

## New Agents and New End Points for Recurrent Gliomas

**TO THE EDITOR:** The new Response Assessment in Neuro-Oncology (RANO) criteria for high-grade gliomas developed by Wen et al<sup>1</sup> are an important step forward because disease assessment has always been difficult to achieve in neuro-oncology; moreover, the criteria should be considered of crucial importance in overcoming the present disadvantages of the classical Macdonald criteria.<sup>2</sup> The latter criteria, used for the last 20 years, take into account not only dimensional imaging modifications in the contrast-enhancing tumor component (reflecting neoangiogenesis), but also modifications in corticosteroid dosage (which can alter the contrast enhancement pattern) and the clinical condition of the patient. This wise combination of tumoral, peritumoral, and clinical factors, developed in the 1990s, was considered worthy until recently.<sup>2</sup> Moreover, by including an evaluation of the patient's clinical condition, this approach anticipated the recently defined concept of clinical benefit, which is used to evaluate the effectiveness of targeted agents but which may also reveal changes in the nonenhancing components of high-grade gliomas.

However, the interaction between tumoral, peritumoral, and clinical factors in defining tumor assessment has made it more difficult to interpret response in brain tumors than in other types of cancer, with the boundaries between tumor response and disease stability being unclear. In view of this limitation, neuro-oncologists have, for several years, used progression-free survival (PFS) rather than response rate as the primary end point in phase II studies; this choice was also in line with the concept that long-standing disease stabilization is both the result of effective treatment and a clinical goal in patients with diseases, such as high-grade gliomas, that have a dismal prognosis.

In a historical analysis of 225 patients conducted by Wong et al<sup>3</sup> in the 1990s, the PFS rate at 6 months for defining the activity of an experimental agent was set at 15% for recurrent glioblastoma multiforme. This rate was recently confirmed by other groups.<sup>4,5</sup>

As stated by Wen et al,<sup>1</sup> the increasing use of antiangiogenic agents for the treatment of recurrent glioblastoma created the need to modify the older Macdonald criteria. These compounds have, in fact, been implicated in neuroradiologic pseudoresponses because of the reduction they cause in contrast enhancement extravasation and edema, secondary to diminished vascular permeability. Thus, tumor response evaluation based on contrast enhancement modifications and on changes in the need for corticosteroids became almost useless. Moreover, because it is impossible to determine the time of tumor progression, PFS rates have also lost their role in determining the activity of antiangiogenic agents. Therefore, the main reference points for disease evaluation were overlooked, with survival being the only certain remaining parameter.

The RANO criteria have been designed as an aid in developing phase II trials, in which primary end points (eg, response rate or PFS rate) may retain clinical significance, and in proceeding to phase III studies using consistent activity data. However, the criteria defined

have not yet been clinically validated, and despite the fact that sound considerations such as an emphasis on the role of T2/fluid-attenuated inversion recovery sequences have been made, the reliability of these new criteria must be evaluated, at least respectively, in clinical series or data warehouses, as was achieved for Response Evaluation Criteria in Solid Tumors (RECIST) criteria<sup>6,7</sup> or, instead, in prospective large trials with survival end points. Moreover, the utility of the rate of T2/fluid-attenuated inversion recovery modifications in dimensions in assessing response or disease progression has yet to be confirmed, and because any interpretation of these changes is influenced by the patient's neurologic condition, the current picture is somewhat like that described in 1977 by Levin et al,<sup>8</sup> who suggested that neurologic examination and neuroradiologic scans were of equal value in predicting response to therapy.

While awaiting the clinical validation of the RANO criteria, we feel it is important to point out that the forthcoming phase II clinical trials with antiangiogenic agents still require worthy end points and, therefore, suggest that overall survival rates might be used as an option because they are the only unbiased parameter available for evaluating the real efficacy of treatment, especially one using antiangiogenic agents. In this context, overall survival rates at 12<sup>5</sup> or 6 months<sup>9</sup> are of interest.

The RANO criteria should be included in phase II clinical trials as an aid in deciding on treatment continuation or interruption, but they should be prospectively validated with a view to decide whether they are to produce clinically relevant results before becoming standard criteria for evaluating response to treatment in a neuro-oncologic setting.

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