Editorial

Treatment of elderly patients with glioblastoma: new lessons from CE.6

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The introduction of radiation therapy (RT) with concurrent temozolomide (TMZ) by the EORTC-NCIC trial (the Stupp trial) resulted in a significant evolution in the treatment of adult patients with glioblastoma. The Stupp trial confirmed a significant improvement in overall survival with the addition of concurrent and adjuvant TMZ to radiotherapy (1). Further, for the first time, patients with glioblastoma began to achieve longer-term survival, with nearly 40% alive at 2 years, and nearly 10% alive at 5 years (2).

Unfortunately, these successes failed to translate into gains for elderly patients with glioblastoma. The EORTC-NCIC enrolled only a minority of patients older than age 65, and patients older than 70 were excluded, and exploratory analyses of the EORTC-NCIC data suggested that increasing age attenuates the benefit of concurrent chemoradiation, with decreased survival benefit among patients 65 to 70 years of age [hazard ratio for death: 0.78; 95% confidence interval (CI): 0.50–1.24; P=0.29] than among younger patients (3). Meanwhile, the incidence of GBM in the elderly population has been rising (4).

Anecdotal evidence and previous trial data offered good reason for these patients to have been excluded from the Stupp trial. Many elderly individuals simply cannot tolerate standard RT, l*et al*one combined therapy (5). Not so long ago, the appropriateness of treating elderly patients with GBM was in itself a question. The answer to this question was clarified by the ANOCEF trial [2007]. In this study, Keime-Guibert and colleagues randomized 85 patients over 70 years of age with newly diagnosed glioblastoma and a Karnofsky performance score (KPS) of 70 or greater to supportive treatment alone to RT (50.4 Gy in 28 fractions) plus supportive care (6). The study was stopped at the first interim analysis due to the finding that survival in the RT plus supportive care group was superior to supportive care alone. Median overall survival for patients who received RT plus supportive care was 6.7 months, compared to 3.9 months in patients treated with supportive care alone. Significantly, Keime-Guibert and colleagues found that the survival benefit offered by RT in elderly patients did not come at the cost of health-related quality of life.

The Nordic Brain Tumor Clinical Study Group (the Nordic trial) extended the paradigm for treatment of elderly patients with glioblastoma even further (7). Malmström and colleagues enrolled 342 patients over 60 years of age with a good performance status (ECOG 0–2) to three single-modality treatment arms: (I) standard-dose TMZ; (II) standard RT (60 Gy in 30 fractions); or (III) hypofractionated RT (34 Gy in 10 fractions). Two hundred and ninety-one patients underwent treatment with a primary endpoint of overall survival and secondary endpoints of health-related quality of life and safety. Patients deemed eligible for combined chemoradiation were excluded. The median overall survival was significantly longer in patients treated with TMZ (8.3 months) or hypofractionated RT (7.5 months) compared to those who received standard RT (6.0 months). O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation was associated with significantly longer survival times in patients treated with

TMZ (9.7 *vs.* 6.8 months), but had no impact on survival in patients treated with RT. No difference in survival was found in patients with an unmethylated MGMT promoter treated with RT or single-agent TMZ (7.0 *vs.* 6.8 months, respectively). Patients in the TMZ group generally reported a better quality of life than did patients in the RT groups, but the ratings for global health status were equal.

On the basis of these studies, several important conclusions regarding the treatment of elderly patients with GBM could be rendered. First, treatment with either chemotherapy alone or RT alone results in superior clinical outcomes as compared to supportive care alone. Second, hypofractioned RT regimens are better tolerated in elderly patients and result in improved outcomes as compared to standard RT regimens. Third, elderly patients with MGMT promoter methylation appear to particularly benefit from TMZ monotherapy, over RT alone. However, the utility of a modified, concomitant chemoradiation strategy in this patient population remained unknown. Specifically, could a combination of hypofractionated RT and TMZ result in better clinical outcomes than hypofractionated RT or TMZ alone?

To answer this question, the Canadian Cancer Trials Group (CCTG), the Trans-Tasman Radiation Oncology Group, and the EORTC joined together to conduct a clinical trial in elderly patients with GBM (the CE.6 trial) (8). Patients in the CE.6 trial were randomly assigned to receive either hypofractionated RT alone or hypofractionated RT with concomitant and adjuvant TMZ. To be eligible for this study, patients had to be 65 years of age or older with newly diagnosed GBM. Additionally, they had to be deemed unsuitable for standard, Stupp protocol chemoradiation. Patients were randomized in a 1:1 ratio, using a dynamic randomization algorithm that minimized imbalance between the trial cohorts. Radiotherapy (40.05 Gy administered in 15 daily fractions, over 3 weeks) utilized a standard 2 cm margin beyond the gross-tumor-volume contour. Concomitant TMZ (75 mg per square meter of body-surface area) was administered for 21 consecutive days, for the duration of radiotherapy. Adjuvant TMZ (150 to 200 mg per square meter of body-surface area) was administered for 5 consecutive days of a 28-day cycle, for up to 12 cycles or until disease progression. The primary endpoint was overall survival. Secondary endpoints included progression-free survival and quality of life assessments. MGMT promoter methylation status was assessed for subgroup analysis.

In total, 562 patients were randomized (281 in each group). The median age was 73 years and almost all patients were followed until they died (n=535; 95.2%). For the group of patients who remained alive at the conclusion of this study, the median follow-up was 17 months. The trial groups were well balanced with no significant differences in sex, age, mini-mental state examination, ECOG status, extent of surgical resection, glucocorticoid use, MGMT status, or geographic location. Treatment adherence was high, particularly with respect to the radiotherapy portion of the treatment protocol. Eighty-six of 281 patients did not receive any adjuvant TMZ, predominantly due to symptomatic progression before adjuvant therapy or intercurrent illness. Adverse events were more common in the RT plus TMZ group, particularly in the rates of grade 3 or 4 hematologic toxicities. Serious adverse events resulting in death were not significantly different between the two groups.

Overall survival was 9.3 months with hypofractionated RT plus TMZ, compared to 7.6 months with hypofractionated RT alone (hazard ratio: 0.67; 95% CI: 0.56–0.80; P<0.001). Extent of resection (partial or complete resection *vs.* biopsy only) and higher MMSE scores correlated with improved survival. Progression-free survival was also improved with hypofractionated RT plus TMZ (5.3 months) compared to hypofractionated RT alone (3.9 months). Interestingly, the treatment effect was noted to marginally increase with age, with patients over 76 years of age experiencing a greater benefit than those 75 years of age or younger.

MGMT promoter methylation analysis was obtained in 354 samples. For patients treated with RT alone, MGMT promoter methylation had no impact on overall survival (7.9 months with unmethylated status; 7.7 months with methylated status). However, for patients treated with concomitant RT plus TMZ, MGMT methylation status had a significant impact on overall survival (10.0 months with unmethylated status; 13.5 months with methylated status). Thus, for a patient with MGMT promoter methylation, treatment with RT plus TMZ resulted in a nearly 2-fold increase in overall survival as compared to RT alone (13.5 *vs.* 7.7 months, respectively). Finally, despite increased nausea and constipation in the RT plus TMZ group, both baseline and longitudinal quality-of-life scores were similar between the two groups.

This trial raises several questions for future investigation. It is of considerable interest that older patients did better in this trial with respect to overall survival, despite conventional data stating that increasing age is a poor

prognostic factor. This paradoxical result is likely due to selection bias within the study population; younger patients who were deemed unfit for standard chemoradiation may have had a more extensive disease burden. As part of the screening process, patients were enrolled in this study if they were determined to be unsuitable for standard Stupp protocol chemoradiation. This is a highly subjective measure, which may be difficult to recapitulate from one medical center to another. Hypofractionated RT protocols have improved patient adherence as compared to standard RT protocols, and this may be the basis for the improved efficacy of hypofractionated RT regimens in this population. Objective criteria to prospectively identify those patients that are unfit for standard chemoradiation and at high risk for poor compliance are needed.

In summary, this trial provides compelling evidence to support the use of concomitant hypofractionated RT and TMZ for elderly patients (≥65 years of age) with newly diagnosed GBM, who are deemed ineligible for standard Stupp protocol chemoradiation. Concomitant therapy is particularly beneficial in patients with MGMT promoter methylation; however, unmethylated patients also derive benefit from this treatment strategy.

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Footnote

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References

1. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-96.
2. Stupp R, Hegi ME, Mason WP, et al. 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;10:459-66.
3. Laperriere N, Weller M, Stupp R, et al. Optimal management of elderly patients with glioblastoma. Cancer Treat Rev 2013;39:350-7.
4. Dolecek TA, Propp JM, Stroup NE, et al. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005-2009. Neuro Oncol 2012;14 Suppl 5:v1-49.
5. Sijben AE, McIntyre JB, Roldán GB, et al. Toxicity from chemoradiotherapy in older patients with glioblastoma multiforme. J Neurooncol 2008;89:97-103.
6. Keime-Guibert F, Chinot O, Taillandier L, et al. Radiotherapy for glioblastoma in the elderly. N Engl J Med 2007;356:1527-35.
7. Malmström A, Grønberg BH, Marosi C, et al. Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. Lancet Oncol 2012;13:916-26.
8. Perry JR, Laperriere N, O'Callaghan CJ, et al. Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma. N Engl J Med 2017;376:1027-37.

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