The Role of Bevacizumab in Glioblastoma

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Glioblastoma (GBM) is the deadliest and most aggressive of the primary brain malignancies. Outcomes for patients remain poor, with the course of the disease often associated with significant neurologic morbidity because of tumor location within the central nervous system (CNS). Although advances in clinical care options for patients have been somewhat limited, the community has seen tremendous progress in the molecular understanding of the disease and how these alterations promote cellular behaviors that produce the morbidity and mortality associated with GBM.

Among the cellular behaviors identified as disease promoters, the process of tumor-associated angiogenesis uniquely impacts the host tissue, especially when occurring in the CNS. GBM-induced angiogenesis serves as an important mechanism of disease progression, and is enhanced by the often hypoxic and necrotic growth patterns of GBM. Additionally, angiogenesis occurring in the brain leads to a highly permeable blood–brain barrier that disrupts and impairs the necessary neural process of cerebral autoregulation of blood flow. It also promotes an environment of intravascular fluid extravasation into the extracellular spaces (vasogenic edema), causing regional ischemia in the brain. Both of these sequelae result in a marked deterioration in neurologic function which, in turn, results in a diminished quality of life in an already vulnerable patient population.

The initial FDA approval for the use of bevacizumab in GBM, and its resulting inclusion in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for CNS cancers (available at NCCN.org) followed the publications of 2 studies: (1) the randomized BRAIN study, which was based on objective response data, and (2) an earlier single-arm study. Time-to-event end points of 6-month progression-free and overall survivals were superior to historic benchmarks for GBM.¹

The evaluation of bevacizumab in newly diagnosed GBM was recently reported after the completion of 2 high-quality, placebo-controlled, randomized studies by the RTOG and Roche.^{2,3} In both studies, fairly similar results were seen, with no difference in overall survival between groups and progression-free survival favoring the treatment group. A substantial effort was made within these studies to collect tumor tissue to perform correlative studies with the goal of determining molecular subtypes and subgroups with newly diagnosed GBM that should respond better to treatment with bevacizumab.

Despite these disappointments, the NCCN Guidelines subcommittee for CNS tumors has aggressively reviewed recommendations and the positioning of bevacizumab within the guidelines. We continue to support the role of bevacizumab as monotherapy and with limited cytotoxic combinations in the setting of recurrent disease.

We would alert the oncology community to a couple of unique aspects concerning the use of bevacizumab in GBM. First, bevacizumab has an impact on diagnostic imaging studies, particularly MRI. A misconception concerning MRI of glioma relates to measuring tumor size. MRI does not measure tumor size directly, but instead evaluates the extravasation of an intravascular contrast agent into the brain parenchyma through a permeable blood–brain barrier. We have used this measurable contrast enhancement as a surrogate for tumor behavior. The use of bevacizumab may alter this by reducing the contrast agent's ability to enter the CNS and, as a result, we may underestimate tumor behavior. The community has generated new response assessment metrics, termed RANO (Response Assessment in Neuro-Oncology) *criteria* to address this challenge.⁴ The metrics are imaging assessment, clinical performance status, and steroid use.

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Second, the NCCN Guidelines (in “Principles of Brain and Spinal Cord Tumor Systemic Therapy” section on page BRAIN-D; available online, in these guidelines, at NCCN.org) indicate that bevacizumab may be continued even in the setting of progressive disease. The rationale supporting this recommendation is that patients with nonenhancing progressive disease on imaging and stable functional status who continue bevacizumab may maintain a better quality of life as a result of reduced vasogenic edema and, therefore, fewer associated neurologic losses.

In summary, bevacizumab has a clear role for patients with recurrent malignant glioma. It not only functions as an antitumor agent but also reduces vasogenic edema, thereby enhancing functional status and improving quality of life. The hope is that continued efforts to better understand molecular subgroups and predictive biomarkers will define subsets of newly diagnosed patients who would benefit from bevacizumab.

References

1. Cohen MH, Shen YL, Keegan P, Pazdur R. FDA drug approval summary: bevacizumab (Avastin) as treatment of recurrent glioblastoma multiforme. *Oncologist* 2009;14:1131–1138.
2. Gilbert MR, Sulman EP, Mehta MP. Bevacizumab for newly diagnosed glioblastoma. *N Engl J Med* 2014;370:2048–2049.
3. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N Engl J Med* 2014;370:709–722.
4. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol* 2010;28:1963–1972.