Bevacizumab--news from the fast lane?

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The introduction of bevacizumab (Avastin), an antibody to the vascular endothelial growth factor (VEGF), into the repertoire of the medical management of malignant gliomas has influenced the area of glioma treatment quite markedly.

First, after decades of aiming at stopping tumor growth and being quite satisfied with documenting “stable disease,” we are suddenly observing objective response rates at a never-seen frequency exceeding 50%. Admittedly, we have not been convinced by any report that the high response rate translates into a gain in survival. The progression-free survival rate at 6 months—our current gold standard of assessing novel treatments for recurrent glioblastoma—may be in the range of 40%, but similar figures are also achieved with dose-intense regimens of temozolomide.

Second, we may need to reconsider the MacDonald response criteria, which overall have served us well in assessing the efficacy of novel treatments, but which are heavily based on contrast enhancement. Yet in the era of antiangiogenic agents like bevacizumab, which may soon be joined by cilengitide or enzastaurin, altered patterns of recurrence resulting from a change from vessel/VEGF-dependent growth to vessel/VEGF-independent tumor growth may necessitate the development of new response criteria.

Third, and perhaps heralding new patterns of toxicity common to the new class of antiangiogenic agents for glioma treatment, the fear of intratumoral hemorrhages may not have been justified, but craniotomy site dehiscence is increasingly noted as a relevant complication in a minority of glioma patients treated with bevacizumab.

Fourth, the impressive effects of the combination of bevacizumab and irinotecan were unexpected and initially suggested strong synergistic potential for two agents that appeared to have limited activity when administered alone. Yet the results from the first randomized trial of bevacizumab alone versus bevacizumab plus irinotecan presented by Cloughesy and colleagues at the 2008 American Society for Clinical Oncology meeting in Chicago appear to confirm the suspicion that irinotecan is contributing little to the overall effect of this novel regimen. Along these lines, switching patients who progress under bevacizumab and irinotecan to another bevacizumab-containing regimen seems to offer little hope for response.

In the current issue of Neuro-Oncology, Ingeborg Fischer and colleagues report on their investigation into histological features of malignant gliomas after treatment with bevacizumab. Five paired tissues obtained prior to and after exposure to bevacizumab were available and compared with four paired tissues from patients never exposed to bevacizumab. Decreased vessel density correlated with radiographic responses to bevacizumab, whereas the levels of VEGF-A and various other histological and immunochemistry parameters did not. While the case numbers of this study are low, such tissues are difficult to assemble, and approaches as outlined here are very important. They are likely to result in the identification of biomarkers associated with response, or the lack thereof, to experimental brain tumor treatments and will help to design a scientific basis and possibly new endpoints for upcoming clinical trials, notably in the emerging field of novel antiangiogenic agents.

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References