Glioblastoma in the elderly

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The article from the Mayo Clinic by Dr. Parney and his colleagues3 addresses an important question: Should older patients (65 years or older) with glioblastomas be treated differently than their younger counterparts? This question has been addressed in the literature by some recent reports that generally have concluded that age alone should not be a reason to deny older patients the potential benefits of resection and adjuvant therapy with radiation therapy (RT) and chemotherapy if tolerated. The article by Parney and colleagues adds some important information to the other recent articles on this topic that they have cited. Importantly, they limited their study to patients treated since 2003, when the modern “standard of care” for glioblastomas was established by the influential paper of Stupp and colleagues2 reporting the benefit of the addition of a temozolomide (TMZ) regime to radiation therapy in these patients. This is important because several of the other reports of results of therapy in elderly patients with glioblastomas include patients who were treated before the TMZ era when only more toxic chemotherapeutic regimens, which were clearly less well tolerated by the elderly, were available. The current review also includes a careful description of perioperative complications and indicates that the frequency and severity of surgical complications in this group of older patients is not substantially different from what has been reported previously when patients with glioblastomas of all ages are considered. Additionally, the current series differs from other recent ones in that the proportion of patients treated with aggressive resection was significantly lower (50% of patients were treated with biopsy only and 50% with resection). This, of course, raises the question of whether in this particular series from the Mayo Clinic age did introduce a bias against treating elderly patients with aggressive resection. This has to be kept in mind when interpreting the most important result of this study, which in our opinion is that progression-free survival (PFS) and overall survival (OS) are not substantially different in elderly patients treated with aggressive resection and adjuvant RT and chemotherapy with TMZ as compared to patients with glioblastomas of all ages.

The Mayo Clinic study included 105 consecutive patients older than 65 years of age who were diagnosed and treated at that institution between 2003 and 2008. Their results can be summarized as follows: As stated above, half of the patients underwent resection and the other half had only biopsy. New persistent neurological deficits developed in the perioperative period in 6.7% of the patients and they were more common in the group of patients who underwent biopsy rather than resection. Forty-nine percent of the patients received both radiation therapy and chemotherapy (mostly TMZ); 27% of the patients underwent RT only, and the rest had only palliative treatment postoperatively. The complications related to chemotherapy were not significantly different from what has been reported for other cohorts of glioblastoma patients of all ages. When considering the entire series, median PFS and median OS were both poor: only 3.5 and 5.5 months, respectively. In multivariate analysis, younger age, single lesion, resection, and adjuvant treatment were factors related to better OS, but only adjuvant treatment was significantly associated with a prolonged PFS. Probably the most important finding of this study, as stated above, is that in those patients who underwent resection, RT, and chemotherapy, the median PFS and OS were 8 and 12.5 months respectively. At the prodding of some of the reviewers, the authors reanalyzed the data for patients who were 70 years or older, since it is this group of truly elderly patients that some clinicians may hesitate to treat aggressively. In this series, patients 70 years or older who were treated with resection followed by RT and chemotherapy had a PFS of 8 months and an OS of 11.5 months, which is not significantly different from the results for the entire series of patients 65 or older.

This study from the Mayo Clinic confirms the widely held opinion that elderly patients with glioblastomas do considerably worse in terms of PFS and OS than their younger counterparts. However, the study also confirms the findings of recent reports that, when such elderly patients are treated with resection and adjuvant RT and chemotherapy, they do almost as well as younger patients treated in this manner. What we cannot know from this
paper, and perhaps the authors can address this in their response to this editorial, is whether such satisfactory results in the patients treated aggressively were due to a significant selection bias whereby only elderly patients with the most favorable prognostic factors (good neurological and general medical condition, superficial tumor in a noneloquent area, single lesion as opposed to multifocal or multicentric tumor, and so forth), were selected for resection and adjuvant therapy. Although we do not have specific data, it is our impression that a 50% rate of attempted resection in this group of elderly patients is considerably lower than the rate of attempted resection when glioblastomas in patients of all ages are considered. The authors tell us that deep location, multifocality, and eloquent location were associated with the likelihood of having biopsy instead of resection. Are multifocal and deep tumors or tumors in eloquent locations more common in elderly patients than in the general population of patients with glioblastomas? We do not have data to answer this question definitely. Again, the authors may comment on this in their response. Accepting the issue of a possible selection bias, which we suspect played a role in the results of this series, the Mayo Clinic paper indicates that, with careful selection, elderly patients with glioblastomas tolerate resection and adjuvant therapy, including RT and TMZ, as well as younger patients and that when they are treated in this manner, they do almost as well (OS of 12.5 months compared to 12.1 month and 14.6 months, respectively, in the groups treated without and with temozolomide in the study by Stupp et al.7).

We are satisfied that the results of this study, as well as those of other recent studies quoted by the authors, strongly support their conclusion that elderly patients with glioblastoma should be treated with maximal “safe” radical resection and adjuvant chemotherapy “whenever this is deemed reasonable,” which obviously means with very careful selection. Finally, the important word “safe” probably has very different meanings to different clinicians. To us, when dealing with glioblastomas, it means that the resection, as planned and executed, should lead to no new prolonged or permanent neurological deficit perhaps with the exception of a partial visual field reduction. We agree that recent data indicate that gross-total, near-total, or even “radical” resection leads to a slightly better OS in patients with glioblastomas, but we feel that such small gains in survival should not come at the expense of a significant decrease in quality of life from a surgically induced complication.

Finally, this study demonstrates that elderly patients with glioblastomas do benefit from treatment with safe surgical excision and adjuvant radiochemotherapy with acceptable risks and toxicity. Although the authors observed that the patients did not seem to experience excessive toxicity related to RT, an abbreviated course, as described by Roa et al.1 may be considered in this population. This abbreviated protocol not only decreases the time of treatment from 6 weeks to 3 weeks, but also appears to decrease the corticosteroid requirements. Since it appears to have been established that the elderly tolerate and benefit from aggressive therapy for glioblastomas, further studies addressing MGMT status, the possibility of pseudoprogression, and the use of the abbreviated RT protocol may further improve management of glioblastomas in older patients.

Disclosure

The authors report no conflict of interest.

References


Response

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We would like to thank Drs. Heros and Heros for their insightful editorial regarding our manuscript about treatment of glioblastoma in the elderly. They have clearly understood and articulated the points we were trying to make. As they point out, our data support the position that aggressive treatment including resection and adjuvant therapy in elderly patients is associated with mean PFS (8 months) and OS (12.5 months) comparable to those seen in younger patients receiving similar treatment, without an unacceptable rate of surgical or other morbidity. However, selection bias is inherent in our retrospective, nonrandomized study and suggests that our findings can only really be extrapolated to “appropriately selected” patients. As Drs. Heros and Heros have correctly surmised, defining which elderly patients with glioblastoma are appropriate for aggressive therapy is the crux of the issue. Patients who had biopsy only in our series were more likely to have tumors that were multifocal and/or in deep and eloquent locations. We cannot comment on whether such tumors are more common in elderly patients, but we think this is unlikely. The rate of biopsy only in elderly patients with glioblastoma in our series (50%) is higher than the biopsy-only rate for all glioblastoma patients at our institution over the same period (33%) (Ballman K et al., unpublished data). This suggests that there may have been a relative reluctance to offer aggressive surgery to elderly patients. While only a prospective randomized trial of biopsy versus resection in this population could definitively answer whether such reluctance is appropriate, retrospective data from our study and studies by other authors suggest it is not. In keeping with this, the rate