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Letters to the editor

Is deferred use of bevacizumab for glioblastoma associated with prolonged survival?

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We read with great interest the article by Piccioni et al[1] which fostered the ongoing debate on the role of bevacizumab in patients with glioblastoma multiforme (GBM). After the failure of the phase III trials evaluating the upfront administration of bevacizumab in newly diagnosed GBM,[2,3] the neuro-oncology community worldwide is trying to assess whether this drug is effective in selected subpopulations and what is the most appropriate timing for starting the treatment.[4] This latest issue was faced by Piccioni et al[1] who examined retrospectively a cohort of 468 GBM patients treated with bevacizumab at different points of the natural history of the disease: upfront ($n = 80$), at first recurrence ($n = 264$), at second recurrence ($n = 88$), and at third recurrence ($n = 36$). Their elegant statistical analysis was focused firstly on recurrent GBM: comparing the 3 groups, the authors found that progression-free survival (PFS) and overall survival (OS) from bevacizumab initiation were not different, that is, PFS and OS were independent from the time in which treatment was started. Therefore, their conclusion was that deferring the use of bevacizumab at later recurrences is not detrimental. Moreover, extending the analysis to the group of patients treated with bevacizumab upfront, the authors found no differences in the survival time after bevacizumab failure, suggesting that there is no effective treatment for GBM recurrence after bevacizumab treatment.

One major issue in that work is the lack of data on OS from the diagnosis of GBM. Looking at median age of recurrent GBM patients, in fact, we noticed that time from diagnosis to the start of bevacizumab therapy was 0.8, 1.4, and 2.1 years in the groups treated at first, second, and third recurrence, respectively. As a consequence, being that OS from the start of bevacizumab therapy statistically was not different among the 3 groups, delaying bevacizumab treatment should have resulted in a prolonged OS from diagnosis; and in fact this was the finding of another recently published work.[5] Data about the comparison of OS from diagnosis between patients treated with bevacizumab upfront and patients treated with bevacizumab at recurrence were also missing: having shown the post-bevacizumab survival for the whole study cohort, it is arguable that these data could have been easily derived by the authors. We recognize that probably the authors aimed at not overestimating the results of their study, due to its retrospective design. However, we believe that these data could contribute to the ongoing debate, also influencing the design of future clinical trials and orienting clinical decision making. In conclusion, we think that this is a significant issue to be addressed.

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Deferred use of bevacizumab for recurrent glioblastoma is not associated with diminished efficacy

We would like to thank D'Alessandris and colleagues for their interest in our study. We agree that following 2 negative phase III trials of upfront bevacizumab, both with significant crossover in the placebo arms, the optimal timing of bevacizumab administration is unclear.[1,2] Our study showed that the deferred use of bevacizumab to later recurrences was not associated with diminished efficacy. Additionally, we suggested that deferring bevacizumab to later recurrences may be beneficial for some, but not all patients.

D'Alessandris and colleagues observed that the time between diagnosis and initiation of bevacizumab was progressively longer in each recurrence cohort, and the overall survival (OS) from bevacizumab administration was statistically similar, which would imply that delayed bevacizumab resulted in an increase in OS. While it is true that the OS from time of diagnosis was progressively longer in each of the recurrence cohorts (first, second, and 3+ recurrences), we intentionally avoided making the conclusion that deferred use of bevacizumab led to an improved OS. Since it is likely that patients receiving bevacizumab at later recurrences were subject to selection bias enriching for those with greater OS, we strongly believe that the limitations of a retrospective study prohibit this conclusion, and suggest that a randomized prospective study is needed to answer this question. In a similar study by Hamza and colleagues, deferring bevacizumab to later recurrences did not change progression-free survival and showed a longer OS from date of surgery, but again this must be interpreted with caution.[3] In both studies, the clinician's judgment to defer bevacizumab to later recurrences presumably selected for less aggressive disease, such as tumors with less edema, mass effect, enhancement, or steroid requirement. Moreover, this highly selected group of patients who deferred bevacizumab to later progressions may be confounded by markers of improved survival such as isocitrate dehydrogenase 1 (IDH1) mutation and methylation of O^6-DNA methylguanine-methyltransferase (MGMT). Our study did not find a difference in MGMT methylation among the cohorts, but the percentage of IDH1 mutations increased with each recurrence cohort, suggesting a selection bias. Hamza et al also point out that data for prognostic markers were not included in their study and that the question of deferring bevacizumab to later recurrences must be examined prospectively.

From our study, we conclude that delaying bevacizumab in recurrent glioblastoma patients is not associated with diminishing effectiveness. Furthermore, we identified patients who were unable to continue therapy at early progressions, and suggest this population might benefit from early bevacizumab. More work is needed to identify both the optimal timing and patient subpopulations to maximize the benefits of bevacizumab therapy.

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