High-grade glioma: elderly patients, older treatments


Patients aged 65 years or older represent half of all patients with glioblastoma. Nonetheless, this older cohort is often excluded from trials. The NOA-08 Phase III trial compared radiotherapy (RT) (60 Gy) versus temozolomide (TMZ; 100 mg/m²) in the elderly patients (65 years and older) with high-grade glioma. Median overall survival was comparable between the two groups (8.6-RT- and 9.6-TMZ-months). Resection extent was the only independent prognostic factor for overall survival. Several concerns arise: the inclusion of patients with a very low Karnofsky Performance Status (KPS; KPS = 20), the lack of an analysis of the impact of KPS and comorbidities on outcome, the salvage therapy administered at tumor progression (RT in the TMZ group and TMZ in the RT group), which could have balanced the effects of primary treatments, the absence of information on spread of disease/tumor site, the mixture of grade II and grade IV histologies. Ongoing trials evaluating RT plus TMZ, RT plus bevacizumab and other treatment modalities in the elderly population are going to change clinical practice in the near future.

Keywords: elderly • glioblastoma • radiotherapy • temozolomide • trial

The elderly population is growing as well as the incidence of high-grade glioma in this population [1]. Approximately half of patients diagnosed with glioblastoma in the USA are 65 years or older [2]. For younger patients, optimal therapy is relatively well codified and consists of cytoreductive surgery followed by radiotherapy (RT) plus concurrent and adjuvant temozolomide (TMZ) [3]. Instead, elderly patients have been frequently treated suboptimally or left out of clinical trials. A population-based review of 4137 patients with glioblastoma aged 65 or older documented that age was the most significant predictor for resection, RT or chemotherapy, and that advancing age was associated with a decreasing use of all three modalities [4,5]. This behavior probably comes from the belief that advanced age is a poor prognostic indicator for this disease [1,6].

With this regard, small, timid steps have recently been taken. A small, randomized study on patients with high-grade glioma showed that survival was significantly longer in patients who underwent surgery versus biopsy (median: 6 vs. 3 months, respectively) [7]. Other larger, nonrandomized studies confirmed this finding [8].

A second step showed that RT improved survival compared with supportive care (median: 7 vs. 4 months, respectively) [9]. A population-based study evaluating 2836 patients with glioblastoma aged >70 years also showed that RT significantly improved survival [10].

The next step would therefore be to evaluate the efficacy of RT plus concurrent and adjuvant TMZ. Data from several nonrandomized studies seem to support an improvement of survival after administration of RT and TMZ in elderly patients [1,2,6,11–13]. Several studies also showed that MGMT promoter methylation is altogether as common in the elderly population and is associated with a positive prognostic effect [1,5,12]. Instead, both the NOA-08 Phase III randomized trial and a Nordic Trial aimed to explore alternative approaches [14,15] because ‘elderly patients with glioblastoma have a short survival. Time-consuming therapy that does not offer longer survival should therefore be avoided’ [15].

Methods & results
The recently published NOA-08 Phase III randomized trial aimed to compare standard RT...
Influenced and balanced the effect of care at initial diagnosis. To and the RT group, respectively, this salvage therapy could have median overall survival time (8.6 and 9.6 months for the TMZ and the RT group, 74 of 106 patients in the RT group (70%) received salvage therapy (mainly RT) and 74 of 106 patients in the RT group (70%) received salvage therapy (mainly TMZ).

Median overall survival was 8.6 months (95% CI: 7.3–10.2) in the TMZ group versus 9.6 months (95% CI: 8.2–10.8) in the RT group (hazard ratio: 1.09; 95% CI: 0.84–1.42; p noninferiority = 0.033), indicating that TMZ was noninferior to RT. Extent of resection (complete vs incomplete vs biopsy) was the only independent prognostic factor for overall survival. Tumor MGMT promoter methylation was significant in the univariate analysis but was not in the multivariate analysis. Age, as a continuous variable or dichotomized at age 70 years, and histology (anaplastic astrocytoma vs glioblastoma) were not independent prognostic factors.

Discussion

The topic of the study by the Neurooncology Working Group (NOA) of the German Cancer Society is very timely, since the elderly population is growing and geriatric neurooncology, especially for patients with high-grade glioma, has become a major focus [1,5,14].

Although the study is interesting, several concerns and open questions arise from this article. A first fundamental issue is the role of Karnofsky Performance Status (KPS) and comorbidities. In this study, the authors included patients with a very low post-surgery KPS (some patients had a KPS = 20) and did not analyze the impact of KPS on outcome. Mortality for elderly patients with a low performance status is very high; a recent Phase II trial showed that median overall survival for patients aged ≥70 years with glioblastoma and postoperative KPS ≤60 who underwent adjuvant TMZ was only 5.8 months [16]. Moreover, the authors did not take into consideration the possible impact of comorbidities on outcome. In clinical practice, comorbidities influence the probability of receiving RT or chemotherapy in this population, and a higher comorbidity index negatively influences survival [11]. Low KPS and comorbidities, instead of age itself, probably represent the true factors determining a poor outcome in elderly patients.

Another possible source of bias was the treatment after disease progression: patients in the TMZ group received RT and those in the RT group received TMZ. In such a short period of time, as demonstrated by the median event-free survival (3.3 and 4.7 months for the TMZ and the RT group, respectively) and the median overall survival time (8.6 and 9.6 months for the TMZ and the RT group, respectively), this salvage therapy could have influenced and balanced the effect of care at initial diagnosis. To evaluate the pure effect of the primary treatments, the authors should have used, at disease progression, the same treatment for both groups, such as bevacizumab or other treatment modalities.

The most intriguing finding in this study is in our opinion the influence of surgery on survival. The authors showed that the resection extent was the only independent prognostic factor for overall survival. Curiously, there is no mention of this in the discussion. This information is fundamental when treating elderly patients with high-grade glioma. In fact, although gross total resection may positively influence survival, elderly patients may not easily recover after a major postoperative deficit, and this means that the adjuvant treatment can be delayed or not administered, thus negatively influencing both survival and quality of life.

Moreover, the authors provided no information on spread of disease (including the presence of multifocal lesions) and tumor site. Tumor location, spread of disease and patient clinical status may prohibit (extensive resection. Finally, the mixture of grade III (40 cases) and IV histologies makes it difficult to compare outcomes. Given these limitations, we believe that the study results should be interpreted with caution.

Five-year view

Median overall survival for the NOA-08 trial was only 8.6 and 9.6 months for the TMZ and for the RT group, respectively. Several nonrandomized studies showed that overall and progression-free survival for elderly patients with glioblastoma treated with RT plus concomitant and adjuvant TMZ may be 13–14 months [1,2,6,11]. Therefore, considering the several study limitations, we also believe that the NOA-08 trial will not change clinical practice. The approach adopted by the NOA-08 study would have been useful for evaluating the efficacy and safety of a palliative treatment for patients with a low KPS and/or a high comorbid index, who are probably not able to complete a Stupp-like protocol.

An European Organization for Research and Treatment of Cancer (EORTC)/Trans-Tasman Radiation Oncology Group (TROG) trial is currently ongoing. This Phase III trial will compare overall survival rates in older patients (65 years and older) with newly diagnosed glioblastoma treated with short-course RT with or without concurrent and adjuvant TMZ [101].

Another interesting ongoing randomized trial (Avastin Plus Radiotherapy in Elderly Patients With Glioblastoma [ARTE]) from the University of Zurich (Germany), will explore the efficacy of bevacizumab (Avastin® [Genentech/Roche]) plus RT compared with RT alone in the treatment of newly diagnosed glioblastoma in the elderly (65 years and older) [101].

The efficacy of bevacizumab is also currently being investigated in the USA [101]. This Phase II trial will evaluate how well giving bevacizumab and TMZ together works in treating older patients (70 years and older) with newly diagnosed glioblastoma or gliosarcoma.

The efficacy of another antiangiogenic drug (Axitinib [Pfizer], not US FDA approved) plus RT will be explored by a Phase II trial of the University of Cincinnati (OH, USA) for patients above the age of 70 with glioblastoma [101].
Within the next 5 years, the results of all these studies should be available and will likely change clinical practice. We hope and think that future trials evaluating new treatment modalities, even in this era of evidence-based, cost–effectiveness-based medicine, will include elderly patients. These patients will soon represent the vast majority of patients with glioblastoma and do not deserve to be treated suboptimally.

Financial & competing interests disclosure
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

Key Paper Evaluation

Key issues
• Patients aged 65 years or older represent half of all patients with glioblastoma. Nonetheless, this older cohort is often excluded from trials. This behavior probably comes from the belief that advanced age is a poor prognostic indicator for this disease.
• The NOA-08 Phase III randomized trial compared standard radiotherapy (RT; 60 Gy) versus temozolomide (TMZ; 100 mg/m²) in elderly patients (65 years and older) with high-grade glioma and found that median overall survival was comparable between the two groups (8.6 and 9.6 months, respectively).
• Study limitations: the inclusion of patients with a very low Karnofsky Performance Status (KPS; even after surgery KPS = 20); the lack of an analysis of the impact of KPS and comorbidities on outcome; the salvage therapy administered at tumor progression (RT in the TMZ group and TMZ in the RT group), which could have balanced the effects of primary treatments; the absence of information on spread of disease/tumor site; and the mixture of grade III and IV histologies.
• Data from nonrandomized studies on the use of RT plus TMZ seem to be encouraging.
• Ongoing trials on the treatment of newly diagnosed glioblastoma in the elderly are going to change clinical practice. These studies will evaluate: the effect of combined RT plus TMZ versus RT (EORTC/TROG); the efficacy of RT plus bevacizumab (Avastin®) versus RT (ARTE, Zurich University, Switzerland); the effect of combined bevacizumab plus TMZ (UCLA’s Jonsson Comprehensive Cancer Center, CA, USA); the efficacy of another antiangiogenic drug (Axitinib, not US FDA approved) plus RT (University of Cincinnati, OH, USA).
• Elderly patients will soon represent the vast majority of patients with glioblastoma and do not deserve to be treated suboptimally: future trials should include this older cohort and stratify patients for comorbidities and performance status.

References

**Website**