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RADIOCHEMOTHERAPY FOR UNRESECTABLE GLIOBLASTOMA MULTIFORME: A MONO-INSTITUTIONAL EXPERIENCE

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ABSTRACT: Introduction: *The purpose of this study was to evaluate the results of a single institution's experience using radiochemotherapy (temozolomide and external beam radiotherapy) in patients with unresectable biopsy proven glioblastoma or partially removed glioblastoma.*

Materials and Methods: *From January 2002 to December 2010, twenty-four consecutive patients received radiation therapy combined with temozolamide for unresectable glioblastoma. All patients underwent biopsy in order to have histology graded according to WHO classification. Patients were treated with radiotherapy (60Gy in 30 fractions) plus continuous daily temozolomide (75 mg/m^2/die, 7 days per week) followed by six cycles of adjuvant temozolomide (200 mg/m^2).*

Eighteen patients (75%) received the intended treatment; 4 (17%) patients interrupted the schedule at the third cycle for progression disease, one patient (4%) at the the first cycle for toxicity and 1 patient (4%) died by cardiovascular disease.

Results: *The analysis showed a median survival of 13.8 months and 15.4 % of patients achieved a 2 years overall survival from diagnosis. Among the patients who completed the protocol we observed a median survival of 16.8 months and 2 years overall survival of 19.8%.*

Conclusions: *Combined treatment consisting in radiotherapy and TMZ (temozolamide) seemed to be an effective and well-tolerated treatment in unresectable or in partially removed glioblastoma patients. This combination improved overall survival with acceptable toxicity.*

INTRODUCTION

Glioblastoma (GBM) is the most common histological form of glioma and remains one of the most difficult cancers to treat at the present time. Maximal safe surgical resection and involved-field radiotherapy have been standard treatments for decades, recently a temozolamide-based chemotherapy added to radiotherapy has been considered the cornerstone of treatment in GBM[1]. It has long been recognized that survival varies with the extent of surgical resection[2]. However, resection may not be feasible for lesions appearing infiltrative or located so close to eloquent gray matter such as thalamus, basal ganglia, brainstem or primary sensory-motor cortical areas. In such cases, the prognosis is very poor and further treatment varies from corticosteroids alone or short-course radiotherapy to extended-course radiotherapy and even combined radiochemotherapy. Data related to treatment tolerance and results are scarce and the management of these patients remains controversial. Since 2000, in our istitution patients with resected glioblastoma multiforme have been treated with a combination of temozolamide and external radio-

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therapy[3] according to EORTC protocol[4]. We also have offered patients with unresectable biopsy proven glioblastoma, the same schedula of treatment. This retrospective review has been undertaken to determine whether unresected glioblastoma patients could benefit from radiochemotherapy regimen routinely used as adjuvant treatment.

PATIENTS AND METHODS

Patient characteristics

The data were collected from 24 patients that received radiochemotherapy in our radiotherapy department for unresectable GBM between January 2002 and December 2010. Stereotactic biopsy or partial resection (with >50% residual tumor) was performed in order to archieve material for neuropathologic diagniosis as well as for further treatment decisions. Tumor histology had to meet the WHO criteria for GBM, 0-6 methylguanine-DNA-methyl transferase (MGMT levels) status was not obtained. In all patients, the clinical workup included a detailed medical history, physical and neurological examination, blood tests and brain magnetic resonance imaging (MRI) and tomography.

Baseline clinical and demographic data have been summarized in Table 1. The analyzed patients had a performance status (PS) ≥60 and a life expectancy of more than 3 months.

All patients received supportive treatment consisted of glucocorticoids at doses adjusted to the patient's clinical status and anticonvulsants were used as indicated medically.

Radical radiochemotherapy

All patients had conformal radiotherapy with 6MV photon beams using CT-assisted three-dimensional treatment planning (PinnacleTM). All patients received a median prescription dose of 60 Gy in 2-Gy fractions to clinical target volume (CTV) included the contrast-enhanced tumor defined radiographically by CT or MRI, excluding edema, plus 3-cm of expansion in all directions.

All attempts were made to administer radiotherapy without interruption. The planned dose was correctly delivered to all patients.

All patients received concurrent chemotherapy with temozolomide 75 mg/m^2, each day during radiotherapy, approximately 1 hour before irradiation for 6 weeks.

During the treatment, patients were monitored for signs of toxicity, and temozolamide dose was modified for myelosoppression.

TABLE 1: PATIENTS CLINICAL AND TREATMENT CHARACTERISTICS

Parameters	No. of patients (%)	Age (years)
	Range	43-81
	Mean	61.21
Age-groups	< 50	4 (16.7)
	51-70	14 (58.3)
	>71 y	6 (25)
Gender	Males	15 (62.5)
	Females	9 (37.5)
Performance status	≤ 60	9 (37.5)
	70	11 (45.8)
	≥ 80	4 (16.7)
Surgery	Macroscopic disease	16 (66.7)
	Biopsy	8 (33.3)
Chemotherapy	Yes	24 (100)
Concomitant TMZ	No	0 (0)
	Suspended	0 (0)
Adjuvant TMZ	>3	18 (75)
	1-3	5 (20.8)
	None	1 (4.2)

Temozolamide continued as long as the absolute neutrophil count (ANC) remained >1500/μL and the platet count remained >100000/ μL. If ANC was between 1000 and 1500/μL or the platet count was between 75000 and 100000/μL, a 25% dose reduction occurred. If ANC was <1000/ μL or the platet count was <75000/ μL, temozolamide was withdrawn for 1 week, and restarted at a 75% dose only after the ANC rose to >1500/ μL and the platet count rose to 100000/μL.

The dose of temozolamide was reduced to 75% after any episode of neutropenia and fever. Four weeks after concurrent radiochemotherapy, temozolomide 150-200 mg/m^2 was administered on days 1-5 a 4-week regimen for 6 cycles. This sequential chemotherapy was administered only in patients with adequate hematological, renal and hepatic functions. The doses of temozolomide were reduced to 50% when hematological grade 2 toxicity was observed on the scheduled day of chemotherapy application. Chemotherapy was withheld at grade 3-4 hematological toxicities.

The adjuvant regimen was delivered to 17 patients (70.8%) with a 4.6 (1-6) mean number of chemotherapy cycles. Five patients (20.8%) interrupted the schedule at the concomitant radiochemotherapy time for progression disease, 1 patient (4.2 %) at the the first cycle for haematological toxicity and 1 patient (4.2 %) died by cardiovascular disease.

Follow-up and restaging

According to an internal protocol, GBM patients were re-evaluated every month. Visits included a clinical assessment consisting of physical examination and complete blood exams. Contrast-enhanced MRI scan (including perfusion and diffusion study) was performed 1 month after radiotherapy and thereafter at 3 months intervals. All analyzed patients received at least two follow-up visits. Adverse events were classified according to National Cancer Institute (NCI) expanded Common Toxicity Criteria, version 3.0, and weekly recorded during radiation therapy and chemotherapy, and during follow-up.

Neuroradiographic responses criteria as defined by Macdonald et al.[5] were used. Tumor progression was defined as an increase in tumor size greater than 25% or presence of at least one new lesion on imaging. If progression occurred, further treatment was at the physician's discretion.

Statistical analysis

The primary endpoint of the study was overall survival. The secondary end-points were: (a) progression-free survival and (b) tolerance to treatment. The Kaplan–Meier method[6] was used to estimate survival and progression-free survival. Differences in survival and in progression-free survival were assessed by the log-rank test. Overall survival was defined as the interval between diagnosis and death or last follow-up. Progression-free survival was defined as the interval of time between the start of treatments and documented disease progression after radiochemotherapy. In this analysis, patients dying in the absence of a disease progression were censored at the time of death and were classified as progression-free. The Cox model[7] was used to identify the risk factors for overall survival and progression-free survival. The following variables at baseline were considered for survival univariate analysis: PS and surgery (partial resection versus biopsy).

All analyses were conducted with SPSS version 13.0 8 (SPSS for Windows, Rel. 13.0 2004. Chicago: SPSS Inc.).

RESULTS

Features of patients at baseline.

Twenty-four consecutive patients were included in the study, 15 male (62.5%) and 9 females (37.5%). Fourteen patients (58.3%) ranged between 51 and 70 years, 6 subjects out of 24 (25%) were over 71 years of age and 4 (16.7%) below 50 years of age.

Patients' characteristics and treatment data are shown in Table 1. The Karnofsky index value was ≤60 in 9 patients (37.5%), 70 in 11 patients (45.8%) and ≥80 in 4 patients.

All patients underwent neurosurgery: partial resection was obtained in 16 patients out of 24 (66.7%), while 8 subjects (33.3%) underwent a stereotactic biopsy.

All patients received adjuvant radiotherapy without interruptions of more than 7 days and completed the planned radiotherapy treatment. Eighteen patients (75%) received adjuvant temozolamide, but only 5 patients (20.8%) underwent the planned 6 cycles.

Follow-up

Mean length of follow-up time was 12.1±6.8 months (range 4–26.6 months) for all patients. No patient was lost at follow-up. During follow-up, a total of 17 deaths occurred with a median time of survival of 13.8 months (95% CI 8.9–18.7). The actuarial overall survival rates at 12 and 24 months were 57.7% and 15.4%, respectively (Fig. 1a). Survival was significantly longer among patients with PS ≥70 (93.3% and 80% at 6 and 12 months, respectively) than among patients with PS ≤ 60 (63.5% and 16.9 % at 6 and 12 months, respectively), (p=0.01 by log-rank test) (Fig. 2). Among the patients who completed the protocol we observed a median survival of 16.8 months and 2 years overall survival of 19.8%.

The results of the univariate analysis are showed in Table 2. The multivariable Cox model included PS and surgery (partial resection versus biopsy) revealed no overall survival difference in patients after adjustment for these prognostic factors.

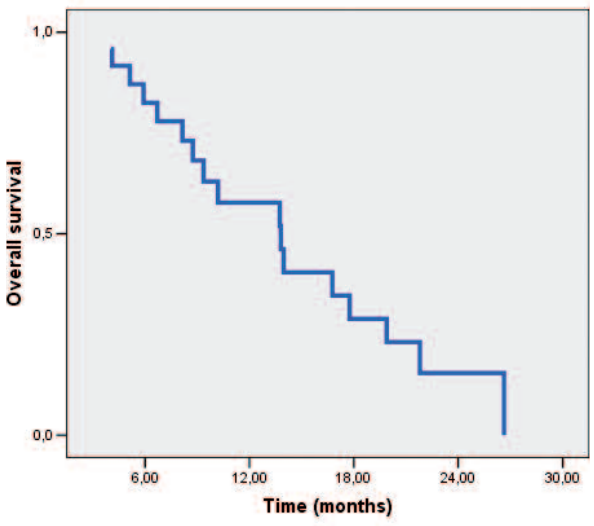

Figure 1. Overall survival curve for all 24 patients evaluated.

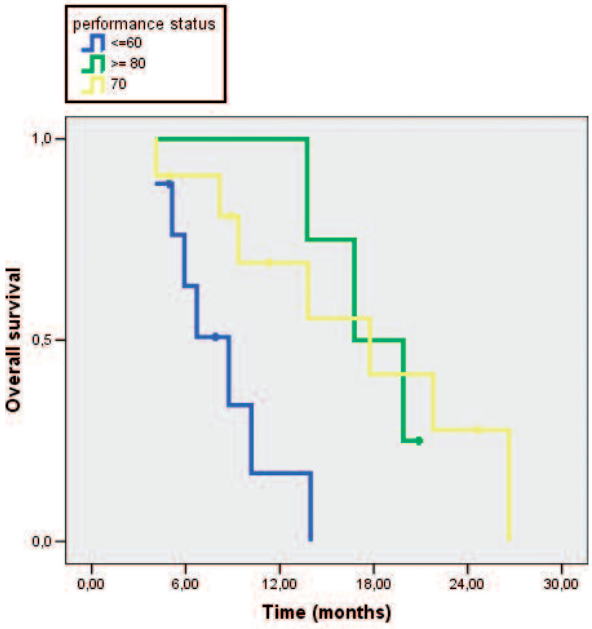

Figure 2. Overall survival distribution by Karnofsky index.

Treatment safety

Acute toxicity correlated to radiochemotherapy was recorded weekly. No treatment-related mortality was found. Main treatment-related toxicities were hematological (14 patients, 58.3%). During concomitant temozolamide, no patient developed grade 3 thrombocytopenia, while 2 patients had grade 2 thrombocytopenia. Temozolamide administration was withdrawn for 1 week, and restarted at a 75% dose after platet count rose to 100000/ μL, whereas the radiotherapy program was completed.

Eighteen patients (75%) experienced neurological toxicity during or immediately after radiotherapy, principally confusion and/or somnolence. Symptoms were reversible in all patients following an increase of steroid dose.

Adjuvant temozolamide therapy was planned in all patients and 18 patients (75%) received at least 3 cycles. Temozolamide was early discontinued in one patient due to hematological toxicity, and in 4 patients because of progression of disease. Only 5 patients (20.8%) completed the planned adjuvant temozolamide treatment. One patient died for cardiovascular accident.

One patient experienced a deep vein thrombosis after 6 cycles and in another a bowel injury was surgically resolved.

DISCUSSION

The combined use of external-beam radiation and temozolamide has been widely recognized as the most effective treatment approach for patients with glioblastoma, increasing the 2-years overall survival rate by 2.5 fold. Based on the results of the EORTC trials[9], worldwide this is now the standard treatment for glioblastoma patients after debulking surgery. In patients with tumors in eloquent or deep areas, with midline tumors, or in those with extensive tumors or multifocal tumors, or in patients with heavily reduced PS, stereotactic biopsy might appearas the most appropriate neurosurgical intervention in the individual case. When surgery is not feasible, the prognosis remains very poor.

Few studies have valuated the management of unresectable glioblastoma patients, so the role of any treatment for this setting of patients is far from definite, even though this subgroup of patients can represent up to 35–40% of all GBM patients[10]. Literature's data show a median survival time of 3 months with best supportive care[11] and 7 months with radiotherapy alone[11].

Adding chemotherapy to radiotherapy increases the efficacy of irradiation without increasing the physical dose. The subgroup assessment of EORTC trial patients who only received biopsy, showed no

TABLE 2: UNIVARIATE ANALYSIS OF SURVIVAL DATA ACCORDING TO VARIOUS CLASSIFICATIONS

Parameters	Groups	β	+ SE	p =	HR (95% CI)
Gender	0: male				
	1: female	,023	,531	,966	1,023 (,361-2,898)
Age category	0: <50				
	1: 51-70				
	2: >71	2,017	,685	,003	5,516 (1.961-28,803)
Performance	0: ≥80				
	1: 70				
	2: ≤ 60	-,970	,440	,028	0,379 (,160- ,899)
Surgery	0: macroscopic disease				
	1: biopsy	-,327	,532	,539	,721 (,254 - 2,045)

statistical increase in median overall survival than in the radiotherapy alone group (9.4 versus 7.9 months).

The aim of the present study was to analyze our experience with the use of radiotherapy regimens combined to temozolamide, routinely applied after surgery, in unresectable or partially resected GBM patients. The overall survival rates at 6-and 12 months were 82.5% and 51.9%, respectively, and the median survival was 13.8 months.

These results are comparable to reported data concerning the same population[9].

Globally, the administration of oral temozolamide concomitantly and after radiotherapy was also well tolerated by patients with poor Karnofsky index. Despite this, twenty-one patients (87.5%) experienced toxicities, most patients had manageable hematological and neurological toxicities resolved with early discontinuation of temozolamide and increasing of steroid dose. The complete outpatient administration of combined radiochemotherapy resulted in excellent patient acceptance.

In conclusion, our data show that an integrated approach with temozolamide added to radiotherapy maintains its activity and feasibility also in unresectable or partially resected GBM patients.

Whenever possible and appropriate, unresectable or partially resected GBM patients, correctly stratified for PS, should be allowed and encouraged to participate in clinical studies.

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REFERENCES

1. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005; 352: 987–996.
2. Chang CH, Horton J, Schoenfeld D, Salazer O, Perez-Tamayo R, Kramer S, Weinstein A, Nelson JS, Tsukada Y. Comparison of postoperative radiotherapy and combined postoperative radiotherapy and chemotherapy in the multidisciplinary management of malignant gliomas. A joint Radiation Therapy Oncology Group and Eastern Cooperative Oncology Group study. Cancer 1983; 52: 997-1007.
3. Cartei F, Api P, Fiorica F, Alberti D, Venturi A, Colella M. Valutazione della tossicità acuta e della "compliance" nella combinazione fra temozolamide e radioterapia in pazienti affetti da glioblastoma multiforme. XIV Congresso Nazionale AIRO.
4. Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, Ludwin SK, Allgeier A, Fisher B, Belanger K, Hau P, Brandes AA, Gijtenbeek J, Marosi C, Vecht CJ, Mokhtari K, Wesseling P, Villa S, Eisenhauer E, Gorlia T, Weller M, Lacombe D, Cairncross JG, Mirimanoff RO; European Organisation for Research and Treatment of Cancer Brain Tumour and Radiation Oncology Groups; National Cancer Institute of Canada Clinical Trials Group. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 2009; 10: 459-466.
5. Macdonald DR, Cascino TL, Schold SC Jr., Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 1990; 8: 1277–1280.
6. Kaplan EI, Meier P. Non-parametric estimation from incomplete observation. J Am Stat Assoc 1958; 53:457–481.
7. Cox DR. Regression models and life tables (with discussion). J R Stat Soc B 1972; 34: 187–220.
8. SPSS Inc. Statistical Package for the Social Sciences (SPSS) for Windows, Rel. 13.0 2004. Chicago (IL):SPSS, Inc.; 2004.
9. Mirimanoff RO, Gorlia T, Mason W, Van den Bent MJ, Kortmann RD, Fisher B, Reni M, Brandes AA, Curschmann J, Villa S, Cairncross G, Allgeier A, Lacombe D, Stupp R. Radiotherapy and temozolomide for newly diagnosed glioblastoma: recursive partitioning analysis of the EORTC 26981/22981-NCIC CE3 phase III randomized trial. J Clin Oncol. 2006;24:2563-9.
10. Fazeny-Dörner B, Veitl M, Wenzel C, Piribauer M, Rössler K, Dieckmann K, Ungersböck K, Marosi C. Second-line chemotherapy with dacarbazine and fotemustine in nitrosourea-pretreated patients with recurrent glioblastoma multiforme. Anticancer Drugs 2003; 14: 437–442.
11. Nieder C, Grosu AL, Mehta MP, Andratschke N, Molls M. Treatment of malignant gliomas in adults Radiotherapy, chemotherapy and integration of new targeted agents. Exp Rev Neurother 2004; 4: 691-703.