

Taming Glioblastoma by Targeting Angiogenesis: 3 Years Later

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In 2007, *Journal of Clinical Oncology* published two landmark articles on the benefit of bevacizumab in progressive glioblastoma. Vredenburgh et al¹ reported a response rate (RR) of 57% and progression-free survival at 6 months (PFS-6) of 46%, while Chen et al² reported a RR of 47% and PFS-6 of 65%. Since then, important information has emerged to support the use of bevacizumab and, on May 5, 2009, the US Food and Drug Administration granted accelerated approval³ to bevacizumab as a single-agent treatment for patients with progressive glioblastoma. Now, oncologists are testing its efficacy as a first-line therapy. In this issue of *Journal of Clinical Oncology*, Lai et al⁴ report the first phase II study of bevacizumab combined with temozolomide and radiotherapy in newly diagnosed glioblastoma subjects. This regimen offers an overall survival (OS) of 19.6 months and PFS of 13.6 months. It compares favorably to a control cohort from the same institution, with OS of 21.1 months and PFS of 7.6 months, and to data from a phase III trial of temozolomide added to radiotherapy, with OS of 14.6 months and PFS of 6.9 months.⁵

When evaluating these new data, it is important to note that Lai et al⁴ conducted a single-arm phase II study. Despite favorable findings, there is still insufficient evidence to warrant the routine clinical practice of adding bevacizumab to initial temozolomide and radiotherapy for newly diagnosed glioblastoma. Oncologists must guard against overinterpretation of the findings, because drugs for glioblastoma often fail in randomized phase III trials despite having favorable data from single-arm phase II studies.⁶ There are a number of reasons for this failure, including poor end point selection to potential patient selection bias.⁶ This has led to a call for randomized phase II studies to better estimate a new drug's efficacy before investing great effort into phase III trials. Nevertheless, there are, at present, two randomized phase III trials investigating the efficacy of upfront bevacizumab for newly diagnosed glioblastoma—one is sponsored by the Radiation Therapy Oncology Group while the other is sponsored by Hoffman-La Roche.

The US Food and Drug Administration's accelerated approval of bevacizumab for progressive glioblastoma is based on the increased objective RR and prolongation of PFS-6 observed in both Genentech-sponsored AVF3708g⁷ and the National Cancer Institute-sponsored 06-C-0064E⁸ trials. OS was not prolonged in either trial; for this reason, bevacizumab was not approved by the European Committee for Medicinal Products for Human Use. Despite the more stringent

regulatory criteria demanded by the European Committee for Medicinal Products for Human Use, European oncologists still believe that bevacizumab is a useful drug for glioblastoma.⁹ This difference in the regulatory requirements between these two agencies is likely rooted in the interpretation of end points in clinical trials. The goal of testing new therapies in a newly diagnosed patient population is different from testing a population who has already experienced disease progression. Therapies for progressive disease are primarily palliative in purpose and, therefore, improvement in quality of life—even without prolongation of OS—should be given a strong consideration. In contrast, treatments given at initial diagnosis are aimed for a cure or prolongation of OS when cure is elusive. Ultimately, the criterion for bevacizumab efficacy in newly diagnosed glioblastoma patients must be prolongation of OS as determined by randomized phase III trials.

The optimal time of bevacizumab administration after a neurosurgical procedure is still unknown. Lai et al⁴ gave bevacizumab to their subjects within 3 to 6 weeks after brain surgery. Because angiogenesis is a critical process in wound healing,^{10,11} premature antiangiogenesis treatment after a craniotomy could lead to serious complications including bleeding, wound dehiscence, and/or secondary infection. The only published studies on the optimal time of introducing bevacizumab before and after major surgery have been performed in patients with colorectal cancer. Of the 56 subjects who prospectively received bevacizumab 5 weeks before and 5 weeks after resection of liver metastases, only one (2%) had bleeding and three (5%) had wound healing complications.¹² In a posthoc analysis of colorectal cancer subjects who received bevacizumab 4 to 9 weeks after abdominal surgery, there were three (1%) of 230 patients with grade 3 or 4 wound healing complications.¹³ The number of hemorrhagic events and wound healing complications at grade 1 or 2 level was unknown.¹³ In the study by Lai et al,⁴ CNS hemorrhage occurred in only two (3%) of 70 patients, and this is similar to the 2% hemorrhage rate in patients who needed early postoperative heparin for thromboembolism after major intracranial surgery.¹⁴ However, four (6%) of 70 patients developed wound infection,⁴ which is higher than the overall 1% to 3% rate reported in the general neurosurgery literature,¹⁵ and bevacizumab's role in contributing to wound infection remains a concern. More studies are needed to determine the best time to administer bevacizumab after resection of glioblastoma.

The optimum bevacizumab dose for the treatment of glioblastoma is unknown. When Stark-Vance¹⁶ first used bevacizumab for progressive glioblastoma, the dosing was empirically adopted from the 5-mg/kg dose, and later 10-mg/kg dose, used for colorectal carcinoma. Meta-analysis of existing literature has been unable to demonstrate a dose response difference, between 5 versus 10 or 15 mg/kg of bevacizumab, with respect to OS, PFS-6, or RR.¹⁷ Similarly, bevacizumab also has an inconsistent dose-response relationship in metastatic colorectal carcinoma,¹⁸ non-small-cell lung cancer,¹⁹ renal cell carcinoma,²⁰ and breast carcinoma.²¹ The reason behind this phenomenon may be due to bevacizumab's mechanism of action. It works by neutralizing vascular endothelial growth factor (VEGF) from the circulation and probably from the extracellular space within the tumor. Because a ligand can interact with multiple receptors, removal of each VEGF ligand can lead to an exponential decrease in VEGF receptor signaling within endothelial cells. Below the required threshold level, the amount of VEGF would be insufficient to trigger angiogenesis and therefore tumor vasculature regresses. This potential threshold effect also suggests that bevacizumab does not need to completely neutralize all VEGF ligands in order to produce clinical benefit. In contrast, VEGF receptor tyrosine kinase inhibitor (TKI) may operate in a linear fashion, requiring the persistent presence of one TKI per receptor, so that antiangiogenesis only occurs when nearly all of the receptors are individually blocked. Recent data from de Groot et al²² demonstrated that bevacizumab, but not sunitinib, blocked the migration of proangiogenic, VEGF receptor 1-expressing CD11b⁺ myeloid cells into orthotopically implanted glioblastoma in mice, resulting in prolonged survival. Furthermore, in a retrospective analysis of patients who failed VEGF receptor TKI, bevacizumab treatment still offered benefit with a response rate of 21% and PFS-6 of 12.5%.²³ Taken together, the data suggest that anti-VEGF therapy may have a greater therapeutic window than VEGF receptor inhibition.

Lai et al⁴ used the Levin's criteria²⁴ in which response to treatment is based on contrast enhancement seen on magnetic resonance imaging (MRI) and changes in neurologic function. Because bevacizumab normalizes vascular permeability of glioblastoma, contrast enhancement disappears, and consequently Levin's criteria²⁴ and Macdonald's criteria²⁵ have become inadequate for assessing treatment response. To address this change in neuroimaging characteristics, Wen et al²⁶ directed the Response Assessment in Neuro-Oncology Working Group to modify Macdonald's criteria. The Response Assessment in Neuro-Oncology criteria²⁶ now take into account the infiltrative pattern of glioblastoma progression by incorporating T2 and fluid-attenuated inversion recovery changes on MRI. This infiltrative pattern of glioblastoma progression,²⁷ as seen on T2 and fluid-attenuated inversion recovery MRI, is due to the underlying biology of malignant glioma cells co-opting and spreading via existing vasculature within the brain,²⁸ which can cause neurologic deficits. With recognition of this pattern of glioblastoma progression during bevacizumab treatment, the next, and major, unanswered question is whether or not early administration of bevacizumab would potentiate the development of glioblastoma invasion. Unfortunately, the molecular mechanisms that trigger this process are incompletely understood, and tumor invasion within the brain remains the biggest challenge facing oncologists treating glioblastomas.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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