Glioblastoma Treatment in the Elderly in the Temozolomide Therapy Era

Linda Coate, Mairéad G. McNamara, Zarnie Lwin, Derek MacFadden, Ahmed Al-Zahraii, Christine Massey, Cynthia Menard, Barbara Ann Millar, Arjun Sahgal, Normand Laperriere, Warren P. Mason

ABSTRACT: Background: Optimal treatment of glioblastoma (GBM) in the elderly remains unclear. The impact of age on treatment planning, toxicity, and efficacy at a Canadian Cancer Centre was retrospectively reviewed. Methods: Glioblastoma patients treated consecutively between 2004 and 2008 were reviewed. Utilizing 70 years as the threshold for definition of an elderly patient, treatments and outcome were compared in younger and elderly populations. Results: Four hundred and twenty one patients were included in this analysis and median overall survival (OS) for the entire cohort was 9.8 months. 290 patients were aged <70 (median age 57, range 17-69) and 131 were aged ≥70 (median age 76, range 70-93). Patients ≥70 were more likely to receive best supportive care (BSC) and all patients >70 who were treated with palliative radiotherapy received <60 Gy (P<0.001), except one. Patients aged >70 demonstrated inferior survival (one year OS 16% versus 54% for those <70, HR 3.46, P<0.001). In patients treated with BSC only, age had no impact on survival (median survival two months in both groups, HR 0.89, P=0.75). For those treated with higher doses of radiotherapy (>30 Gy to <60 Gy), one year survival was 19% versus 24% in patients aged >70 versus <70 (HR 1.47, P=0.02) respectively. Conclusion: In this retrospective single institution series, elderly patients were more likely to be treated with BSC or palliative doses of radiotherapy. Randomized phase III study results are required for guidance in treatment of this population of patients.
All these factors may account for the exclusion of elderly patients from clinical trials and thus explain the lack of evidence-based guidelines. Older age and poor performance status have been shown to be negative prognostic factors in GBM\(^6,9\) and despite treatment advances, to date, the survival of elderly GBM patients is usually less than 12 months\(^7\).

Following maximal feasible surgical resection, radiotherapy has been shown to improve overall survival in patients with GBM, and is offered to the majority of patients with this disease\(^8\). Although, a radiotherapy dose of 60 Gy in 30 fractions is considered as optimal treatment, shorter courses at a lower dose are often offered to poor performance and elderly patients\(^2,9,10\).

The practice-transforming study by Stupp et al\(^11\) resulted in concurrent and adjuvant temozolomide combined with radiotherapy emerging as the standard of care for most patients with GBM\(^12\). However, patients older than 70 years were excluded from this study, therefore the suitability of this regimen for elderly GBM patients is unclear.

We performed a retrospective analysis of our ambulatory experience of consecutive elderly GBM patients who presented to Princess Margaret Cancer Centre to capture the treatments they received and how they benefited when compared to their younger counterparts.

**MATERIALS AND METHODS**

**Patients**

From January 2004 to July 2008, 517 consecutive newly-diagnosed patients with GBM were identified through the Cancer Care Ontario registry and those who received treatment at Princess Margaret Cancer Centre, Toronto were analyzed. Patients who were <16 years-of-age, those who were not newly diagnosed at the time of registration, were consulted at our institution for a second opinion only, did not have pathological confirmation of GBM or had GBM of the spinal cord were further excluded.

Data were retrospectively extracted from the electronic patient record by three investigators (ZL, AAZ, and DMeF). Of the 421 eligible patients, patient-related, tumour-related, and treatment related variables were extracted from the patients’ records and entered into an electronic database. Data on patient demographics, Eastern Cooperative Oncology Group (ECOG) performance status, extent of surgery, treatments planned and delivered including combined modalities, radiotherapy dose, total number of adjuvant temozolomide cycles received, toxicity of all therapies and outcome were captured. Partial resection was defined as less than 90% tumor removal, subtotal resection was defined as less than 100% but greater than 90% tumor removal as per post-operative neurosurgical documentation. Treatment options included best supportive care (palliative care) only, aggressive treatment with 60 Gy radiotherapy concurrent with temozolomide +/- adjuvant temozolomide, palliative active treatment consisting of either palliative dose radiotherapy (30 Gy or less) or more aggressive palliative radiotherapy (>30 Gy but less than 60 Gy). We documented those treated with an abbreviated course of radiotherapy (40 Gy in 15 fractions over three weeks) as this dose had been adapted in our institution based on a previous prospective study by Roa et al in which no difference in survival was seen when compared to the standard 60 Gy in 30 fractions over six weeks in post-operative GBM patients, age > 60 years\(^{10}\). For our study, a threshold of 70 years-of-age was deemed as the cut off to draw comparisons of all data. Overall survival was calculated from the time of diagnosis to death. Patients with incomplete follow-up were censored on the last date they were known to be alive. 0(6)-methylguanine DNA methyltransferase (MGMT) promoter methylation status was not available for patients as this was not routinely requested in the time period studied.

Adverse events were recorded utilizing the descriptions and grading scales found in the revised National Cancer Institute Common Terminology Criteria for Adverse events, version 4.0. Our study was approved by relevant institutional ethics review boards.

**Statistics**

Categorical variables were summarized using frequencies and percentages. Continuous variables were summarized using medians and ranges. Toxicities during treatment were analyzed using Fisher’s exact test, the Cochran-Armitage trend test and logistic regression models.

Overall survival was measured from the date of diagnosis until the date of death. Patients alive at last follow-up were censored. Survival times were investigated using Kaplan-Meier plots, log-rank tests and Cox proportional hazards models.

Linearity assumptions in regression models were tested with quadratic terms. Proportional hazards assumptions were tested using phreg’s assess statement and time-varying covariates.

Additional univariable associations were analyzed using Fisher’s exact test and the row mean score test, as appropriate.

All analyses were generated using SAS software, Version 9.2 TS Level 2MO of the SAS System for Windows, copyright © 2002-2008 (SAS Institute Inc., Cary, NC, USA). Cases with missing values were excluded from all analyses. All \(P\)-values reported are two-sided and exact values are given where feasible.

**RESULTS**

**Patients**

In our study, 421 patients with newly-diagnosed GBM were identified for analyses. Of these, 290 were <70 years and 131 were \(\geq\)70 years old at diagnosis. The median age at diagnosis for the entire cohort was 62 years (range 17-93 years). For patients aged less than 70 years, the median age at diagnosis was 57 years (range 17-69) and for patients aged 70 and older, the median age at diagnosis was 76 years (range 70-93). Elderly patients were more likely to have a worse performance status (\(P\leq0.001\)), and were more likely to be female although this trend did not reach statistical significance (Table 1).

**Treatment**

Treatment data were available for all 421 eligible patients. In the younger group (\(N=290\) (<70 years), 59 (21%) had biopsy only, 180 (62%) had partial resection and 51 (17%) had subtotal resection. In the elderly cohort (\(N=131\) (\(\geq\)70 years), 52 (40%) had biopsy only, 54 (41%) had partial resection and 25 (19%) had subtotal resection. The elderly cohort (\(\geq\)70 years) was more likely to have treatment planning as either best supportive care (palliative care), or purely palliative treatment (radiotherapy \(\leq 30\))
temozolomide in newly diagnosed glioblastoma. Two patients (≥70 years) were enrolled in the randomized phase III study of temozolomide and short-course radiotherapy versus short course radiotherapy alone in the treatment of newly diagnosed glioblastoma in elderly patients.

### Survival

Of the 421 patients, 328 had died by last follow-up. The median survival for the entire cohort was 9.8 months (2 days-5.2 years). Of the 290 younger patients, 79 (27.2%) were still alive at last follow-up, with a median follow-up of 1.8 years (2 days-5.3 years). Of the 131 elderly patients, 14 (10.7%) were still alive at last follow-up with a median follow-up of 0.6 years (9 days-1.2 years). When we compared the entire cohort by age, there was a statistically significant reduction in survival in patients aged 70 years and older (median survival was 0.33 years) in contrast to patients younger than 70 years (median survival of 1.09 years) (P<0.001) (Figure 1).

When we investigated age–related differences in survival with respect to specific treatments there was no difference in those planned for palliative care only (P=0.75) (Figure 2). Specifically, for patients who received palliative dose radiotherapy (≤30 Gy), there was no significant difference in survival between younger (<70 years) and elderly patients ≥70 years. Furthermore, for those treated with more aggressive palliative radiotherapy regimens (≥30 Gy but <60 Gy), elderly patients had a one year survival of 19% compared to their younger counterparts (24%) (P=0.02) (Figure 3). As only one patient ≥70 years received 60 Gy radiotherapy, survival comparisons based on age for conventional doses of radiotherapy was not possible.

### Table 1: Demographics for entire cohort of patients (N=421)

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<tr>
<th>Variable</th>
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<th>Aggressive</th>
<th>Palliative Active ≤30 Gy</th>
<th>Palliative Active  &gt;30 Gy but ≤60 Gy</th>
<th>Palliative Active &gt;60 Gy</th>
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<td>37.3</td>
<td>101</td>
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<tr>
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<td>68.9%</td>
<td>68.9%</td>
<td>68.9%</td>
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<td>13.1%</td>
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<td>13.1%</td>
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</tr>
<tr>
<td></td>
<td>≥70 Years N=131</td>
<td>86.9%</td>
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<th>Variable</th>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total N=421</td>
<td>56.5%</td>
<td>19.7%</td>
<td>11.5%</td>
<td>7.7%</td>
<td>2.1%</td>
<td>2.8%</td>
<td>&lt;0.001</td>
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<tr>
<td>Gender</td>
<td>Male</td>
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<td>35.0%</td>
<td>24.2%</td>
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<tr>
<td></td>
<td>Female</td>
<td>63.8%</td>
<td>65.0%</td>
<td>44.7%</td>
<td>32.7%</td>
<td>15.3%</td>
<td>5.8%</td>
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</tr>
<tr>
<td>Age at Diagnosis</td>
<td>&lt;70 Years N=290</td>
<td>68.9%</td>
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<td>68.9%</td>
<td>68.9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥70 Years N=131</td>
<td>31.1%</td>
<td>31.1%</td>
<td>31.1%</td>
<td>31.1%</td>
<td>31.1%</td>
<td>31.1%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>N=421 100%</td>
<td>68.9%</td>
<td>68.9%</td>
<td>68.9%</td>
<td>68.9%</td>
<td>68.9%</td>
<td>68.9%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Aggressive; concurrent radiotherapy 60 Gy with temozolomide +/- adjuvant temozolomide. *Palliative Active; palliative dose radiotherapy (≤30 Gy) or more aggressive palliative radiotherapy (>30 Gy but <60 Gy). *Palliative Care; best supportive care, *ECOG; Eastern Cooperative Oncology Group.
In a multivariable analysis, factors affecting outcome were age, treatment and ECOG performance status. When age was included in the cox proportional hazards regression model and an interaction between age and treatment were included in the multivariable model, there was a significant interaction demonstrated between age at diagnosis and treatment effect (P=0.006) (Table 2).

Toxicity

Sixty five patients (22%) < 70 years experienced some toxicity on treatment, with 20 (7%) experiencing thrombocytopenia and two of these patients having grade 3 thrombocytopenia. Fourteen patients (5%) < 70 years had neutropenia, 9 (3%) anaemia and 8 (3%) fatigue. Nine patients (7%) ≥ 70 years had toxicity recorded with three (2%) having thrombocytopenia. No grade 4 adverse events were recorded. There was no evidence of an association between age and increased toxicity in our analysis but this is likely due to fewer number of elderly patients receiving temozolomide. In the entire cohort, younger age and female sex were associated with increased toxicity (P=0.002).

DISCUSSION

In this retrospective analysis of a large ambulatory practice at Princess Margaret Cancer Centre, only one patient with a diagnosis of glioblastoma who was ≥70 years was treated with radiotherapy at a dose of 60 Gy. Our cohort time frame reflects the treatment era immediately following data published from the landmark European Organisation for Research and Treatment of Cancer-National Cancer Institute of Canada (EORTC-NCIC) study11, which had cemented the new standard of care in the treatment paradigm of newly diagnosed GBM. In our study,

### Table 2: Univariable and multivariable analysis outcomes for Overall Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>95% Confidence Interval (CI)</td>
<td>Wald test P-value</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>1.8  1.6</td>
<td>2.0  &lt;0.001</td>
</tr>
<tr>
<td>Treatment</td>
<td>3.6  2.9</td>
<td>4.7  &lt;0.001</td>
</tr>
<tr>
<td>Gender</td>
<td>17.7 11.8</td>
<td>26.7  &lt;0.001</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td>1.0  0.8</td>
<td>1.3  0.76</td>
</tr>
</tbody>
</table>

4HR: Hazard Ratio, 5Palliative Active: palliative dose radiotherapy (≤30 Gy) or more aggressive palliative radiotherapy (>30 Gy but <60 Gy), 6Aggressive: concurrent radiotherapy 60 Gy with temozolomide +/- adjuvant temozolomide, 7Palliative Care: best supportive care, ECOG: Eastern Cooperative Oncology Group.
patients ≥70 years with a diagnosis of GBM were more likely to receive best supportive care or palliative doses of radiotherapy. This is probably an appropriate decision, since at the current time there is no evidence to support radiotherapy treatment at 60 Gy in elderly patients, given that patients ≥70 years were excluded from the original EORTC-NCIC study published in 2005. The five year follow-up analysis of this study did however include a subset analysis by age. In this subset, 170 patients (30%) were aged between 61 and 70 years. In this elderly subset, median survival for those who received concurrent radiotherapy with temozolomide followed by adjuvant temozolomide was 10.9 months (range 8.9-14.9) compared to 11.8 months (range 10.4-12.7) for those who received radiotherapy alone and compared to 14.6 months (range 13.2-16.8) for the entire cohort inclusive of all age groups.

Furthermore, in the Nordic Elderly phase III Trial of newly diagnosed elderly GBM patients (≥70 years)\(^\text{15}\), survival was better with temozolomide alone (200 mg/m\(^2\) on days 1-5 every 28 days for up to six cycles) or with hypofractionated radiotherapy (34 Gy) than with standard radiotherapy alone (60 Gy) (Hazard Ratio (HR) for temozolomide versus standard radiotherapy 0.35 [95% confidence interval (CI) 0.21-0.56], \(P<0.0001\); HR for hypofractionated versus standard radiotherapy 0.59 [95% CI 0.37-0.93], \(P=0.02\)). This study concluded that both temozolomide and/or hypofractionated radiotherapy should be considered as standard treatment options in elderly patients with glioblastoma.

A smaller prospective trial in 43 consecutive elderly patients with GBM treated with hypofractionated radiotherapy (30 Gy over two weeks) followed by up to 12 cycles of adjuvant temozolomide (150-200 mg/m\(^2\) for five days during each 28 day cycle) resulted in a median overall survival of 9.3 months in these elderly patients with GBM while maintaining a good quality of life\(^\text{16}\). Another earlier prospective study in 79 consecutive elderly patients (>65 years) with glioblastoma who underwent surgery reported that overall survival was better in patients who received radiotherapy (59.44 Gy in 33 fractions) plus adjuvant temozolomide (150 mg/m\(^2\) for five days every 28 days (Group C) compared to patients receiving the same radiotherapy dose alone (Group A) (14.9 months versus 11.2 months, \(P=0.002\)), but there was no statistical differences found between Group A and those receiving the same radiotherapy plus adjuvant chemotherapy with procarbazine, lomustine, and vincristine (Group B) or between Groups B and C\(^\text{17}\).

A median overall survival of 10.6 months was reported in a prospective trial of 32 consecutive elderly patients with glioblastoma who had surgery followed by standard radiotherapy at 60 Gy plus concomitant temozolomide at 75 mg/m\(^2\) per day followed by six cycles of adjuvant temozolomide (150-200 mg/m\(^2\) for five days during each 28 day cycle)\(^\text{18}\). A phase II study of short course radiotherapy (40 Gy in 15 fractions over three weeks) plus concomitant (75 mg/m\(^2\)) and adjuvant temozolomide (150-200 mg/m\(^2\) for five days during each 28 day cycle) in elderly patients (>70 years) with glioblastoma, reported a median overall survival of 12.4 months, and in a one year and two year overall survival rate of 58% and 20% respectively\(^\text{19}\).

The multi-centre randomized study group of Neuro-oncology working group (NOA-08) phase III trial reported that dose-intensified temozolomide (100 mg/m\(^2\) in one week on/one week off schedule) alone was non-inferior to radiotherapy (54-60 Gy in 30 fractions) alone for patients with anaplastic astrocytoma or GBM aged >60 years and a Karnofsky performance score of 60 or higher. However, patients who received temozolomide in this trial had a higher risk of death compared to those who received radiotherapy (HR 1.24, 95% CI 0.94-1.63)\(^\text{20}\). The NOA-08 study did report that MGMT promoter methylation status seemed to be a useful biomarker for outcomes by treatment and could aid decision-making in the elderly population in the future as MGMT promoter methylation was associated with longer overall survival than the unmethylated status (11.9 months [95% CI 9.0 – not reached] vs. 8.2 months [95% CI 7.0-10.0]) and event free survival was longer in patients with MGMT promoter methylation who received temozolomide than in those receiving radiotherapy alone (8.4 months, [95% CI 5.5-11.7] versus 4.6 months [95% CI 4.2-5.0]). The opposite was true for patients with no methylation of the MGMT promoter (3.3 months [95% CI 3.0-3.5] versus 4.6 months [95% CI 3.7-6.3]). Only one patient ≥70 years in our study received concurrent radiotherapy with temozolomide and six elderly patients received temozolomide in the adjuvant setting and 11 elderly patients received temozolomide on progression of disease, therefore firm conclusions on the benefit of temozolomide in our elderly cohort cannot be made.

Although the treatments offered to elderly GBM patients have become more aggressive, survival gains to date are very modest at best. We await the results of the multi-institutional (NCIC Clinical Trials Group CE.6, EORTC, Trans-Tasman Radiation Oncology Group (TROG) and Japanese group) randomized phase III study of concurrent temozolomide, 75 mg/m\(^2\) daily orally, with short course radiotherapy over three weeks followed by adjuvant temozolomide, versus short course radiotherapy alone in the treatment of newly diagnosed glioblastoma in elderly patients >65 years\(^\text{12}\). Results from this multi-institutional study should provide further guidance on the management of this special population. Methylation status of the MGMT promoter and quality of life data is also being collected.
in this study and should provide informed evidence for future therapy decisions.

In conclusion, maximal safe surgical resection should be offered to elderly patients where appropriate, with follow-up radiotherapy given at a safe dose if the patient has maintained a good performance status. Temozolomide alone could also be considered post surgery\textsuperscript{15,20}. Temozolomide at standard dose\textsuperscript{11,16,18,19} could also be considered either concurrently and/or in the adjuvant setting in selected good performance status patients and MGMT promoter methylation status may also guide treatment in the future.

REFERENCES

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