	19-73	25-72	
Type of surgery			0.13
Total	8	14	
Subtotal	8	3	
Biopsy	4	3	
Age (years)			1.00
≤50	10	10	
>50	10	10	
Time between diagnosis and treatment (days)			0.04
Average	12.95	8.30	
95% CI	9.11-16.78	5.61-10.99	

RT: radiotherapy, TEM: temozolomide

Solid Tumors (RECIST) as complete response, partial response, stable disease and progressive disease.

Adverse events were classified according to National Cancer Institute Common Toxicity Criteria, version 2.0. Grade 1 indicates mild adverse events, grade 2 moderate, grade 3 severe and grade 4 life-threatening adverse events.

Statistical analysis

The main objective was to evaluate median PFS and median OS by using the Kaplan-Meier method. OS was calculated from the date of starting RT to the date of death or the last visit. PFS was the period between the date of starting RT and the time of tumor progression or the date of withdrawal from the study for any reason. Log-rank test was used for comparison of PFS and OS between the 2 groups. The level of significance was set at $p < 0.05$.

Results

There were 10 (50%) women and 10 men (50%) in the RT-alone group. The RT plus temozolomide group consisted of 9 men (45%) and 11 women (55%). In the RT-alone group the youngest patient was 19 and the oldest 73 years old; the average age was 51.05 ± 14.01 years (mean±SD), and the median age 51.5 years. In the RT plus temozolomide group, the youngest patient was 25 and the oldest 72 years old; the average age was 50.55 ± 13.52 years, and the median age 52.5 years. In the RT-alone group 8 (40%) patients had complete tumor resection, 8 (40%) subtotal excision and in 4 (20%) patients only biopsies were taken. In the RT plus temozolomide group, 14 (70%) patients had total tumor excision, 3 (15%) subtotal excision and in 3 (15%) patients only biopsies were performed.

The median time between diagnosis and treatment initiation was 8.30 days in the RT plus temozolomide group, and 12.9 days in the RT-alone group ($p=0.04$). The median RT duration was 42.1 days in the RT plus temozolomide group and 42.2 days in the RT-alone group ($p = 0.91$). All patients had KPS values ≥80 before treatment initiation.

Subsequent temozolomide treatment was given to 19 patients in the combined treatment arm. One patient did not receive subsequent temozolomide after RT due to disease progression, and 3 patients did not complete subsequent temozolomide because of disease progression after the 4th cycle. In one patient temozolomide was stopped on the 4th cycle due to grade 4 thrombocytopenia. A total of 15 patients completed all 6 treatment cycles as planned.

Treatment toxicity

All 40 patients were assessed for toxicity (Table 2). Temozolomide plus RT combination (concomitant and subsequent) was well tolerated. The main side effect was myelosuppression. In the concomitant RT plus temozolomide phase, grade 3 leucopenia was seen in 3 patients. Grade 3 and 4 thrombocytopenia developed in 3 patients after the 4th week of subsequent temozolomide, and 1 patient developed grade 2 anemia after the 5th week of temozolomide. During subsequent temozolomide therapy 1 patient developed grade 3 thrombocytopenia after the 4th cycle of temozolomide, 1 grade 2 anemia and 1 grade 2 leucopenia after the 6th cycle of temozolomide.

Non-hematologic toxicity was mild. In the combined treatment group 3 patients developed treatment-related rash, 2 had constipation, and 1 arthralgia. There were no late neurological side effects.

In the RT-alone group no hematologic side effect was observed. Among nonhematologic side effects, 20 patients had grade 1 acute skin reaction, 3 had grade 1 nausea and vomiting, and 4 complained of fatigue.

Treatment after disease progression

Three patients in the RT-alone group and 5 patients in the RT plus temozolomide group were administered salvage chemotherapy with fotemustine.

Survival

Survival results are shown in Figures 1 and 2. When data analysis was performed in September 2007,

Table 2. Hematologic toxicity in patients treated with temozolomide

Toxicity	*Concomitant temozolomide (n=20) (%)*	*Subsequent temozolomide (n=15) (%)*	*During whole study period (n=20) (%)*
Leucopenia			
Grade 1	–	–	–
Grade 2	–	1 (6.6)	1 (6.6)
Grade 3	3 (15)	–	3 (15)
Grade 4	–	–	–
Thrombocytopenia			
Grade 1	–	–	–
Grade 2	–	–	–
Grade 3	2 (10)	1 (5)	3 (16.6)
Grade 4	1 (5)	–	1 (5)
Anemia			
Grade 1	–	–	–
Grade 2	1 (5)	1 (6.6)	2 (11.6)
Grade 3	–	–	–
Grade 4	–	–	–

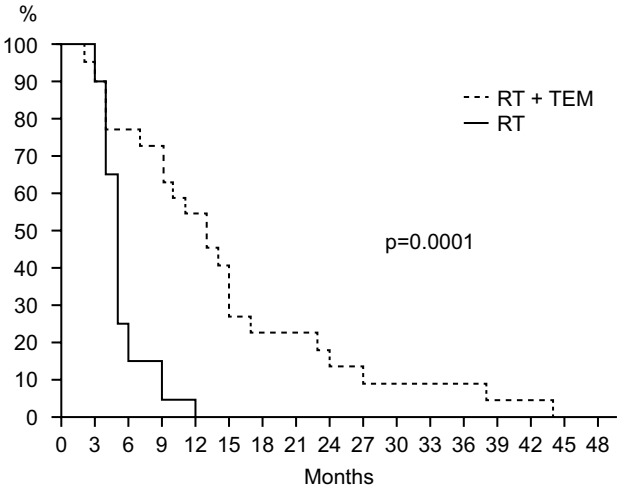

Figure 1. Progression free survival. RT: radiotherapy, TEM: temozolomide.

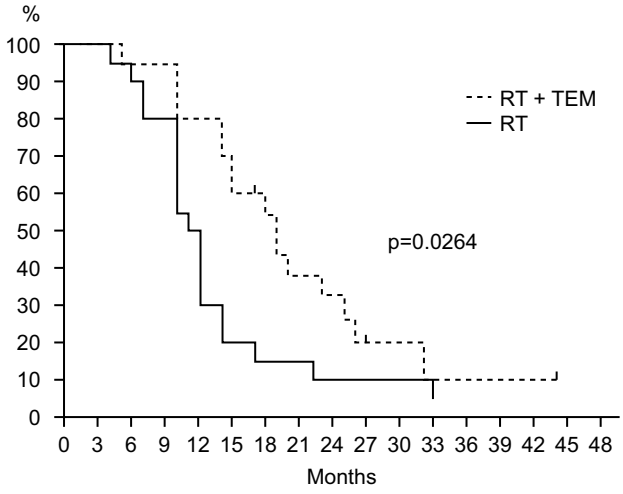

Figure 2. Overall survival. RT: radiotherapy, TEM: temozolomide.

19 (95%) of 20 patients had died, and 1 (5%) was still alive with disease progression. In the RT plus temozolomide group, 16 (80%) of 20 patients had died, 4 (20%) were alive, of which 2 had disease progression and the other 2 had stable disease.

Median PFS in the RT plus temozolomide group and in the RT-alone group were 13 months and 5 months, respectively (hazard ratio 0.3735; 95% confidence interval 0.06929-0.3882; log-rank test, p = 0.0001; Figure 1).

Median OS was 19 months in the RT plus temozolomide group, and 11.5 months in RT-alone group (hazard ratio 0.504; 95% confidence interval 0.2073-0.9068). Log-rank test showed a significant difference in survival between the two groups (p=0.0264; Figure 2).

Of 8 patients in the RT-alone group with complete tumor resection relapse occurred after a median of 12 months (range 8-14); median OS was 14 months (range 5-73). Of 14 patients in the RT plus temozolomide group with complete tumor resection 7 relapsed after a median of 12 months (range 8-19) and 9 after a median of 24 months (range 17-28). Median OS was 25 months (range 6-45).

Discussion

RT is still the standard therapy for high grade gliomas following resection. Diffuse tumor infiltration of normal brain tissue precludes the total resection of the primary tumor in many patients. A few clinical studies performed in the late 1970s showed that postoperative RT had significantly improved survival [13,14].

Temozolomide is an effective agent in the treatment of malignant gliomas, with improved safety profile compared to other nitrosoureas. In some studies, it has been shown that temozolomide has *in vitro* and *in vivo* radiosensitizing properties [7,15]. A study conducted by Athanassiou et al. [16] underlined the dose intensification for temozolomide (temozolomide was given at 75 mg/m^2/day during RT and 150 mg/m^2, 5 days every 28 days for 6 cycles). This study confirmed the efficacy and safety of RT and temozolomide combination (concomitant and subsequent), and the superiority of this combination over RT alone in newly diagnosed GBM patients. The primary endpoints of this study (PFS and OS) were significantly longer in the RT plus temozolomide group (median PFS 5.2 vs. 10.8 months; median OS 7.7 vs. 13.4 months) compared to the RT-alone group. Yet, improved PFS and OS rates were obtained with the combined therapy in the majority of the patients (60%), although they had KPS ≤80. In a study performed by Stupp et al. [17], only 36% of patients with GBM had KPS ≤80, and the median OS survival was 15.8 months. This implies that PS is an important prognostic factor in GBM patients.

In the EORTC phase III study, 573 newly diagnosed GBM patients were randomized to receive standard RT (in daily fractions of 2 Gy given in 30 days, for a total of 60 Gy) or RT with concomitant and subsequent temozolomide [18]. That study showed that combination therapy significantly improved median PFS (7.2 vs. 5 months; p < 0.0001) and median OS (15 vs. 12 months; p < 0.0001; 2-year survival 26 vs. 8%; p < 0.0001) compared to RT alone in GBM patients. In a phase II study by Athanassiou et al. [17], PFS improvement in the RT plus temozolomide group compared to RT-alone group (10.8 vs. 5.2 months) was superior compared with the results obtained in the EORTC study (PFS 7.2 vs. 5 months). Two possible explanations for this situation include different patient populations and more sensi-

tive detection of radiologic progression in the EORTC study. In our study PFS was 13 months in the concomitant treatment group and 5 months in the RT-alone group (p=0.0001). Median OS in the RT and concomitant-subsequent temozolomide and the RT-alone group was 19 and 11.5 months, respectively (p=0.0264).

In the study conducted by Athanassiou et al. [16], the main side effect was reversible and noncumulative myelosuppression both in concomitant and subsequent phases of therapy in the RT plus temozolomide group. Concomitant RT plus temozolomide administration were well tolerated, and grade 3 and 4 leukopenia (3.5%) and thrombocytopenia (5.2%) rates were low. However, a patient in this group died of sepsis. The general treatment compliance in the subsequent temozolomide phase was satisfactory; 46 of 57 patients (80%) received at least one cycle and 35 of 57 patients (61.4%) completed 6 cycles of subsequent adjuvant temozolomide therapy. Due to protracted schedule in the subsequent phase, grade 3 and 4 leucopenia and thrombocytopenia were observed only in 2% and 5% of the patients, respectively. Previous RT concomitant with temozolomide did not increase toxicity in the subsequent phase. Non-hematological adverse events were rare. Grade 3 and 4 nausea and vomiting were virtually eliminated by standard antiemetics.

In our study, patients in the RT plus temozolomide group had statistically significant PFS and OS benefit compared to the patients in the RT-alone group. Median PFS in the combined treatment group and RT-alone group were 13 months and 5 months, respectively. In respect with median OS, in the combined treatment group and RT-alone group these parameters were 19 and 11.5 months, respectively (p=0.0264).

Conclusion

The results of the present study demonstrated that RT concomitant with temozolomide, followed by 6 cycles of subsequent temozolomide therapy was superior to RT alone in newly diagnosed GBM patients. This regimen improved PFS and OS rates. In addition, temozolomide was safe and well tolerated, and patients continued the treatment with reasonable side effects.

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