Editorial

Postoperative chemoradiotherapy for elderly patients with glioblastoma: worsening frailty or increasing survival?

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Recently published by Perry and colleagues, the data of the trial (ClinicalTrials.gov number, NCT00482677) funded by the Canadian Cancer Society Research Institute (CCSRI), European Organisation for Research and Treatment of Cancer (EORTC) and by the Trans Tasman Radiation Oncology Group (Australia and New Zealand) (1) provided further insight into the role of combined chemoradiotherapy in 65 years of age or older patients with glioblastoma (GBM) and finally answer whether chemotherapy concomitant to radiotherapy (RT) could yield survival benefit or potentially impairing quality of life for these patients.

Due to population growth, the management of the elderly with cancer is a challenge for the medical community. In 2020, approximately 60% of all cancers will affect the elderly (2). In light of the increasing number of elderly cancer patients in need for treatment, geriatric oncology is now at the forefront of oncology practice. Cancer disease also has a dramatic impact on the autonomy of the elderly, because often increases the progressive deterioration that occurs during aging. For this reason, if they are not given the best treatment available, there will be a negative impact on prognosis (3). Despite accumulating evidence of treatment benefit and the relatively good health of many patients diagnosed with cancer, older adults are often undertreated, which contributes to poor outcomes (4), especially in case of GBM diagnosis. Moreover, recent data show an increased incidence of GBM in the elderly population, with a peak between 65 and 84 years (5). The elderly GBM patients often have a poorer outcome and different authors have been investigated unusual post-surgical treatment schedules to reduce the hospitalization (6-10). According to a retrospective study on GBM elderly patients treated at Memorial Sloan-Kettering Cancer Center (6), the therapeutic strategy for these patients have incorporated a more aggressive treatment, which may lead to survival benefit.

Unfortunately, such a curative and more aggressive approach is far from being widespread adopted by the clinicians.

The impact of altered RT fractionation in patients 70 years old have been evaluated in the past and after some randomized trials (6-10) the hypofractionated RT is becoming the standard for GBM elderly patients. Roa *et al*. (8) reported no significant change in median overall survival (OS) comparing standard fractionated RT (30 fr × 2 Gy, 60 Gy in 6weeks) to hypofractionated RT (15 fr × 2.66 Gy, 40 Gy in 3weeks) for patients older than 60 years. The median OS was 5.6 and 7.3 months for conventional and hypofractionated RT group respectively. However, the most important question whether the OS in elderly GBM patients may be increased by chemotherapy in addition to RT was still without a satisfactory answer. Some prospective and retrospective studies, including a recent analysis of the National Cancer Database (NCDB) for patients aged ≥65 years diagnosed with GBM between 2005 and 2011, show that patients treated with chemoradiation may have better outcomes than patients treated with chemotherapy or RT alone (11-14).

The data of the NCIC EORTC TTROG trial (1) definitely confirm and clarify that concomitant and adjuvant chemotherapy with temozolomide (TMZ) together with a daily RT treatment for a reduced total dose as compared with RT alone is able to increase progression-free survival and OS also in elderly and frail GBM patients. The authors found that the addition of TMZ to short-course RT extended the median survival from 7.6 to 9.3 months. The patients with O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation had a median survival of 13.5 with chemoradiotherapy and 7.7 months with RT alone, as in younger patient groups with long-course chemoradiotherapy. Benefit from the concomitant approach was also observed in patients with unmethylated MGMT status.

In addition, the study found that there was no difference in physical, cognitive, emotional and social functioning between the two treatment arms using standard EORTC QLQ-C30 and BN20 questionnaires and serious adverse events due to the treatment were observed in two patients for each group. Extent of surgery was confirmed to have a favourable impact on OS as well as pre-treatment MMSE score. As a matter of fact, other factors besides age, such as novel imaging and molecular biomarkers, are needed to allow for more accurate selection of patients who would benefit from adjuvant therapies (14).

So far, there are some molecular markers already tested as part of the pathological evaluation of GBM patients such as epidermal growth factor receptor (EGFR), tumour suppressor protein TP53, phosphatase and tensin homolog (PTEN), VEGF, cancer stem cells and *p16INK4a* gene, as well as the more widespread MGMT and isocitrate dehydrogenase (IDH) (15). Detailed characterization of these molecular features or other more specific for older age could facilitate a more tailored therapeutic approach.

Certainly, Perry *et al.* provided an important achievement in the clinical decision-making for the elderly GBM patients. Nevertheless, many questions remain unresolved, including the most appropriate definition of "elderly", the impact of the patients' geriatric assessment for comorbidity on treatment results, the role of the biomarkers and the optimal RT fractionation schedule for elderly patients with high performance status. Indeed, as the authors wrote, a common clinical rationale for selecting shortened courses of RT is poorer functional status functional status, despite the quality of life is also correlated with the treatment duration.

Advanced age is a major prognostic factor in GBM, frequently driving treatment decisions. Nevertheless, neither age alone nor performance status is independently predictive of survival (16).

It is tempting to conclude that elderly GBM patients have to be active treated to increase their survival and quality of life, mostly taking into account that patients 70 years of age or younger appeared to benefit quite less than older patients in this recently published trial (1). Therefore, short-course chemoradiotherapy in elderly GBM patients might be an attractive approach to reduce the burden of care without losing clinical effectiveness nor quality of life.

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