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Elderly Patients with Glioblastoma Multiforme – An Underestimated Subpopulation?

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Glioblastoma multiforme (GBM) is the most common and most aggressive primary brain tumor in adults and can occur at any time with a mean age of 62 years at first diagnosis [1]. However, in most elderly patients GBMs arise abruptly and grow quickly with impairing cognition and functional independence, rather faster than in younger patients. In addition, in older people GBM treatments seem to be less effective and more toxic than in younger ones.

In this issue of *Neuroepidemiology*, Kita et al. [2] have evaluated 715 GBM cases at a population level diagnosed in the canton of Zurich (Switzerland) in 1980–1994. Interestingly, the study revealed a marked tendency towards limited treatment with advancing patient age: 82% of the patients younger than 65 years were treated either with surgery followed by radiotherapy, surgery alone or radiotherapy alone. In contrast, only 47% of the patients older than 65 years and only 25% of those over 75 years underwent surgery and/or radiotherapy, while the remaining patients were given best supportive care (BSC). These data are also reflected in the mean age dependent on the treatment modality: 54.5 years for those treated with surgery and radiotherapy, 58.3 years for surgery alone, 62.2 years for radiotherapy alone and 69.2 years for BSC. Furthermore, among the patients who were treated with surgery plus radiotherapy and those undergoing radiotherapy alone, the younger patients (<60 years) had a significantly higher survival rate than the older ones (>60 years). In contrast, no significant difference in survival was observed between the younger and older patients treated with surgery alone or receiving BSC, suggesting that lower survival rates in elderly patients with GBM may, at least in part, be due to a lesser response to radiotherapy.

Recently, Iwamoto et al. [3] studied the survey of patterns of practice and treatment outcomes in a large cohort of 4,137 patients, who were 65 years of age or older at the time of diagnosis. In a multivariate regression analysis the age at first diagnosis was the most significant predictor of rates of tumor resection, radiotherapy and chemotherapy: 61% of the GBM patients had undergone a surgical tumor resection, 65% had received radiotherapy, 10% had received chemotherapy and 35% had had neither radiation nor chemotherapy and presumably got BSC. The most elderly patients were the ones who were least likely to have had a surgical resection, postoperative radiotherapy or adjuvant che-

motherapy. The factors associated with decreased likelihood of receiving radiotherapy or chemotherapy or less aggressive treatment choices included more comorbidities and unmarried marital status. The median overall survival time from initial diagnosis was only 4 months, and the shortest survivals were seen in the most elderly GBM patients.

A first weak point of both studies (Kita et al. [2] and Iwamoto et al. [3]) is that data on the performance status, which have repeatedly also been found to be a prognostic survival factor in GBM patients, are missing. A second drawback is that both studies do not consider the beneficial effects of temozolomide (TMZ) chemotherapy with or without radiotherapy. In 2005, Stupp et al. [4] published the results of a large clinical trial examining the role of adjuvant TMZ chemotherapy in the management of newly diagnosed GBM (aged between 18 and 70 years). This study created a new standard therapy regime for newly diagnosed GBM including maximal surgical tumor resection followed by TMZ applied concomitantly and adjuvantly to local field radiotherapy. This ‘new standard of care’ resulted in significantly longer tumor control, patient survival (median = 14.6 months from the time of diagnosis) and – due to fewer side effects – in a good quality of life. However, practice shows that GBM patients of all ages seem to benefit from intensified treatment, although the magnitude of the benefit decreases with the age at first diagnosis in elderly GBM patients.

Often older GBM patients have not been recruited in clinical trials and were never studied as a separate and distinct subpopulation. Therefore, the treatment of older subjects varies widely. In Austria elderly patients with good performance status – and generally fewer comorbidities – are treated identically to younger patients, receiving a maximal tumor resection, a 6-week course of local field radiation (60 Gy) concomitantly with TMZ and after a 4-week break adjuvant TMZ for at least 6 months. However, in other countries, elderly GBM patients are managed by less intensive therapeutic approaches or more palliative ones.

Because of the lack of good data, we currently do not have a ‘standard treatment strategy for the elderly GBM subpopulation’. Only 2 randomized trials have studied radiotherapy approaches in this subgroup. Roa et al. [5] demonstrated that a short 3-week radiation course (40 Gy in 15 fractions over 3 weeks) and the standard 6-week course of radiotherapy treatment (60 Gy in 30 fractions over 6 weeks) are similarly effective. Furthermore, Keime-Guibert et al. [6] showed that a moderate-dose radiotherapy over 5 weeks (focal radiation in daily fractions of 1.8 Gy given 5 days per week, for a total dose of 50 Gy) plus BSC was superior to BSC alone. Patients with a poor performance status were excluded from both studies. Therefore, we can hypothesize that the survival of elderly patients is prolonged by radiation, and that shorter radiation schedules may be similarly beneficial.

Currently, we do not have conclusive data addressing the role of TMZ in elderly GBM patients. Because of the prolonged tumor con-

trol and survival as well as good quality of life under combined radiotherapy and TMZ in younger GBM patients, this treatment approach may also be beneficial for older subjects. However, in recently published papers such a chemoradiotherapy approach in older GBM patients seems to be less effective with higher toxicity rates compared to younger patients [7, 8]. Because TMZ may be more toxic in older patients, a personalized pretreatment test (e.g. the identification of the *MGMT* promoter methylation status) could be useful to distinguish responders from nonresponders [9].

However, more data are necessary to define a 'standard therapy of elderly GBM patients'. At present, the National Cancer Institute of Canada, Clinical Trials Group, the European Organization for the Research and Treatment of Cancer and multiple neuro-oncology centers in Australia conduct a clinical trial for GBM patients aged 65 and older, comparing TMZ plus radiation with radiation alone. The quality and length of life will be key endpoints, and the *MGMT* status will be assessed.

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