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

Weller, M ; Yung, W K A

DOI: https://doi.org/10.1093/neuonc/not106

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) in addition to radiotherapy over radiotherapy alone. Since then numerous efforts to build on this new regimen have been explored, mostly testing the hypotheses that prolonged administration of TMZ or inhibition of angiogenesis will provide survival benefit. The most promising anti-angiogenesis agent was bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF). This was based on encouraging response rates and progression-free survival data upon landmark analyses at 6 months. Other VEGF-targeting agents such as cediranib or VEGF trap were less convincing, both regarding safety and tolerability as well as efficacy.

The conditional approval by the FDA in 2009 for bevacizumab in patients with recurrent glioblastoma was linked to the future demonstration of its efficacy in prospective trials in patients with newly diagnosed disease. Two such trials were performed largely in parallel, one by the RTOG (RTOG-0825) in the US, and one by Roche (AVAGlio), largely in Europe (1). Rather mature results from both trials were presented at the 2013 ASCO Meeting in Chicago (2,3). The results from both trials provide a rather uniform picture: Progression-free survival is significantly prolonged, quality of life during progression-free survival is preserved in the AVAGlio trial, but not in RTOG-0825, overall survival is not improved, and safety and tolerability are acceptable. Subgroup analyses, as available so far, do not identify specific subgroups of patients with a particularly convincing benefit from bevacizumab, and the comparison of both trials suggests no major impact 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 setting. This does not exclude the possibility that subgroup and molecular analyses may show 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 where it provides quality of life benefit for many patients and probably a progression-free survival benefit, too. 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 prize 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 escape from VEGF inhibition appear to be the most promising road to success for adding VEGF inhibitors into current treatment paradigms for glioblastoma.

Michael Weller, MD

Associate Editor, EANO

Al Yung, MD

Editor-in-Chief

References

1 Chinot O, Wick W, Mason W, Henriksson R, Saran F, Nishikawa R, Hilton M, Abrey L, Cloughesy T. Phase III trial of bevacizumab added to standard radiotherapy and temozolomide for newly diagnosed glioblastoma: mature progression-free survival and preliminary overall survival results in AVAGlio. Neuro-Oncology 2012;14:Suppl 6(vi101-vi105)

2 Gilbert MR, Dignam J, Won M, Blumenthal DT, Vogelbaum MA, Aldape KD, Colman H, Chakravarti A, Jeraj R, Armstrong TS, Wefel JS, Brown PD, Jaeckle KA, Schiff D, Atkins JN, Brachman D, Werner-Wasik M, Komaki R, Sulman EP, Mehta MP. RTOG 0825: Phase III double-blind placebo-controlled trial evaluating bevacizumab (Bev) in patients (Pts) with newly diagnosed glioblastoma (GBM). J Clin Oncol 2013;31:Suppl(abstr 1)

3 Wick W, Cloughesy TF, Nishikawa R, Mason W, Saran F, Henriksson R, Hilton M, Kerloeguen Y, Chinot OL. Tumor response based on adapted Macdonald criteria and assessment of pseudoprogression (PsPD) in the phase III AVAglio trial of bevacizumab (Bv) plus temozolomide (T) plus radiotherapy (RT) in newly diagnosed glioblastoma (GBM). J Clin Oncol 2013;31:Suppl(abstr 2002)