Editorial

Being old is no fun: treatment of glioblastoma multiforme in the elderly

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He was an old man who fished alone in a skiff in the Gulf Stream and he had gone eighty-four days now without taking a fish. In the first forty days a boy had been with him. But after forty days without a fish the boy’s parents had told him that the old man was now definitely and finally salao, which is the worst form of unlucky, and the boy had gone at their orders in another boat which caught three good fish the first week.

ERNEST HEMINGWAY
The Old Man and the Sea

Like the old man in Hemingway’s novel, the elderly can be affected by the worst form of unluck, “salao,” when it comes to treatment of glioblastoma multiforme (GBM). In fact, there is a general sense that multimodal treatment shown to provide improved survival, quality of life, and freedom from tumor progression may not be pursued as often with patients whose age is more than 65 years and, in fact, may be even less likely to be offered to patients whose ages are 75 years or greater. The epidemiological study by Barnholtz-Sloan and colleagues reported in this issue of the Journal of Neurosurgery appears to confirm this: the elderly (age ≥ 75 years) were less likely to receive multimodal treatment for GBM, at least for the time period analyzed in the study (1991–2001). Interestingly, if they were treated with a multimodal regimen, their survival approached that of the younger patient population. In fact, multimodal treatment of elderly patients with GBM was associated with a statistically significant improvement in survival compared with a single treatment regimen.

The authors collected data by analyzing the data set from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program, which collects information on demographics, prognosis, treatment, primary tumor type, and histology in cancer cases and represents 26% of the US population. They then linked this information to Medicare files to identify individuals that were ≥ 65 years old because Medicare is the primary health insurer for 97% of the elderly. They were thus able to identify 1753 patients with GBM and 205 patients with anaplastic astrocytoma (AA) and link each of them to 1 of 5 treatment categories (biopsy only; surgery only; biopsy and radiation; surgery and radiation; or surgery, radiation, and chemotherapy), based on a number of variables, with the relevant one being age at diagnosis (66–74 vs ≥ 75 years).

They report that there were no age-related differences in the type of treatment provided to patients with AA, with 93 of 205 patients receiving some form of multimodal treatment (usually surgery and radiation), 87 of 205 receiving single-modality treatment (usually radiation), and 25 of 205 remaining untreated. Interestingly, very few, if any, of these patients were treated with the combined modality of surgery, radiation, and chemotherapy.

In contrast, the findings were very different if the histological diagnosis was GBM: here, age was a significant factor in determining the types of treatment patients received. Patients who were 66–74 years old at diagnosis were more likely to be treated with combination therapy (641 [65%] of 984 cases) compared with patients who were ≥ 75 years old (359 [47%] of 769). Not too surprisingly, survival was increased in individuals who received surgery and radiation compared with those who received biopsy only, surgery only, or biopsy and radiation, regardless of age or histology. The findings thus seem to confirm the impression that elderly patients (those patients ≥ 75 years of age) are less likely to be treated with the best possible treatment for GBM—multimodal (combination) therapy.

It should be noted that the study was only able to capture data pertaining to a quarter of the US population with GBM during this time period; this population may not be completely representative of the US population because it includes a higher percentage of foreign-born and urban-dwelling individuals (http://seer.cancer.gov/registries/). Other possible differences in populations are not recorded in the database. In addition, since Karnovsky Performance Scale scores are not reported in the queried databases, the study is also limited by the inability to determine how much performance status, a proven variable that affects survival, contributed to provider and patient decisions to pursue combined treatments. One also notes that for the group of patients with GBM there was a significant difference in marital status between the 66–74 and ≥ 75 years of age groups, while this difference was not significant for the group of patients with AA. Given the linkage of social support to
the selection of more aggressive diagnostic procedures and therapy, one wonders if the data could also be interpreted to mean that the presence of a spouse led physicians and patients to consider combined treatments, irrespective of patient age.

Although Barnholtz-Sloan and colleagues evaluated cases involving individuals who were treated before the advent of concomitant temozolomide and radiation therapy, their results suggest that physicians may have a bias against pursuing combined treatments (surgery and radiation) in older patients with GBM. Such bias against treating the elderly has been abundantly described in the literature. For example, although the elderly represent 60% of the population with cancer, only a quarter of patients > 65 years of age participate in clinical trials. A review of barriers to participation was recently published: ageism in clinical medicine may arise from physicians’ concerns about inferior outcomes, absent or poor social support, interactions in polypharmacy, expense and adequate reimbursement, comorbidities, patients’ declining cognitive abilities, and exclusion criteria. In particular, in neurooncology, older age has been associated with poorer outcome of treatment, leading to reluctance to treat elderly patients with multimodal therapies. Reasons for this association have been linked to the genetics of gliomas in the elderly, to the existence of comorbidities and interest in maintaining quality of life, to the effect of radiation on the elderly brain in terms of neurocognitive decline, and to the decreased capacity to overcome chemotherapy-induced side-effects. In fact, studies have been published supporting the concept that limited treatments should be provided to elderly patients with GBM. Yet, recent studies indicate that combined therapies may actually be beneficial in such patients. In a recent trial performed at 10 centers in Europe, patients > 70 years of age with GBM were randomly assigned to receive supportive care only or a combination of radiotherapy and supportive care. The trial had to be discontinued early because of the benefit observed in the radiotherapy group: the median survival for this group was 29.1 weeks (vs 16.9 weeks for the supportive care group), and there were no between-group differences in quality of life or the results of cognitive evaluations. The findings reported by Barnholtz-Sloan et al. thus seem to confirm findings from other retrospective and prospective analyses suggesting that treatment of elderly patients with GBM employing multimodal therapies does lead to superior outcomes without affecting their mental abilities or producing unbearable side effects.

As the population continues to age in the next decades, neurosurgeons and neurooncologists will increasingly be asked to provide recommendations related to radical surgery, radiation, temozolomide chemotherapy, and/or inclusion into clinical trials for patients with GBM who are in their 7th, 8th, or 9th decade of life. The study by Barnholtz-Sloan et al. provides an impetus to examine how we, as physicians, can reduce the elderly’s “salvo” with respect to GBM. It is becoming evident that treatment recommendations should rely more on performance status rather than biological age. To finish with another quote from Hemingway’s novel, the old man (Santiago), who is able to catch his marlin only to be vexed by several sharks that attack his craft, says: “But man is not made for defeat. A man can be destroyed but not defeated.” Similarly, more and more highly functioning older individuals see their GBM as something to fight against even if it is likely to destroy them and not something to acquiesce to in defeat. We need to help them in their fight.

References


Response: We thank Dr. Chiocca for his thoughtful and insightful comments. The treatment of the elderly is an increasingly encountered but poorly understood clinical challenge and represents an important area of study. While it is clear from our study and others that the elderly appear to be treated less aggressively, it is usually unclear why this is so. Does this difference in treatment reflect ageism or bias on the part of the treating physicians, the patients, or their families? Alternatively, does it reflect a rational decision based
on a patient’s decreased performance status and/or lack of social support? Unfortunately, a critical limitation of the SEER-Medicare linked database used in this study is the lack of Karnofsky Performance Status and/or other performance data which may have contributed to our understanding of this phenomenon. Another important limitation to our understanding of treatment of glioma in the elderly is the systematic exclusion of patients ≥ 70 years of age from most large glioma trials, including trials undertaken by large European-sponsored consortia as well as those of consortia sponsored by the National Institutes of Health. Indeed, while one might imagine that the availability of an effective, well-tolerated, oral agent such as temozolomide might lead to increased use of chemotherapy in the elderly compared to the period included in this study, during which the standard of care, BCNU (carmustine), required intravenous infusion; the landmark study leading to the adoption of this agent as the standard of care did not include patients ≥ 70 years of age. Additional clinical studies will be needed to address these critical and increasingly common questions. (DOI: 10.3171/JNS/2008/108/4/0639)

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