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CLINICAL STUDY - PATIENT STUDY

# Hypofractionated radiotherapy followed by adjuvant chemotherapy with temozolomide in elderly patients with glioblastoma

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**Abstract** *Objectives* The optimal treatment for elderly patients (age >70 years) with glioblastoma (GBM) remains controversial. We conducted a prospective trial in 43 consecutive elderly patients with GBM treated with hypofractionated radiotherapy (RT) followed by adjuvant temozolomide. *Patients and methods* Forty-three patients 70 years of age or older with a newly diagnosed GBM and a Karnofsky performance status (KPS) ≥ 60 were treated with hypofractionated RT (6 fractions of 5 Gy each for a total of 30 Gy over 2 weeks) followed by up to 12 cycles of adjuvant temozolomide (150–200 mg/m$^2$ for 5 days during each 28 day cycle). The HRQOL was assessed with the EORTC Quality of Life Questionnaire C30. The primary endpoint was overall survival (OS). Secondary endpoints included progression free survival (PFS), toxicity and quality of life. *Results* The median OS was 9.3 months and the median PFS was 6.3 months. The 6 and 12 month survival rates were 86% and 35%, respectively. The 6 and 12 month PFS rates were 55% and 12%, respectively. In multivariate analysis KPS was the only significant independent predictive factor of survival ($P = 0.008$). Neurological deterioration occurred during or after RT in 16% of patients and was resolved in most cases with the use of steroids. Grade 3–4 hematologic toxicity occurred in 28% of patients during the adjuvant chemotherapy treatment with temozolomide. The treatment had no negative effect on HRQOL, however, fatigue ($P = 0.02$) and constipation ($P = 0.01$) scales worsened over time. *Conclusions* Hypofractionated RT followed by temozolomide may provide survival benefit maintaining a good quality of life in elderly patients with GBM. It may represent a reasonable therapeutic approach especially in patients with less favourably prognostic factors.

**Keywords** Glioblastoma · Elderly · Radiotherapy · Chemotherapy · Temozolomide

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## Introduction

Glioblastoma (GBM) is increasing among elderly patients and accounts for the majority of primary brain tumours [1, 2]. Current treatment includes surgery, radiotherapy (RT) and chemotherapy, however, optimal management of GBM in the elderly is still debated.

Both standard and abbreviated courses of RT have been employed in elderly patients with GBM [3–15]. A median survival of 4–8 months has been reported following both standard RT [10–12, 14] and abbreviated courses of RT [4–8, 13, 15] in patients >70 years. The association of standard RT and temozolomide has been advocated as an effective treatment in elderly patients with good prognostic factors, with a reported median survival of 8–14 months [16–19]. However, the potential toxicity of combined

aggressive treatment in this group of patients is of concern, especially in patients with a less favourable functional status, leading many physicians to choose less aggressive treatment.

The potential survival benefit and toxicity of a combination of short-term RT and chemotherapy is not defined. The purpose of this study was to assess the effect of hypofractionated RT followed by adjuvant temozolomide on survival and quality of life in elderly patients >70 years with GBM.

## Patients and methods

Forty-three patients 70 years or older with histologically confirmed GBM according to the World Health Organisation (WHO) classification, and KPS $\geq$ 60, were enrolled in this prospective study.

All patients were required to have normal haematological, liver, and renal function before treatment. No patient received previous RT or chemotherapy. Concurrent medications at the time of treatment included anticonvulsionants ($n = 9$) and dexamethasone ($n = 18$). Main commorbodities were represented by diabetes ($n = 8$), hypertension ($n = 14$) and cardiovascular disease ($n = 7$).

All patients received focal RT followed by adjuvant temozolomide. RT started within 4 weeks of surgery and consisted of fractionated focal irradiation, at the dose of 30 Gy delivered in 6 fractions over 2 weeks (5 Gy per fraction 3 times per week), with 3 or 4 orthogonal beams. The gross target volume (GTV) was defined by postoperative contrast-enhanced lesion on T1-weighted magnetic resonance imaging (MRI). The planning target volume (PTV) was defined as GTV plus 2–3 cm margin in three dimensions. Conformal RT was carried out using a three-dimensional (3D) planning system and delivered with 6 MV linear accelerator using a multileaf collimator.

Adjuvant temozolomide was started within 4 weeks after the end of RT and delivered for 5 days every 28 days up to 12 cycles. The dose was 150 mg/m$^2$ for the first cycle and was increased to 200 mg/m$^2$ from the second cycle. The dose was reduced to 150 mg/m$^2$ for patients who developed Grade 3 or 4 haematological toxicity, and suspended in patients with disease progression or Grade 3–4 nonhaematological toxicity.

Patients were assessed before and weekly during the RT. Subsequently a clinical assessment of neurological status and tolerance to treatment was performed every month. Patients were monitored by blood counts before each cycle of adjuvant temozolomide. Safety and tolerability were measured using the national Cancer Institute Common Toxicity Criteria (version 2). Neuroradiographic response criteria as defined by Macdonald et al. [20] were used. Radiological response in all patients was evaluated by the same neuroradiologist (A.B.). Tumour progression was defined by an increase in tumour size more than 25% or by the presence of a new lesion on imaging. MRI was repeated before RT, before the first cycle of adjuvant temozolomide and thereafter every 8 weeks.

The patients completed the health-related EORTC questionnaire (QLQ-C30) immediately before RT, 3–4 weeks after RT (immediately before the starting of chemotherapy), and every 2 cycles of chemotherapy. The QLQ-C30 questionnaire comprises five function scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, nausea and vomiting, and pain), and six single-item scales (dyspnoea, insomnia, appetite loss, constipation, and financial effect of treatment), and overall quality of life. Raw scores were transformed to a linear scale ranging from 0 to 100, according to recommended EORTC procedures, with higher scores on the global health status and functioning and lower scores on the symptom scales indicating better performance. All patients provided written informed consent form prior to study participation. The study protocol was approved by the local ethics committees.

The primary endpoint was overall survival (OS). Secondary endpoints included progression free survival (PFS), tolerance to treatment and health-related quality of life (HRQOL). OS and PFS were estimated using the Kaplan–Meier method calculated from the time of surgery. The longrank test was used to compare survival according to the prognostic factors. A multivariate Cox proportional hazards regression model was used to test the effect of prognostic factors on OS and PFS. Changes in KPS and HRQOL were assessed using by ANOVA analysis for repeated measures. Data are expressed as mean $\pm$ standard error (SE).

## Results

Between February 2002 and October 2006, 43 patients (21 males and 22 females) were enrolled in this study (Table 1). Median age was 73 years (range 70–79). The median KPS before RT was 70 (range 60–100). Surgical treatment consisted of gross total resection in seven patients, of subtotal resection in 19 patients, partial resection or biopsy in 17 patients. Histological diagnosis of GBM was confirmed in all patients. In two patients RT was not terminated because of severe neurological deterioration.

The median OS was 9.3 months (95% CI 7.5–11.1) (Fig. 1). The 6 and 12 month survival rates were 86% (95% CI, 76–96%) and 35% (95% CI, 23–47%), respectively. Tumour progression was the primary cause of death

**Table 1** Characteristics of elderly patients with glioblastoma

| Characteristics | No. of patients (%) |
|---|---|
| Age (years) | 73 |
| Median (range) | (70–79) |
| Sex | |
| Male | 21 |
| Female | 22 |
| Karnofsky performance status | |
| Median (range) | 70 (60–90) |
| 60 | 9 |
| 70 | 20 |
| 80 | 10 |
| 90 | 4 |
| Extension of resection | |
| Total | 7 |
| Subtotal | 19 |
| Partial/biopsy | 17 |
| No of chemotherapy cycles | 200 |
| Median (range) | 4 |

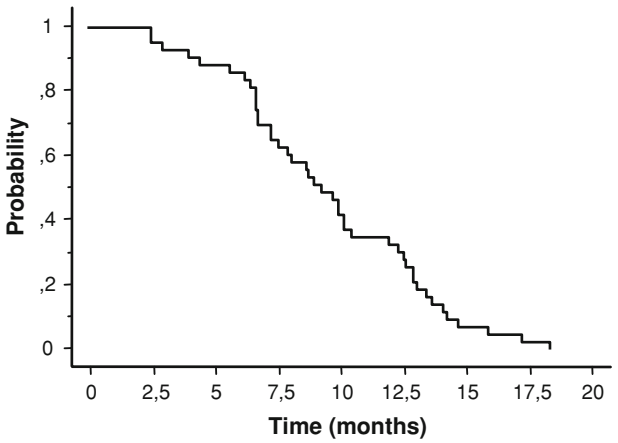


**Fig. 1** Kaplan–Meier analysis of overall survival

in 41 patients. Two patients died primarily of other causes, including one patient who had pulmonary embolism (2 weeks after RT) and one patient who had CHD during the 6th cycle of chemotherapy.

The median PFS was 6.3 months (95% CI 4.8–7.8) (Fig. 2). The 6 and 12 month PFS rates were 55% (95% CI, 36–69%) and 12% (95% CI, 5–27%), respectively.

KPS and extent of resection were significant predictors for survival on univariate analysis ($P = 0.0001$ and $P = 0.01$, respectively). However, in multivariate Cox proportional hazards regression model, KPS was the only significant independent predictive factor (hazard ratios = 0.2, $P = 0.008$). OS was 12.6 months in patients with KPS >70 and 7.9 months patients with KPS $\leq$ 70

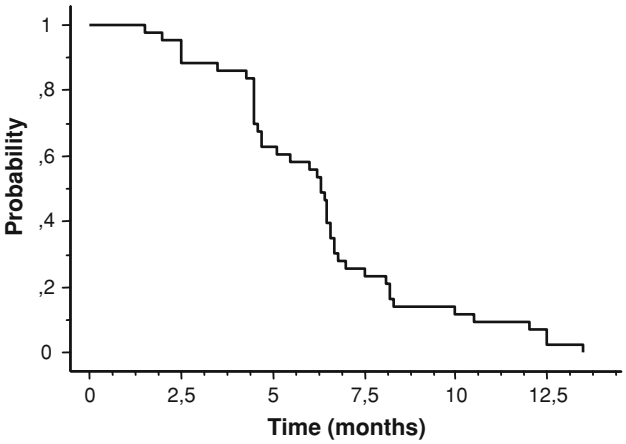


**Fig. 2** Kaplan–Meier analysis of progression free survival

($P = 0.005$), respectively. In univariate analysis KPS had an effect on PFS ($P = 0.006$). Age, sex, site of tumour and presence of commorbidity had no effect on OS and PFS, however, a negative trend was observed between age and survival ($P = 0.08$). A partial response was observed in five patients and a minimal response in eight patients. Responses occurred in four patients after RT, in two patients after 2 cycles of temozolomide, in five patients after 4 cycles and in two patients after 6 cycles.

Table 2 shows mean scores for HRQOL measures at baseline, after RT and during the first 6 cycles of temozolomide (the analysis was restricted to this period because the number of patients was too small after the 6th cycle of TMZ). Data were available in 84% of patients. During treatment, scores of functioning scales and the global health status did not change significantly, however fatigue ($P = 0.02$) and constipation ($P = 0.01$) scales slightly worsened over time. For physical, role and social functioning and fatigue mean score deteriorated significantly between baseline and second follow-up ($P < 0.01$). During the study period (or until tumour progression) KPS did not change significantly ($P = 0.2$). KPS improved in nine patients, remained stable in 28 and worsened in six patients.

## Toxicity

All patients were evaluated for toxicity during RT, the adjuvant-therapy period, and the entire study period. RT could not be completed in two patients because of severe neurological deterioration. Six other patients experienced neurological deterioration after RT (Grade 2/3 confusion and/or somnolence), which was reversible with the use of steroids in four patients. MRI findings (T2 hyperintensities) suggestive of focal periventricular (Grade 1) or diffuse (Grade 2) leukoencephalopathy were recorded in two

**Table 2** Scores for health-related quality of life (QLQ-C30 version 3.0) in 43 elderly patients with GBM during radiotherapy and adjuvant chemotherapy

| Parameter | Score | | | | | *P*-value |
|---|---|---|---|---|---|---|
| | T0 | T1 | T2 | T3 | T4 | |
| Global health status | 58.3 ± 3.7 | 54.3 ± 5.1 | 61.5 ± 5.3 | 60.8 ± 5.4 | 57.9 ± 6.8 | NS |
| Functioning scales | | | | | | |
| Physical | 64.53 ± 3.2 | 58.0 ± 3.8* | 63.7 ± 4.3 | 61.8 ± 4.4 | 60.9 ± 7.4 | NS |
| Role (daily activities/hobbies) | 62.7 ± 2.49 | 53.4 ± 3.5* | 59.8 ± 3.7 | 56.9 ± 4.2 | 58.7 ± 6.1 | NS |
| Emotional | 68.1 ± 2.3 | 67.2 ± 3.4 | 66.4 ± 3.3 | 69.4 ± 3.5 | 67.3 ± 5.6 | NS |
| Cognitive | 66 ± 3.0 | 63.6 ± 3.6 | 66.2 ± 3.7 | 64.6 ± 5.1 | 62.2 ± 7.1 | NS |
| Social | 61.2 ± 2.6 | 53.3 ± 3.2* | 57.7 ± 3.7 | 58.7 ± 3.6 | 56.6 ± 7.3 | NS |
| Symptoms scale | | | | | | |
| Fatigue | 42 ± 2.5 | 50.3 ± 3.2* | 43.6 ± 3.3 | 44.8 ± 4.0 | 48.0 ± 6.7 | 0.02 |
| Nausea and vomiting | 4.7 ± 1.4 | 5.7 ± 1.6 | 6.2 ± 1.9 | 5.4 ± 2.2 | 6.4 ± 5.2 | NS |
| Insomnia | 15.1 ± 3.4 | 14.6 ± 3.8 | 16.8 ± 3.3 | 17.3 ± 3.5 | 19.1 ± 5.7 | NS |
| Constipation | 14.6 ± 3.3 | 14.7 ± 5.0 | 22.3 ± 5.8 | 21.8 ± 5.5 | 25.5 ± 7.7 | 0.01 |

* $P < 0.05$ (T1 vs. T0)

T0, before RT; T1, after RT; T2, T3 and T4 after 2, 4 and 6 cycles of temozolomide

patients who survived more than 12 months. This was associated with mild memory loss and dizziness in one patient.

During temozolomide therapy, a total of 200 cycles were administered with a median of 4 cycles for patient. Grade 3 or 4 thrombocytopenia occurred in 11 patients, Grade 3 neutropenia in four patients and Grade 3 anaemia in two patients. Overall 12 patients (28%) had Grade 3/4 haematological toxic effect. Chemotherapy was stopped in six patients, delayed in 10 patients and reduced in eight patients. Non-haematological adverse events included a moderate-to-severe fatigue (35%), nausea (10%), constipation (22%), and skin rush (9%). Two patients had a lung infection (pneumonia).

## Discussion

Radiotherapy is a common treatment in elderly patients with GBM and both standard and abbreviated courses of RT have been employed in the past with a reported median survival benefit in the region of 4–8 months [3–15]. Mohan et al. [10] reported a median survival of 7.3 months in 58 patients >70 years treated with standard RT. Villà et al. [11] reported an OS of 8 months in 18 elderly patients >70 years treated with standard RT and similar results have been reported by others [12, 14]. Data from some randomised and prospective studies have suggested similar survival benefit in patients receiving abbreviated courses of RT [6–8, 13–15]. In a prospective randomised clinical trial of 100 patients with GBM > 60 years, Roa et al. [14] found a similar survival of approximately 6 months amongst patients receiving standard RT or short-course RT (40 Gy in 15 fractions over 3 weeks). A recent French randomised trial [15] showed an OS of 29.1 weeks in 39 elderly patients treated with RT (50 Gy in 20 fractions over 4 weeks) as compared with 16.9 weeks in patients who received supportive care alone. Similar survival of 6 months has been reported in elderly patient treated with 30 Gy in six fractions over 2 weeks [6, 7, 13].

Temozolomide has been recently advocated as an alternative treatment in newly diagnosed elderly patients with GBM [12, 21, 22]. Chinot et al. [21] reported an OS of 6.4 months in 32 patients treated with temozolomide alone, with a one-year survival of 25%. Glantz et al. [12] reported a median survival of 6 months in 32 patients treated with temozolomide alone, with a one-year survival rate of 12% and similar results have been reported by others [22].

We have treated 43 elderly patients with GBM with an hypofractionated RT regimen of 30 Gy in 6 fractions over 2 weeks followed by adjuvant temozolomide. The median OS and PFS were 9.3 and 6.3 months, respectively. The 6 and 12 month OS were 86% and 35% and respective PFS were 55% and 12%. Our results compare favourably with previous series on the use of RT [1–15] or chemotherapy alone [11, 12, 21], suggesting that the combination of hypofractionated RT and temozolomide may provide survival benefit in older patients with GBM.

In our study we have used a regimen of 30 Gy in 6 fractions over 2 weeks based on two considerations: (1) there is a general consensus that aggressive treatment can be associated with high morbidity and may be not appropriate for elderly patients with limited life expectancy,

especially for those patients with less favourably prognostic factors; (2) a short-course of RT may provides similar survival benefit to that obtained with radical treatment [14], representing a reasonable treatment option for older patients with GBM.

Only recently, few series have shown survival benefit in elderly patients treated with a combination of standard RT and temozolomide. Brandes et al. [16] reported an OS of 14.9 months in 22 patients with GBM > 65 years who presented with good prognostic factors treated with standard RT plus adjuvant temozolomide. We have recently reported an OS of 10.6 months in 32 elderly patients older than 70 years with GBM treated with standard RT plus concomitant and adjuvant temozolomide [18], and similar findings have been reported by others [17, 19].

The present study, therefore, demonstrates a potentially lesser survival benefit than obtained with combined standard RT and temozolomide. Certainly, difference in survival using a short-course of RT can, at least in part, be a reflection of patient selection. In fact, most of the patients in our study were in RTOG RPA classes V or VI which are associated with less survival advantage of the combined treatment of RT and temozolomide [23]. Moreover, temozolomide was given only adjuvantly whereas part of its mechanism of action is through enhancement of radiation response [24]. So far, the question remains whether an abbreviated course of RT may provide an equivalent survival benefit to that obtained with radical RT, and future randomised studies needs to evaluate the impact of different schedules of RT plus concomitant and adjuvant temozolomide on survival and quality of life in this subgroup of patients.

Multivariate analysis showed that KPS was the only factor predictive for survival, and this is consistent with previous studies [10, 11, 16, 18]. More recently, epigenetic inactivation of the DNA repair enzyme methylguanine methyltransferase (MGMT) has emerged as an independent strong factor for outcome in patients treated with temozolomide [25]. We have not tested the presence of MGMT promoter methylation and this is a clear limitation for the study. Patients whose tumours do not have MGMT promoter methylation may have less benefit from the addition of temozolomide chemotherapy and could require alternative treatment strategies. Thus, analysis of MGMT needs to be considered in future protocols for better stratification of elderly patients with GBM.

Only few patients had severe neurological deterioration during or after RT, suggesting that hypofractionated RT is associated with less toxicity than standard RT [5, 14, 18, 19] and can safely employed in elderly patients with less favourably prognostic factors. Grade 3–4 myelosuppression occurred in 28% of patients, leading to the early discontinuation of chemotherapy in half of them. In the other patients temozolomide cycles were delayed or dose reduced. Two patients developed MRI findings suggestive of leukoencephalopathy and this was associated with mild clinical neurocognitive dysfunction in one patient. Leukoencephalopathy is a well recognized complication following large volume brain irradiation and has been reported in patients receiving whole brain radiotherapy [26, 27]. Although more severe cases are associated with chronic confusional state and dementia, most patients with Grade 1/2 radiologic leukoencephalopathy did not show any significant neurocognitive decline [26, 27].

Our findings confirm that temozolomide is well tolerated and relatively safe in elderly patients as previously reported [12, 16, 18, 21, 22], with no more toxicity than in younger patients [28, 29].

The evaluation of health-related quality of life in elderly patients with GBM is relevant. KPS was stable or improved in the majority of responding and stabilised patients until tumour progression. The QLQ-C30 questionnaire, performed in 84% of patients, showed that only fatigue and constipation worsened slightly over time, whereas all functioning scales and global health status did not deteriorate. Overall, the association of hypofractionated RT and temozolomide in our group of elderly patients had no negative effect on HRQOL.

In conclusion, the combination of hypofractionated RT and adjuvant temozolomide is a feasible treatment in elderly patients with newly diagnosed GBM. In particular, it may represent a reasonable therapeutic approach in patients with less favourably prognostic factors, prolonging survival and maintaining an acceptable quality of life. Randomised studies need to determine the impact of different combined regimens of RT and temozolomide on survival and quality of life in this subgroup of patients.

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