Editorial

Elderly patients with glioblastoma: where are we going?

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The recent publication in the New England Journal of Medicine of the multicentric randomized trial in elderly glioblastoma patients led by Dr. Perry and his colleagues (1) addresses an important question: should older patients be treated with the combination of radiation therapy and temozolomide followed by maintenance temozolomide?

This randomized, phase 3 trial enrolled patients 65 years of age or older with a newly histologically diagnosed glioblastoma. Noteworthy, patients were deemed by their physicians to be unsuitable for conventional radiotherapy in combination with temozolomide. Another important inclusion criterion was ECOG PS 0–2. Patients were randomized to receive either radiotherapy alone or radiotherapy plus temozolomide. Radiotherapy consisted of a total dose of 40.05 Gy, administered in 15 daily fractions over a period of 3 weeks. In the combination arm, temozolomide was administered at a dose of 75 mg per square meter of body-surface area per day for 21 consecutive days during radiotherapy and adjuvant temozolomide was administered at a dose of 150–200 mg per square meter per day for 5 consecutive days of a 28-day cycle for up 12 cycles or until disease progression.

From September 2003 to November 2007, 562 patients were randomized and MGMT status was determined in 354 samples by real-time methylation-specific PCR. Baseline demographic and clinical characteristics were well balanced between the arms; in general, 31.7% of the patients underwent biopsy, about 30% were 65–70 years old and 46.6% were MGMT methylated.

Primary endpoint of the study was overall survival: patients in the combination arm had an overall survival of 9.3 months (95% CI, 8.3–10.3) versus 7.6 months (95% CI, 7.0–8.4) for patients treated with radiotherapy alone. The estimated hazard ratio was 0.67 (95% CI, 0.56–0.80; P<0.001). Baseline factors correlating with overall survival were the extent of resection and Mini-Mental State Examination (MMSE). Interestingly, treatment effect appeared to increase with age: in patients aged less or equal to 70 years, median overall survival was 8.7 months with temozolomide and radiotherapy while the older patients had a median overall survival of 10.0 months with the combination treatment.

Secondary endpoints of PFS also favored the combination arm. Analyzing overall survival by MGMT status, in patients with methylated MGMT, the median survival was significantly longer among patients treated with radiotherapy and temozolomide than among those who received radiotherapy alone (13.5 *vs.* 7.7 months, P<0.001); on the contrary, patients with unmethylated MGMT showed no statistically significant difference between the two arms, although there was a trend for longer survival in the combination treatment (10.0 *vs.* 7.9 months, P=0.055); however, at 24 months from the start of treatment, the number of living patients with unmethylated MGMT who were treated with radiotherapy and temozolomide was almost double that of those treated with radiotherapy alone (6.7% *vs.* 3.8%).

Analyzing the study, several considerations come to mind. The first point is the consolidation of shorter-course hypofractionated radiation therapy in elderly patients with

glioblastoma; indeed, in previous studies, it has already appeared to be at least as effective as longer-duration radiotherapy (2). So, hypofractionated radiation therapy should be the standard radiation treatment for elderly patients. The second point is the unexpected result that the treatment effect of the combination therapy appeared to increase with the age; as suggested by the authors, a selection bias in the younger elderly patients was likely. Indeed; patients 65 to 70 years of age may still be offered a full 6-week course of radiotherapy plus temozolomide and it is possible that, in this trial, patients who were more likely to have worse outcome were enrolled. On the other hand, some retrospective studies that included patients 65 to 70 years of age showed a major benefit of standard rather than hypofractioned radiotherapy in association to temozolomide (3). So, this trial did not clarify the best treatment for patients aged 65–70 years, although age alone is an insufficient surrogate for biologic aging; indeed, comparing this trial and the trial led by Stupp (4) with patients less or equal to 70 years, we can see that the impact of the combination treatment in reducing mortality versus radiotherapy alone is similar: the estimated hazard ratio was 0.67 (95% CI: 0.56–0.80; P<0.001) and 0.63 (95% CI: 0.52–0.57; P<0.001), respectively. Likely, among inclusion criteria other than ECOG PS and age, a validated geriatric assessment tool, such as g-8 tool, should be added in order to select a homogeneous population of elderly glioblastoma patients and to identify patients who are likely to benefit from the treatment. The third point is the strong predictive role of methylated MGMT in terms of PFS and OS for the combination treatment; indeed, this trial showed a clear major efficacy of radiation therapy plus temozolomide versus radiotherapy alone in patients with methylated MGMT; on the contrary, the best treatment for patients without methylation appeared unclear. Indeed, we have a trend for longer survival and a clinical benefit in the combination arm but without statistical significance. However, observing the number of patients alive at 24 months from starting treatment, 6.7% and 3.8% were treated with radiation therapy plus temozolomide or radiotherapy alone, respectively. Another bias could be the incorrect result of MGMT methylation by PCR; indeed, with this method, about 10–20% of cases can result in a "grey zone" with an unclear final result (5). Very interesting could be the performance of a new test of methylation by pyrosequencing. However, in our opinion, due to the clear clinical and prolonged benefit, elderly patients with unmethylated MGMT should be treated with radiotherapy and temozolomide. Moreover, previous studies showed a similar efficacy between hypofractioned radiotherapy and temozolomide in elderly glioblastoma patients with methylated MGMT (6); thus, in these patients, the efficacy of radiotherapy plus temozolomide as compared with temozolomide alone still remains an open issue. On the other hand, in patients with methylated MGMT, the combination treatment could be more efficacious; indeed the patients with methylated MGMT treated with radiation therapy plus temozolomide reported by Perry *et al.* (1), had a longer overall survival than the patients treated with temozolomide alone by Malmström *et al.* (6) (13.5 *vs.* 9.7 months, respectively).

The fourth point is the similar quality-of-life scores between the two groups and the high adherence to the combination treatment. Only nausea and constipation were worse during chemoradiotherapy than during radiotherapy alone. The median number of adjuvant cycles delivered was five. In general, the combination treatment was also well tolerated with 27.2% of patients showing grade 3–4 lymphopenia, 10.3% grade 3–4 thrombocytopenia and 8.3% neutropenia; however, two serious adverse events leading to death in each arm were attributed to treatment by investigators.

In conclusion, this well-designed multicenter, randomized study showed that hypofractioned radiotherapy plus temozolomide appears to be the standard of care for elderly patients with glioblastoma eligible for combination therapy.

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Footnote

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aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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