Editorial

Bevacizumab in recurrent glioblastoma

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In May 2009, the U.S. Food and Drug Administration granted accelerated approval for the use of bevacizumab in patients with progressive glioblastoma (GBM), the most common malignant primary brain tumor in adults (1). Neovascularization is a morphologic hallmark of GBM, driven in part by vascular endothelial growth factor A (VEGF-A) which is targeted and neutralized by bevacizumab. Favorable results in early uncontrolled studies on the use of bevacizumab as salvage treatment in GBM led to wider use and further investigation in recurrent WHO grade II and III gliomas, which often exhibit enhancement akin to that seen in GBM. Until recently, only retrospective uncontrolled studies on the effect of bevacizumab in recurrent lower grade gliomas have been reported; van den Bent and colleagues offer results of the first and largest randomized trial in which the use of bevacizumab alone or in combination with maintenance-dose temozolomide was investigated in patients with a first and contrast-enhancing recurrence of WHO grade II or III astrocytoma (2).

In this phase 2 trial, 155 patients were enrolled. A total of 101/155 (65%) patients were determined to have a mutation in isocitrate dehydrogenase (*IDH*). Acceptable prior treatment included radiation only, temozolomide or PCV alone, or radiation with concurrent temozolomide. High-dose radiation, stereotactic radiation, and brachytherapy were only allowed if treatment-induced necrosis was ruled out by histologic confirmation of tumor recurrence, though repeat surgery was otherwise not required for enrollment. Patients at high-risk of developing adverse effects such as those with a history of thrombosis, hemorrhage, clinically significant vascular disease, or recent gastrointestinal complications were also excluded. The primary endpoint was overall survival (OS) at 12 months, and secondary endpoints included best overall response, median OS, Kaplan-Meier estimates of progression-free survival (PFS) and OS, safety profile, and patient-oriented outcomes such as quality of life and neurocognitive status. Recognizing the prognostic effect of mutations in IDH 1 or 2, the authors included prospectively defined exploratory subgroup analysis according to *IDH* mutational status.

The authors found no difference in response rate, OS, or PFS with the combination of bevacizumab and temozolomide compared to temozolomide alone, and despite exclusion of high-risk groups there was a higher rate of serious adverse events including but not limited to hematological, infectious, allergic, and embolic complications in the combination group. One limitation of this study, which the authors acknowledged, was that it was underpowered for formal comparison; however, enrollment was high and the allocation between the two groups was well-balanced.

The results of this study are preceded by a number of randomized trials evaluating the efficacy of bevacizumab in newly diagnosed and recurrent GBM that have demonstrated similar OS and yet improved PFS when bevacizumab was added to standard care treatment (3-5). This contrast may be explained by vascular gene expression patterns in lower-grade gliomas which are less severe than GBM but distinct from normal vessels (6). In

particular, IDH wild-type gliomas are molecularly distinct from IDH-mutated gliomas in such a way that results in increased angiogenesis due to upregulation of multiple genes including *ANGPT2*, *MCAM*, *WEE1*, *SPRY1*, *NOX4*, and *SERPINH1* which are similarly upregulated in GBM vasculature (7). More than half the per-protocol population in TAVAREC harbored a mutation in IDH, which possibly influenced the overall results.

While a clear anti-tumor effect by bevacizumab is unlikely to ever be shown, the drug may still be useful as a steroid-sparing agent in selected cases of highly symptomatic brain edema. While the findings do not justify a phase 3 study, further exploration of bevacizumab in IDH wild-type WHO grade II and III gliomas ought to be considered; however, we must also continue our efforts to identify more effective and better tolerated agents against these tumors.

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Footnote

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References

1. Cohen MH, Shen YL, Keegan P, et al. FDA drug approval summary: bevacizumab (Avastin) as treatment of recurrent glioblastoma multiforme. Oncologist 2009;14:1131-8.
2. van den Bent MJ, Klein M, Smits M, et al. Bevacizumab and temozolomide in patients with first recurrence of WHO grade II and III glioma, without 1p/19q co-deletion (TAVAREC): a randomised controlled phase 2 EORTC trial. Lancet Oncol 2018;19:1170-9.
3. Taal W, Oosterkamp HM, Walenkamp AM, et al. Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): a randomised controlled phase 2 trial. Lancet Oncol 2014;15:943-53.
4. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med 2014;370:699-708.
5. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. N Engl J Med 2014;370:709-22.
6. Zhang L, He L, Lugano R, et al. IDH mutation status is associated with distinct vascular gene expression signatures in lower-grade gliomas. Neuro Oncol 2018;20:1505-16.
7. Dieterich LC, Mellberg S, Langenkamp E, et al. Transcriptional profiling of human glioblastoma vessels indicates a key role of VEGF-A and TGFbeta2 in vascular abnormalization. J Pathol 2012;228:378-90.

