

Radio-chemotherapy with Temozolomide in Elderly Patients with Glioblastoma. A Mono-institutional Experience

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Abstract. *Aim: The aim of the present study was to evaluate the toxicity and clinical outcome of radio-chemotherapy with temozolomide in patients with glioblastoma aged more than 65 years. Materials and Methods: The analysis was performed in 20 male and 20 female patients with a mean age at diagnosis of 71.2 (range=65-81) years, with Karnofsky performance status greater than 70 without important comorbidities. Results: Toxicities related to temozolomide and concomitant radiochemotherapy were similar to those reported for younger patients. The median time to progression and median overall survival of the entire cohort, from the date of diagnosis, were 10.6 (range=6.7-14.4) months and 19.3 (range=17.8-20.7) months, respectively. No significant results for overall survival analysis were found for age at diagnosis and cardiovascular risk factors, as covariates, with hazard ratios of 1.00 (95% confidence interval=0.92-1.10) and 0.9 (95% confidence interval=0.43-1.88), respectively. Conclusion: Considering the relative good toxicity profile and the efficacy of treatment, our experience supports the use of radiochemotherapy with temozolomide in older patients with glioblastoma.*

Glioblastoma (GBM) is the most frequent primary malignancy of the central nervous system (CNS) with a peak of incidence on the fifth/sixth decades of life (1). Due to the progressive ageing of the developed country population, more than a half of new cases occurs in patients older than 65 years (2). Elderly patients with GBM vary considerably in health status and functional reserve, and the challenge is

objectively evaluating the risk of treatment complications (3). In developed countries, the increased life expectation and the improvement in quality of life, not only lead to an increase of the elderly population but research indicates that the new aging population seems healthier, more active and demanding than traditional geriatric patients (4).

However, senior adults have been historically consistently underrepresented in clinical trials, particularly in neuro-oncology settings. As a result, there is a lack of detailed knowledge concerning the efficacy, tolerability and toxicity of cancer therapies in the elderly. For patients older than 70 years, data from large, prospective, randomized trials evaluating the role of radiochemotherapy are not available, and only few studies can be examined (5-9). Moreover, in elderly patients with GBM the available literature showed limited benefit from surgery or radiochemotherapy (6-9).

In an attempt to combine the best therapy for each elderly patient, the European Organization for Research and Treatment of Cancer (EORTC) highly recommends to classify elderly patients as frail, vulnerable or healthy on the basis of a comprehensive geriatric assessment, before starting an oncology treatment. However, in many clinical studies, currently recruiting older patients with GBM, no geriatric diagnostic or prognostic evaluation (10, 11) is performed. In the clinical setting, physicians generally deal with elderly patients using the Karnofsky performance status (KPS), the presence of comorbidities, epigenetic factors and the concomitant medical therapies that could interfere with the metabolism and pharmacokinetics of anticancer drugs (7, 12). All these clinical factors make the population of patients aged more than 65 years very heterogeneous (7-9).

Since 2005, when the EORTC and National Cancer Institute of Canada (NCIC) study was published, the standard treatment of GBM has been postoperative radiotherapy with concomitant temozolomide (13). This trial enrolled patients with GBM aged less than 70 years (median age=57 years). Considering the relatively low frequency of adverse events ($\leq 10\%$) and the age-independent pharmacokinetics, several

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Table I. Baseline patient characteristics.

Number of patients	Gender (male)	Age years (range)	Histology	Supratentorial tumors (%)	Percentage of radical resection	Prevalence of diabetes	Prevalence of hypertension
40	20	71.2 (65-81)	Glioblastoma	100	42.5%	5%	27.5%

clinicians surmise that this regimen is applicable even for older people. Thus, in many hospitals, combined treatment of radiotherapy and temozolomide was considered the standard approach for patients older than 70 years, with good KPS and without important comorbidities. However, one clinical experience of a different treatment documented that greater age at diagnosis was a negative prognostic factor in patients with GBM (14). Recently, the publication of the effect of the methylation of promoter of *O*⁶-methyl-guanine–methyl-transferase (*MGMT*) on clinical response to temozolomide added new information for deciding treatment of GBM (15).

The aim of the present retrospective study was to evaluate the response to radiochemotherapy with temozolomide in terms of toxicity, overall survival (OS) and time-to-progression (TTP) in patients with newly-diagnosed GBM, aged more than 65 years and treated at the Pisa University Hospital since 2005. Moreover, as a secondary objective, we investigated the influence of age and medical history on the OS of the present cohort. Thirty-three patients with GBM selected for this analysis participated in a prospective phase II study carried-out since 2004 at Pisa University Hospital. That trial evaluated the safety and the activity of a cycle of temozolomide given one month before the beginning of radiochemotherapy with temozolomide in patients with GBM.

Patients and Methods

Forty patients with a diagnosis of GBM grade IV World Health Organization Classification (WHO), KPS more than 70 and older than 65 years, were treated at Pisa University Hospital from February 2005 to October 2012 with radiotherapy and temozolomide. Ethics Committee approval for patient clinical notes review was obtained (approval number: 3304/2011).

From the Hospital database, we retrieved data for 20 male and 20 female patients with a mean age at the diagnosis of 71.2 (range=65-81) years. A partial resection of tumor was performed in 19 patients (47.5%), a radical excision in 17 (42.5 %) and a stereotactic biopsy in 3 (7.5%). In one patient, a pathological diagnosis was not performed for the site of tumor, only a radiological diagnosis of high-grade glioma was available.

Radiotherapy was delivered as a conventionally fractionated regimen. A total dose of 60 Gy in 30 fractions, five days per week was applied. During radiotherapy, temozolomide was continuously administered at a daily dose of 75 mg/m². After 4-5 weeks, Magnetic resonance imaging (MRI) was performed and then temozolomide was administered at 200 mg/m² for five consecutive

days, every 28 days. A maximum of 12 cycles were prescribed if MRI showed no disease progression and temozolomide was well tolerated. Adverse effects were graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0 [16], with a score of 1 indicating mild adverse effects, a score of 2 moderate adverse effects, a score of 3 severe adverse effects, and a score of 4 life-threatening adverse effects.

The general status of patients was determined at baseline (before starting treatment) only with a standard medical examination. Thirty-three (82.5%) patients enrolled in a phase II trial at Pisa University received one cycle of chemotherapy with 200 mg/m² temozolomide for five days one month before begin combined radiochemotherapy. After disease relapse, 10 (25.0%) patients underwent a second surgery and 22 (55.0%) second-line chemotherapy. TTP and OS were calculated from the date of diagnosis (surgery or first MRI if surgery was not performed) to progression or death respectively.

Statistical analysis. Descriptive analysis was conducted for all study variables. Mean, standard deviation, median (range) are reported for continuous variables; frequency and percentages are reported for the categorical variables. TTP and OS were analyzed using the Kaplan–Meier method. A univariate analysis using the Cox proportional regression analysis was used to examine the effect of multiple prognostic factors on TTP and OS. These factors included age, sex, medical history (cardiovascular risk factors: hypertension, diabetes, previous cardiovascular events) and type of resection (total vs. partial). All reported *p*-values are two-sided and differences were considered statistically significant when the *p*-value was less than 0.05. The SPSS program version 21 (Inc., Chicago, Illinois) was used for the statistical analysis.

Results

Overall, enrolled patients presented a relative good general clinical status. Medical history revealed that two patients (5.0%) were affected by type-2 diabetes mellitus, 11 patients (27.5%) were treated for high blood pressure, and in one case, a myocardial infarction had occurred two years before the diagnosis of GBM (Table I).

Treatment tolerability analysis revealed that hematological toxicities related to treatment with temozolomide and concomitant radiochemotherapy were anemia G4 in one patient (2.5%) and G1-G2 in five (12.5%); leucopenia G4 in one patient (2.5%) and G1-G2 in five (12.5%); thrombocytopenia G3-4 in six patients (15.0%) and G1-G2 in 13 (32.5%). One patient experienced a bone marrow aplasia that caused their death. In all patients treated with the

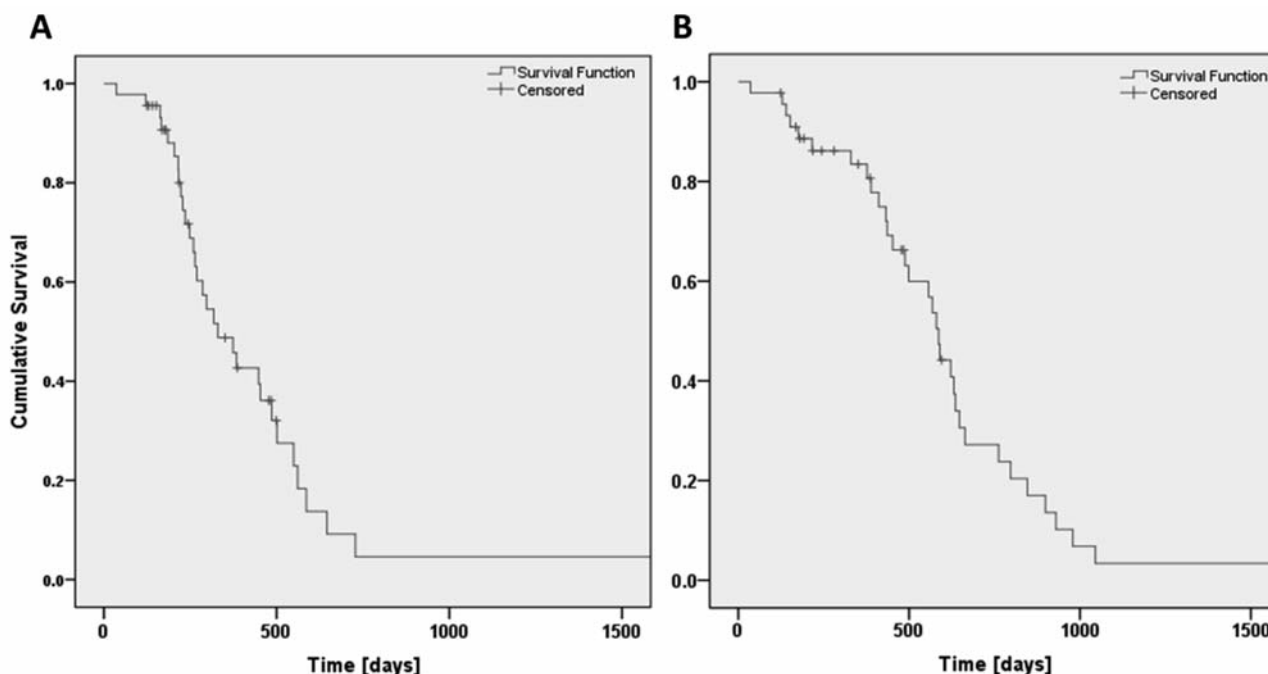


Figure 1. Kaplan–Meier analysis of time to progression (A) and overall survival (B) of study cohort (patients with glioblastoma).

induction cycle of temozolomide, the start of concomitant radiochemotherapy was not delayed due to toxicity related to chemotherapy.

The median TTP and the median OS of the entire cohort were, from the date of diagnosis, 10.6 (6.7-14.4) months and 19.3 (17.8-20.7) months, respectively (Figure 1). The Cox regression analysis of covariates is reported in Table II; no significance associations with OS were found for age at diagnosis and cardiovascular risk factors (diabetes and hypertension) as covariates.

Discussion

The approach to treating GBM in elderly patients is still controversial. Different treatments are often provided to geriatric patients with GBM without the aid of guidelines based on large randomized trials. After the results of EORTC and NCIC trial in 2005, radiochemotherapy with temozolomide has become the standard therapy for young adults with GBM with KPS greater than 60, and although patients older than 70 years were not enrolled in that trial, it has been applied to a selected population of patients older than 70 years (13). Our results, obtained in a cohort of elderly patients with small burden of concomitant chronic disease and with a relative good KPS, confirmed that a full dose of combined radiochemotherapy is feasible in those older than

Table II. Cox regression analysis of age at diagnosis (per 1-year of increment) and cardiovascular risk presence (diabetes/hypertension) as covariates.

Factor	HR	CI
Age	1.002	0.90-1.11
Cardiovascular risks	1.23	0.55-2.76

HR: Hazard ratio; CI: 95% confidence interval.

65 years and the OS and toxicity profile observed are comparable with the toxicity observed in a younger population (13). Two previous non randomized studies in elderly patients with GBM treated with an intensive radiochemotherapy regimen found similar results in terms of OS and tolerability. Combs *et al.* evaluated the efficacy and toxicity of postoperative radiochemotherapy with temozolomide in 53 patients older than 65 years. The median OS was 11 months (18 months for patients who underwent complete resection and six months for those after biopsy only). The treatment was well-tolerated in most patients (17). In 2009, Brandes *et al.* also reported the results of 58 patients with GBM older than 65 years treated with postoperative radiochemotherapy with temozolomide. The median TTP and median OS were 9.5 months and 13.7 months, respectively (7).

Other significant results on GBM treatments in the elderly were reported in three recent studies, although the authors did not apply an intensive treatment regimen and enrolled patients with various performance status (20). The large Nordic trial randomly assigned patients with GBM older than 70 years to three treatment arms (standard radiotherapy delivered in 30 sessions, exclusive chemotherapy with temozolomide, hypo-fractionated radiotherapy). The study showed that a standard radiation treatment had a high dropout rate due to decline in functional status and the chemotherapy offered the best advantages in terms of survival and quality of life compared to radiotherapy alone (18). In 2011, the NOA-08 trial randomized patients with GBM over 65 years into two arms (radiotherapy alone at 60 Gy in 30 fractions, or chemotherapy alone with temozolomide at 100 mg/m², with one week-on/one week-off). Results revealed radiotherapy was not inferior to chemotherapy, with satisfactory toxicity (19). In 2012, Minniti *et al.* published data from a phase II study with 71 patients older than 70 years with GBM. All patients were treated with a hypofractionated radiotherapy (40 Gy in 15 fractions) followed by 12 months of chemotherapy with temozolomide. OS was 12.4 months and tolerance to treatment was good (only 8% of patients discontinued chemotherapy due to myelotoxicity) (20). Although the authors of these studies present encouraging results on GBM treatment, they did not study a full dose of radiochemotherapy with temozolomide. Our results also appear comparable to that obtained by Minniti *et al.* in a small cohort of elderly (>70 years) patients with GBM treated with concomitant radiochemotherapy with temozolomide. The authors evaluated the impact of methylation of the promoter of *MGMT* on OS and interestingly found a significant relationship between the promoter methylation status and better median OS (21). In details, patients with *MGMT* methylated promoter had a median OS of 15.3 months while unmethylated patients had an OS of 10.2 months ($p=0.0001$). Since most of our patients were treated for GBM before the publication of the effect of *MGMT* promoter methylation on OS, we did not have such epigenetic data to perform specific analyses (15).

The sub-analysis of covariates using Cox regression of OS of the entire cohort showed that age and cardiovascular risk factors were not associated with worse OS. The negative effect of age observed in the Stupp trial in younger people (13) seems not to have a significant impact on the OS of elderly patients with GBM, as shown by our results. However, this finding should be interpreted with caution due to a possible beta error considering the heterogeneity of our patients and the relative small number of patients. Overall, our data on OS are similar to those reported in other clinical experiences with younger patients treated with concomitant radiochemotherapy with temozolomide (8, 13). It is

noteworthy that our population was well-selected in terms of KPS and in good clinical condition (KPS of our patients was greater than 70 without important comorbidities at the time of diagnosis of GBM). This finding suggests that in elderly patients, the general clinical health status may be the most significant factor to be considered for the oncology treatment choice.

Hematological toxicity related to chemotherapy was comparable to that observed in the study of the EORTC and NCIC published in 2005 that enrolled only patients younger than 70 years (13). We recorded one fatal event probably related to temozolomide for the development of bone-marrow aplasia. This event could be considered a rare complication of the treatment, not predictable and not age related.

If a selected subgroup of patients older than 65 years with GBM might benefit from standard radiochemotherapy with a good safety, as well as younger patients treated in the same way, a geriatric assessment at baseline could be a useful tool for selecting older patients with comorbidity or disability which represent the majority of cases in the clinical setting. Multi-dimensional comprehensive geriatric assessment includes a compilation of reliable and valid tools to assess geriatric domains such as comorbidity, functional status, physical performance, cognitive status, psychological status, nutritional status, medication review and social support (22). With such an assessment, it should be possible to better-define the patient prognosis and the risk of treatment toxicity and make the choice of therapy for such patients more accurate and well balanced.

Our conclusions are that radiochemotherapy could be applied for selected elderly people with GBM with a good performance status. In order to apply an aggressive regimen of radiochemotherapy to elderly patients with reduced performance status or with comorbidities, a multi-disciplinary team composed of a neurosurgeon, neuroradiologist, pathologist, clinical oncology, geriatrician and neurologist should be recommended and future studies are warranted to validate the effectiveness of comprehensive geriatric assessment.

In conclusion, considering the relative good toxicity profile and the efficacy of treatment, our experience supports the use of a specific schedule of treatment in the older population with GBM, although the differences in study populations and responses warrant future confirmative studies.

Conflicts of Interest

None of the authors have any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work.

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Nothing to disclose.

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