Response to Weltman and Fleury Malheiros, re Lassman et al.

In Reply to Weltman and Fleury Malheiros:

We thank Drs. Weltman and Fleury Malheiros for their comments on our recent article.1 We agree that our analyses were performed on a retrospective dataset, and interpretations are thus subject to limitations and potential biases inherent to any retrospective study. For example, as we discussed in the article, neither central review of pathology nor imaging was performed. Multivariate analyses attempted to control for potential confounding variables, but only a randomized prospective study would definitively address this concern. However, we believe that our conclusions (and cross-comparisons) are supported not only by our own observations but also by recent data and treatment trends in neuro-oncology.

For example, in our study, treatment group imbalances did not contribute to differences in outcome in the Cox model. Groups were reasonably well balanced for potential confounders, such as performance status.

In addition, Weltman and Fleury Malheiros suggest that standard of care for anaplastic oligodendrogliomas includes radiotherapy as part of the initial treatment regimen. We agree that radiotherapy has well-established efficacy and, for many years, was the standard approach. However, treatment options have evolved since the initial studies during the 1960s–1980s cited by Drs. Weltman and Malheiros. It is now well established that oligodendrogliomas, especially those harboring 1p19q co-deletion, respond to chemotherapy. For example, the recently publicized long-term follow-up of RTOG 9402 demonstrated that chemo-radiotherapy doubled median survival relative to radiotherapy alone in 1p19q co-deleted cases (14.7 vs. 7.3 years).2 Moreover, the German NOA-04 trial of newly diagnosed anaplastic gliomas also suggested that primary chemotherapy is equi-efficacious as primary radiotherapy.3 Furthermore, survival with 1p19q codeleted anaplastic oligodendrogliomas is at least several years. Accordingly, radiotherapy-induced dementia as a late toxicity4 is a real concern. Consequently, many neuro-oncologists advocate for chemotherapy alone and defer radiotherapy until disease progression in 1p19q codeleted cases. The same concern is well established in the controversies surrounding late neuro-cognitive toxicity from early radiotherapy in the treatment of low-grade gliomas, primary central nervous system lymphoma, and resected brain metastases. Therefore, the acknowledged limitations of our retrospective design notwithstanding, our results are concordant with these studies suggesting that overall survival was not compromised by deferring radiotherapy.1 Absent a clear survival advantage, deferred radiotherapy in favor of chemotherapy alone is certainly a reasonable initial strategy.

We are not alone. For example, 42% of neuro-oncologists surveyed in 2005 recommended deferring radiotherapy in codeleted cases.5 Similarly, 57% of patients in our retrospective dataset who receive a diagnosis of codeleted tumors since 2005 were treated with chemotherapy alone (almost exclusively temozolomide).6 Therefore, as stated in our publication, “subject to the limitations of study design, our data suggest that initial treatment with chemotherapy alone may be a reasonable option for patients with 1p19q codeleted tumors.”1 Regardless of advised therapy, in our clinical experience, many patients refuse radiotherapy because of perceived concerns about neuro-toxicity. Therefore, although ongoing or future prospective studies may show that deferred radiotherapy adversely affects survival, concerns about cognitive injury are important in determining optimal therapy, and survival may not be the only end point of clinical importance. The CATNON or CodeL phase III trials (for non- or codeleted anaplastic gliomas, respectively) may help to assess quality of life outcomes.

Clearly, neuro-oncology is a multidisciplinary field, and treatment requires individualization that depends on discussion among both physicians and patients of risks and benefits of various strategies.


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References


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