LETTERS TO THE EDITOR

In Reference to Lamborn et al. (Neuro-Oncology. 2008;10:162–170)

Dear Editor,

A recent article in this journal evaluating the significance of progression-free survival as a major end point in neuro-oncology clinical trials (Progression-free survival: An important end point in evaluating therapy for recurrent high-grade gliomas [Neuro-Oncology 2008;10:162–170]) stated that, due to the lack of validated instruments for the assessment of symptomatic end points, time to symptom deterioration would probably not be a useful end point. To readers less familiar with this literature, that statement may obscure the fact that, especially for neurocognitive function, validated instruments exist and are currently used, that the feasibility and tolerability of neurocognitive assessment in brain tumor patients has been well demonstrated, and that neurocognitive outcomes are increasingly being incorporated into clinical trials of new antineoplastic agents. Cognitive dysfunction predicts survival better than clinical prognostic factors alone in patients with primary brain tumors, leptomeningeal disease, and parenchymal brain metastases. There is also evidence that neurocognitive decline may precede progression on neuroimaging, suggesting that neurocognitive surveillance may be more sensitive to tumor progression than MRI. These alternative end points can be considered in the drug approval process. For one agent, the U.S. Food and Drug Administration (FDA) indicated that “radiological response alone is not acceptable for approval. However, improvement in neurocognitive function or delay in neurocognitive progression are acceptable endpoints” (minutes of end-of-phase II meeting, 10/21/98). The conclusion of a workshop sponsored by the FDA, American Association for Cancer Research, and American Society of Clinical Oncology evaluating end points for registrational trials of new agents to treat primary brain cancer stated that “the limitations of imaging-based assessment can in part be ameliorated by incorporation of additional clinically observed, neurocognitive, and patient reported outcomes into a composite progression endpoint.”

Management of this disease remains difficult, and long-term survival, if achieved, is often accompanied by significant disability. Thus, freedom from symptomatic progression in itself represents a benefit. This issue was highlighted by the report of the Brain Tumor Progress Review Group, which stated that there was an immediate need to measure quality of life and other surrogate benefit markers to better assess therapeutic response in all brain tumor clinical trials. Longer life and better life should be integrated; longer life is only truly beneficial if it is better life.

Sincerely,
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References


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In Reference to Maschio et al.  
(Neuro-Oncology. 2008;10:106–107)

Dear Editor,

With great interest we read the comments of Maschio et al. (Neuro-Oncology. 2008;10:106–107) concerning our manuscript “The course of neurocognitive functioning in high-grade glioma patients” (Neuro-Oncology. 2007;9:53–62).

In the comments, Maschio and colleagues regretted that we attributed the poorer neurocognitive performance in patients with tumor progression (compared to those without progression) to the use of antiepileptic drugs (AEDs) without further differentiating between the effects of older and newer AEDs.

Many brain tumor patients are confronted with epilepsy and will receive AED treatment in the course of their disease. Especially in brain tumor patients, refractoriness of the epilepsy is very common. Interactions between chemotherapeutic drugs, corticosteroids, and enzyme-inducing AEDs may lead to insufficient control of the epilepsy and/or antitumor effect. Development of a new generation of AEDs as mentioned by Maschio and colleagues could bypass this effect because they do not induce coenzymes of the cytochrome P450 pathway.

Unfortunately, large studies on the effect of these newer AEDs on seizure control or the side effects in brain tumor patients are still lacking.

The primary aim of our study was to include all newly diagnosed high-grade glioma patients who were going to be treated with radiotherapy and to evaluate neurocognitive function in the course of the disease. Patients were included irrespective of having epilepsy or of the type of AED they were using. Inclusion took place in six centers in the Netherlands, where at the time of inclusion the use of these newer AEDs was not common practice. This means that all of our included patients were receiving mono- or polytherapy treatment with the older AEDs such as valproic acid, carbamazepine, and phenytoin.

Because evaluation of the effects of AED treatment was not our primary objective, patients used different dosages of mono- or polytherapy; and because our sample size was rather small, we did not further specify the AED regimes of each patient.

On the other hand, it was interesting to find that impaired neurocognitive function in the patients with tumor progression, compared to those without progression, was indeed influenced by the use of AEDs. By adding the sentence in the abstract “the possibility of the deleterious effects is important to consider when prescribing an AED(s)” we do emphasize that this is an important issue in the treatment of brain tumor patients.

Recently, we started a longitudinal multicenter trial on the effect of levetiracetam in glioma patients and its effect on neurocognitive function and health-related quality of life.

We strongly support the efforts that teams like Maschio and colleagues are making to further investigate the effects of AED treatment in brain tumor patients. We therefore thank Maschio and her team for once more making it clear in their letter that further investigation is needed.

Sincerely,

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