Identification of Patients Who Benefit From Bevacizumab in High-Grade Glioma—An Easy Question Turned Difficult: Treat the Scan or the Patient?

To the Editor: Bevacizumab has activity in the CNS, with a randomized trial documenting its ability to reduce symptoms associated with radiation necrosis and a reproducible impact on symptoms associated with tumor-related edema in recurrent glioma. In addition, population-based assessments have suggested that the incorporation of bevacizumab into the treatment armamentarium has incrementally improved outcomes in high-grade glioma.

However, we believe that recent articles in Journal of Clinical Oncology add to the perpetuation of two inadequately evidenced beliefs. The first is that bevacizumab clearly delays progression of high-grade glioma. The second is that the observed effects of bevacizumab must represent antitumor efficacy and that the challenge now is to identify the patients who respond in the face of contradictory data with regard to quality of life (QOL) related neurologic death at this late stage.

Taphoorn et al reported statistically longer deterioration-free survival with the addition of bevacizumab to chemoradiation for glioblastoma, which could potentially lead the readership to conclude that bevacizumab either slows tumor progression or improves symptoms in this setting. However, the authors themselves state that “the addition of bevacizumab did not worsen or improve patients’ health-related QOL over time compared with the addition of placebo.”5 If bevacizumab improves neither QOL nor overall survival, how is longer deterioration-free survival reported? This end point was defined to include radiographic progression, which has provided the foundation for Food and Drug Administration approval (in a nonrandomized study) of this agent in high-grade glioma. Radiographic assessment as an end point is, at best, a puzzling justification for clinical use in this setting. The mechanism of bevacizumab should uniquely disqualify radiographic features, such as enhancement and edema, as measures of antitumor activity until correlation with patient-centric measures establishes a survival or QOL benefit. It is telling that Taphoorn and colleagues rely on observations limited to conventional cytotoxic therapies (temozolomide and radiation) to assert a connection between radiographic outcomes and QOL.

More recently, Sandmann et al retrospectively assessed molecular profiles of tumors from the AVAglio (A Study of Avastin [Bevacizumab] in Combination With Temozolomide and Radiotherapy in Patients With Newly Diagnosed Glioblastoma) trial to identify patient subsets that may benefit from bevacizumab. Although we applaud the efforts to identify a subset of tumors that derive a patient-centric (survival) benefit, they can only be viewed as hypothesis generating. Furthermore, this entire approach implies that a subset of high-grade gliomas is uniquely responsive to bevacizumab in that there is an antitumor (rather than antivascular) activity of bevacizumab in this setting. Although a preclinical rationale exists for the study of antiangiogenic therapy in glioma, the clinical data to date suggest only that bevacizumab reduces vascular permeability, not progression of tumor growth. Indeed, mouse models of glioma have demonstrated that the antiedema effect of antiangiogenic therapy may be observed in the face of persistent tumor growth. Similarly, continued infiltrative growth of tumors has been suggested by diffusion magnetic resonance imaging in the setting of antiangiogenic treatment in patients, a factor that is not incorporated into current Response Assessment in Neuro-Oncology criteria.

Despite the absence of compelling randomized data that show clinical benefit in de novo or recurrent high-grade glioma, bevacizumab has been adopted as the backbone for recurrent high-grade glioma studies. Although, the recent BELOB (A Randomized Phase II Study on Bevacizumab Versus Bevacizumab Plus Lomustine Versus Lomustine Single Agent in Recurrent Glioblastoma) trial9 suggested a potential positive impact of the combination of lomustine and bevacizumab on overall survival in recurrent glioblastoma, bevacizumab monotherapy was found to have an insufficient impact on overall survival to justify further study, and a definitive trial to evaluate this has just been completed.

In the absence of compelling data that show improvement of patient-centric measures, we urge caution against the routine use of bevacizumab for progression let alone surmising that a subset of patients will benefit from up-front bevacizumab. We believe that bevacizumab can provide profound palliation for symptomatic radiation necrosis and/or peritumoral edema. However, in the absence of symptoms, this therapy is an expensive, potentially morbid treatment without data to suggest a delay in actual tumor progression. Such an expensive therapy with real treatment-related adverse effects should not be used to treat asymptomatic leaky blood vessels. Based on available data, this practice treats the scan, not the patient.

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