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Optimal management of elderly patients with glioblastoma

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ABSTRACT

Median age at diagnosis in patients with glioblastoma (GB) is slowly increasing with an aging population in Western countries, and was 64 years in 2006. The number of patients age 65 and older with GB will double in 2030 compared with 2000. Survival in this older cohort of patients is significantly less than seen in younger patients. This may in part be related to more aggressive biology of tumor, reduced use of standard management approaches, increased toxicity of available therapies, and increased presence of comorbidities in this older patient population. Limited data do support the use of more extensive resection in these patients. Randomized data support the use of post-operative radiotherapy (RT) *versus* supportive care, but do not demonstrate a benefit for the use of the standard 6 weeks course of RT over hypofractionated RT given over 3 weeks. Preliminary data of randomized studies raise the possibility of temozolomide alone as an option for these patients. The use of 6 weeks of RT with concurrent and adjuvant temozolomide has been associated with reasonably good survival in several uncontrolled small series of selected older patients; however, this better outcome may be related to the selection of better prognosis patients rather than the specific therapy utilized. The current National Cancer Institute of Canada (NCIC) and European Organization for Research and Treatment of Cancer (EORTC) CE.6/26062/22061 randomized study of short course RT with or without concurrent and adjuvant temozolomide will help determine the optimal therapy for this older cohort with currently available therapies.

Introduction

Glioblastoma (GB) is a uniformly fatal illness associated with a median survival of less than one year. For the past several decades, post-operative radiotherapy (RT) had been the mainstay of therapy as the only treatment to significantly prolong survival following surgery.[1] The European Organization for Research and Treatment of Cancer (EORTC) and National Cancer Institute of Canada (NCIC) randomized study of RT alone or RT with concurrent and adjuvant temozolomide demonstrated a significant improvement in median survival from 12.1 to 14.6 months, and an improvement in 2-year survival from 10% to 26%, respectively.[2,3] Patients age 65 or older now form half of all patients with GB and they fare considerably less well than their younger counterparts, with a population based median survival of approximately 6 months.[4–6] The role of chemotherapy in addition to RT in the elderly has remained controversial. The RT dose used in the EORTC–NCIC CTG study was 60 Gy in 30 fractions and the study population was restricted to age 18–70 with an ECOG performance status of 0–2. Exploratory sub-group analysis of the results from this study revealed a persistent but diminishing benefit from the addition of temozolomide with increasing age (Table 1).[7] This preliminary analysis served as the basis for the current ongoing NCIC CTG–EORTC randomized trial of the use of temozolomide in elderly patients with GB.[7] In a subgroup analysis of the EORTC/NCIC trial, the influence of patient age suggested a diminishing relative benefit from the addition of TMZ to radiotherapy, in particular in patients older than 65 years (60–65 years: HR = 0.64 [0.43–0.94, $p = 0.02$]; 65–70 years: HR = 0.78 [0.50–1.24, $p = 0.29$]) (R. Stupp, personal communication). However, the number of patients per subgroup analyzed is small, and data needs to be interpreted with caution.

The optimal management of older patients with GB beyond RT remains unresolved. Older age is often associated with increased

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Table 1
Hazard ratio by age group in the EORTC–NCIC trial demonstrating a diminishing benefit of temozolomide with increasing age.[7].

Age, years (number of patients)	Hazard ratio	*p* Value
<50 (171)	0.5	0.001
50–60 (220)	0.63	<0.05
61–65 (114)	0.64	0.096
66–70 (83)	0.78	0.340

toxicity to many drugs, possibly related to increased vulnerability of multiple organ systems that have experienced a reduction in functional reserve, and resulting in increased likelihood of myelosuppression, mucositis, neurotoxicity and cardiotoxicity.[8] Increased toxicity in patients 65 or older has also been documented with the use of biologic agents. Retrospective analysis of two trials for advanced lung cancer with erlotinib and bevacizumab revealed significantly higher levels of toxicity in the older patients compared with the younger patients in those studies.[9,10] The risk and degree of radiation-related neurotoxicity has also been noted to increase with age.[11,12]

Lawrence and colleagues from the Radiation Therapy Oncology Group (RTOG) performed a retrospective review of neurotoxicity of acute and late grade $\geqslant 3$ neurotoxicity in 2761 patients from 14 prior RTOG trials in high-grade gliomas from 1983 to 2003. All patients had received either chemotherapy (83%) or a biologic agent (17%) during RT (median dose 60 Gy). The incidence of acute neurotoxicity (defined as grade 3 or greater events by RTOG Acute Morbidity Scoring Criteria occurring within 3 months of starting therapy) was associated with older age, poor performance status, aggressive surgery, pre-existing neurological dysfunction, poor mental status, and twice-daily radiation on univariate analysis. Acute neurotoxicity was associated with poorer median survival (7.8 *versus* 11.8 months).[13]

Of note, older patients have often been excluded from participation in clinical trials and as a result of limited controlled data, may receive overly aggressive or inadequate reduced-intensity treatment. It is becoming increasingly important that future trials either focus on older patients or include older patients, as they currently represent 50% of all patients with GB, and will soon represent the majority of patients with GB. In view of the poor outcomes associated with increasing age, quality of life becomes an increasingly important issue in this population of patients in addition to survival; unfortunately, this is poorly documented in the current published retrospective series, and will only come from prospective ongoing trials.

Epidemiology

An important predictor of outcome in GB is age. Recent large population-based cohorts of patients with GB demonstrated a marked decrease in median survival with increasing decade of age, and in particular showed a median survival of approximately 6 months in patients age 65 and older.[4–6,14]

With an aging population and improved diagnostic tools the incidence of GBM has been steadily increasing over the last 20–30 years, and this increase is almost exclusively observed in patients older than 70 years.[15] Median age at diagnosis for GB was 64 years over the years 2002–2006 from a large United States (US)-based cancer registry.[16] In the US, the number of adults aged 65 or older increased from 25 million in 1980 to 35 million in 2000, and is expected to increase to 72 million by 2030.[17,18] This "silver tsunami", as characterized by the US National Institute on Aging, will lead to at least a doubling of cases of GB in patients age 65 or older over the next two decades, and this age group will account for two-thirds of all cases of GB by 2030.[8,19] Similar demographic data exists for most Western countries, including Canada, Australia, and most European nations.

Patterns of care

GB arising in older patients tends to present with a relatively short symptomatic phase of a few weeks and tends to rapidly impair cognition and functional independence.[20] In view of its aggressive biology, short survival, limited efficacy of available therapies, and common presence of comorbidities in this population, older patients with GB are less likely to receive standard therapy than younger patients. In a population-based review of the management of 3279 adult patients with GB in Ontario, Paszat and colleagues documented that with the odds ratio set at 1.00 for the age group 60–69, patients aged 70–79 and those aged $\geqslant 80$ years had an odds ratio of 0.77 and 0.25 for total/subtotal resection respectively. Similarly those two age groups had an odds ratio of 0.40 and 0.13, respectively, for having received any radiotherapy.[6] Similar results were reported from three other population-based reviews and are in part felt to be related to the general poorer condition of older patients with newly diagnosed GB as well as an increasing incidence of comorbidities in this older cohort.[1,5,6,14] In a review by Kita and colleagues, best supportive care only was increasingly the treatment given to older patients: in those aged 55–64, 65–74, and $\geqslant 75$ years it was given in 27%, 44%, and 75% of patients, respectively.[5] In addition, the report on the Ontario experience documented that the proportion of patients spending 100% of their survival time in hospital in the age groups 60–69, 70–79, and $\geqslant 80$ increased from 21.9%, to 38%, and 49.5%, respectively, so that clearly the quality of survival decreases with increasing age in a population-based review.[6] A population-based review of 4137 patients with GB 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] The same study showed that the presence of comorbidities was also associated with a decreasing likelihood of receiving RT and chemotherapy. In a population-based review of 715 cases of GB in the Canton of Zurich, Switzerland, that were diagnosed between 1980–1994, Kita et al. noted that only 25% of patients aged 75 or older had undergone surgery (gross total or subtotal resection) and/or RT as compared with 47% of patients aged 65 or older and 82% of patients aged <65 years.[5] A population-based review of 1753 patients with GB older than 65 years also documented lower rates of surgical resection and RT in patients aged 75 years or older compared with patients aged 66–74.[14]

There are also concerns about an increased likelihood of toxicity from treatment in elderly GB. Sijben et al. reported a 42% rate of grade 3 or 4 toxicity (grade 3: 1 fatigue, 1 liver enzyme elevation, 1 pneumocystis pneumonia; grade 4: 1 syndrome of inappropriate anti-diuretic hormone release, 1 urosepsis, 3 myelosuppression) in 19 patients aged 65 or older who received 6 weeks of RT with concurrent and adjuvant temozolomide. This was a significantly higher rate than in the EORTC–NCIC randomized study, where the comparable rate was 16% in 287 patients aged 18–70.[3,21] Grade 3–4 hematologic toxicity occurred in 28% of a series of 32 consecutive patients aged 70 or older treated with 6 weeks of RT with concurrent and adjuvant temozolomide.[22] Grade 3–4 hematologic toxicity occurred in 28% of a series of 43 patients aged 70 or older treated with hypofractionated RT (30 Gy in 6 fractions over 2 weeks) followed by adjuvant temozolomide.[23]

In summary, population-based data demonstrate an increased likelihood of biopsy, a lower rate of resection, a lower use of RT and chemotherapy, and a higher incidence of toxicity. These patterns of care were related to older age and the presence of increased comorbidities within the population of elderly patients.