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Editorial

Angiogenesis inhibition for glioblastoma at the edge: beyond AVAGlio and RTOG 0825

The standard of care for patients with newly diagnosed glioblastoma was redefined in 2005 when the EORTC NCIC trial showed the superiority of concomitant and maintenance temozolomide (TMZ) and radiotherapy over radiotherapy alone. Since then, numerous efforts have been made to build on this new regimen, mostly testing the hypotheses that prolonged administration of TMZ or inhibition of angiogenesis will provide a survival benefit. The most promising anti-angiogenesis agent, bevacizumab, is a monoclonal antibody that targets vascular endothelial growth factor (VEGF). Bevacizumab produced encouraging response rates and progression-free survival data at 6-month landmark analyses. Other VEGF-targeting agents, such as cediranib or VEGF trap, have shown less convincing results in their safety, tolerability, and efficacy.

Bevacizumab's conditional approval by the FDA in 2009 for patients with recurrent glioblastoma was linked to future demonstrations of its efficacy in prospective trials in newly diagnosed patients. Two such trials were performed, largely in parallel—one by the RTOG (RTOG-0825) in the United States, and one by Roche (AVAGlio), mostly in Europe.[1] Rather mature results from both trials were presented at the 2013 American Society of Clinical Oncology meeting in Chicago.[2,3] The results from both trials provide a uniform picture: Progression-free survival was significantly prolonged, and quality of life was preserved in the AVAGlio trial, but not in RTOG-0825. Overall survival was not improved, but safety and tolerability were acceptable. The subgroup analyses available so far do not identify specific subgroups of patients who particularly benefitted from bevacizumab, and a comparison of both trials suggests no major effect of cross-over at progression.

As it stands, the overall survival data from both trials do not support the routine use of bevacizumab in the upfront treatment setting. This does not exclude the possibility that subgroup and molecular analyses will reveal a beneficial effect of bevacizumab in subgroups of patients with glioblastoma. Another important question is whether bevacizumab should remain available for patients with recurrent disease because it provides quality of life and progression-free survival benefits. Answers to other important questions are also pending. Are we sure that the gain in progression-free survival reflects a true impact on disease activity and not just altered imaging? If there is a true modification of disease biology, do some tumors become more invasive and more malignant? Is maintaining quality of life early in the course of disease worth paying the price of rapid clinical deterioration later on, possibly based on induced refractoriness to all available further lines of treatment? Answering the latter question and deriving new strategies to prevent resistance or the escape from VEGF inhibition appear to be the most promising roads to success for adding VEGF inhibitors to current treatment paradigms for glioblastoma.

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