Antiangiogenic Therapy for Glioblastoma: Complex Biology and Complicated Results

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Angiogenesis is one of the classic and diagnostic features of glioblastoma. These newly formed blood vessels are typically tortuous, forming vascular glomeruli, and they are notable for the lack of the tight junctions and complete pericyte coverage. This leads to peritumoral edema and extravasation of intravenous contrast on computed tomography or magnetic resonance imaging. Because angiogenesis is such an important aspect of glioblastoma biology, targeting this process has been considered a therapeutic priority.

Vascular endothelial growth factor A is the most prominent and common mediator of angiogenesis, although there are a variety of other factors that have been identified in glioblastoma. Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor A, showed activity in a variety of solid tumors. However, brain tumors were excluded from early studies of bevacizumab because of concerns regarding the risk of intracranial hemorrhage. A presentation in 2005 of a small number of patients with recurrent glioblastoma who were safely treated with bevacizumab led to larger formal clinical trials.1,2 These initial studies combined bevacizumab with irinotecan, emulating the successful treatment regimen in colorectal cancer, and demonstrated imaging response rates in the 30% to 40% range. These studies confirmed that the rate of intracranial hemorrhage was low and that the systemic toxicities were on par with this treatment regimen in other cancers.

Two subsequent trials solidified these early results. The BRAIN Trial was a multicenter, randomized, noncomparative phase II study that treated patients with recurrent glioblastoma with bevacizumab either as a single agent or in combination with irinotecan.3 A parallel study was done at the National Institutes of Health, where patients were treated with bevacizumab in a single arm but at progression, irinotecan could be added.4 The results of these two studies were quite consistent with objective response rates ranging from 28% to 38%. The median overall survival (OS), measured from entry onto these studies, was similar. However, in the absence of a treatment arm without bevacizumab, assessment of the impact on OS was difficult. On the basis of the response rates, bevacizumab was granted accelerated approval by the Food and Drug Administration for treatment of patients with recurrent glioblastoma.5

Beveracizumab was then tested in newly diagnosed glioblastoma in two international placebo-controlled, double-blinded randomized phase III trials, AVAGlio and RTOG 0825. These studies added bevacizumab to the standard first-line treatment of glioblastoma, which combines external beam radiation with concurrent daily temozolomide followed by six to 12 cycles of single-agent temozolomide.6,7 Both studies demonstrated prolonged progression-free survival (PFS) with bevacizumab; although because of differences in statistical design, the PFS difference was statistically significant in AVAGlio but not in RTOG 0825. However, neither study showed a difference in OS.

A subsequent three-arm phase II trial in patients with recurrent glioblastoma, BELOB, randomly assigned patients to single-agent lomustine, single-agent bevacizumab, or the combination of lomustine and bevacizumab.8 This study enrolled approximately 50 patients per arm and was designed to look for a survival signal, designating the 9-month survival rate as the metric of success. Only the combination arm of bevacizumab and lomustine surpassed the preset threshold of a 9-month survival rate of 55%. The EORTC 26101 phase III trial was designed as the confirmatory trial. Patients with recurrent glioblastoma were randomized to either lomustine or the combination of lomustine with bevacizumab. The results were recently presented at the annual meeting of the Society for Neuro-Oncology.9 No survival difference was noted between the two treatment arms, although there was a difference in PFS.

The article accompanying this editorial has the results of the GLARIUS trial,10 an open-label, randomized study that compared the standard treatment for newly diagnosed glioblastoma (chemoradiation with temozolomide, followed by maintenance temozolomide) with radiation followed by the combination of bevacizumab and irinotecan. Eligibility was restricted to patients with centrally confirmed glioblastoma that on molecular testing demonstrated that the promoter region of the O6-methylguanine DNA methyltransferase (MGMT) gene was unmethylated. These patients have a worse prognosis and the benefit of temozolomide is modest at best, allowing temozolomide to be excluded from the experimental arm.11 The primary end point of the trial was the progression-free rate at 6 months, a metric more commonly used for clinical trials for recurrent glioblastoma where statistical parameters are well established.12 The results did demonstrate a statistically significant difference in this metric, but the secondary end point of OS was not different between the two treatment arms. There were, however, a high percentage of crossovers, with patients on the control (temozolomide) arm receiving bevacizumab at progression and, conversely, patients on the experimental (bevacizumab and irinotecan) arm receiving temozolomide at recurrence.

How do we interpret this large composite of clinical trials? The gold standard benchmark of efficacy in cancer clinical trials is...
improving OS. This is particularly germane for glioblastoma, where the median survival in clinical trials rarely exceeds 18 months. The interpretation of OS results from randomized trials testing bevacizumab may be difficult because there are varying percentages of patients who receive bevacizumab at a later time after disease progression. The impact of this crossover effect is difficult to assess, leading to great interest in examining the progression-free end points. However, measuring response and failure when using brain imaging, typically magnetic resonance imaging, to evaluate antiangiogenic therapies has proven to be challenging.

First, antiangiogenic agents improve the integrity of the blood-brain barrier, with reductions in contrast enhancement as early as 48 hours after treatment. Therefore, a decrease in enhancement may not reflect tumor response but rather a pseudoresponse. New criteria entitled Response Assessment in Neuro-Oncology, which include assessment of the T2-weighted fluid-attenuated inversion recovery (FLAIR) technique, are likely less susceptible to changes resulting from blood-brain barrier effects and may detect increases in tumor even in the absence of contrast enhancement. Although widely adopted, interpretation of T2-weighted FLAIR has proven to be more challenging because differences in magnetic resonance machine magnet strength, acquisition protocol, and machine manufacturer can alter the T2-weighted FLAIR image. Therefore, even with the use of the Response Assessment in Neuro-Oncology criteria, the declaration of progression may occur earlier in patients not on the antiangiogenic agent because the contrast-enhancing mass is more readily quantified in this group.

Second, whereas an antiangiogenic agent may cause a pseudoresponse, worsening of contrast enhancement is often noted soon after completion of the combined chemotherapy and radiation treatment. In many patients, this is not disease progression but a reversible process termed pseudoprogression. This has been estimated to occur in 9% to 25% of patients within the first 3 months after the completion of radiation. Imaging studies (including magnetic resonance perfusion, diffusion, and spectroscopy) cannot reliably distinguish pseudo from true progression, but over time pseudoprogression gradually improves. Bevacizumab effectively prevents pseudoprogression. Thus, in the context of a clinical trial where patients with pseudoprogression are at greater risk of being erroneously declared as having progression and are taken off treatment, a potential bias is created that favors those patients on the antiangiogenic treatment.

The GLARIUS trial provides an opportunity to evaluate important aspects of clinical trial designs, interpretation of results, and the subsequent impact on future trials and standards of care. The investigators were successful in implementing a multicenter clinical trial that required molecular analysis of tumor tissue in a rapid timeframe to establish eligibility and allow randomization to occur. This permitted the study design to have an experimental arm that did not incorporate the standard of care, because the addition of temozolomide to the bevacizumab and irinotecan regimen would likely have markedly increased toxicity. Taken independently, the efficacy results would suggest some benefit to the bevacizumab and irinotecan combination in the patients with MGMT unmethylated tumors and a comparatively poorer prognosis, whereas the lack of improvement in OS could be attributed to a high percentage of crossovers. Should these data be used to recommend a new treatment regimen, even though it was powered as a phase II study that would typically be used as preliminary evidence of efficacy before embarking on the resource-intense phase III trial? As described above, the promising results of the BELOB study did not translate in the definitive phase III EORTC trial. Furthermore, in the larger, double-blinded phase III trials, similar improvements in PFS did not translate into survival benefit. This brings into question the use of antiangiogenic treatment in the front-line setting because bevacizumab-refractory glioblastoma has proven to be resistant to existing salvage regimens.

The future of antiangiogenic treatment of glioblastoma remains unclear. Tumor biology would argue that this should be an important therapeutic target. However, because the current treatment regimens were adapted from other cancers, questions regarding the optimal dosing for glioblastoma have been raised. Also, recent studies suggest that there are distinct molecular subtypes of these cancers that specifically benefit from bevacizumab treatment. Confirmation of benefit in the molecular subtypes will require additional prospective studies. Finally, in an era of cancer research that is notable for the increasing interest in immunotherapy, bevacizumab may have a role both as a modulator (in lieu of immunosuppressive corticosteroids) of inflammation-induced brain swelling and for its inherent immunomodulatory activity. Regardless, these future clinical trials would be well served to build on the challenges and experiences already faced by prior studies that have tested antiangiogenic agents in brain tumors.

**AUTHOR’S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

Disclosures provided by the author are available with this article at www.jco.org.

**REFERENCES**


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