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Editorial

Neurocognitive function: an emerging surrogate endpoint for neuro-oncology trials

Pediatric neuro-oncologists are familiar with the challenge that their potentially curative treatments may come at a high price because they may improve survival, but not without developmental delays and persistent neuropsychological sequelae in a significant proportion of patients. The view that the radiological determination of response or stable disease is a sufficient parameter to ascertain that "my patient is doing well" has long been challenged in adult neuro-oncology in the primary CNS lymphoma field as well as in cohorts of brain metastasis patients treated with whole-brain radiotherapy. In contrast, neurocognitive function in malignant glioma patients has traditionally been assumed to roughly reflect the status of tumor control. This has often been true because the treatment modalities administered to these patients have been less aggressive, in part because of their non-curative nature and because the lengths of survival have often been too short to allow patients to experience long-term adverse effects of treatment.

Neurocognitive function has now become an interesting endpoint from another angle. The introduction of bevacizumab, an antibody to vascular endothelial growth factor (VEGF), and other VEGF-targeting agents into the repertoire of medical options for malignant glioma patients has challenged the view that our current imaging criteria are sufficient to estimate the benefit derived from all new agents, irrespective of their mode of action (1). In fact, the assessment of neurocognitive function may now become an important more-than-surrogate marker to determine whether an apparently successful treatment as assessed by neuroimaging truly translates into a clinical benefit for the patient. Fortunately, this issue was recognized when the BRAIN trial, which assessed the safety and efficacy of bevacizumab with and without irinotecan in patients with recurrent glioblastoma, was designed. Wefel and colleagues (2) now report the development of neurocognitive function in the first 24 weeks after study entry in a major proportion of the participants of the BRAIN trial. They found that most patients with at least stable disease at 24 weeks also had stable or improved neurocognitive function, whereas patients with progressive disease commonly had cognitive decline. In the absence of the demonstration of a survival benefit for bevacizumab in recurrent glioblastoma, because no study with an appropriate bevacizumab-free control arm was performed, these data are reassuring because they indicate that the responses seen by neuroimaging were most often associated with the preservation or improvement of neurocognitive function. The most interesting subgroup of patients is the one of approximately 30% that exhibited some neurocognitive decline in the absence of documented tumor progression. Although no correlative analyses with the MRI patterns were reported, it is tempting to assume that patients with non-enhancing diffuse progression, which escapes response criteria heavily based on contrast-enhanced imaging, may have been in that subgroup. On the other hand, cognitive decline preceding MRI-documented progression has also been noted in the pre-bevacizumab era (3).

Neurocognitive function remains a difficult endpoint to assess and interpret, given the multitude of confounding factors such as co-medication, notably with antidepressant drugs, and psychiatric disorders, notably depression. Nevertheless, efforts such as the present analysis in the BRAIN trial are necessary and welcome to better estimate the clinical impact of new treatments administered in an eventually palliative setting.

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References

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