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Predicting glioblastoma response to bevacizumab through marker profiling?

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See the article by Baumgarten et al, on pages 173–183.

Bevacizumab is a humanized monoclonal antibody directed against the vascular endothelial growth factor (VEGF). It has been approved for antiangiogenic treatment in various cancers including colorectal carcinoma[1] and has received accelerated approval for glioblastoma in the United States. Despite 2 initially promising phase 2 trials for bevacizumab in recurrent glioblastoma,[2,3] 2 large randomized phase 3 clinical trials in 2014 only showed a benefit in progression-free survival and no impact on overall survival in newly diagnosed glioblastoma.[4,5] In recent years, there have been extensive discussions about whether there is a specific group of glioblastoma patients who will benefit most from treatment with bevacizumab.

In this issue of *Neuro-Oncology*, Baumgarten et al[6] correlated the clinical response to bevacizumab treatment with the expression levels of VEGF and its receptors and co-receptors. Expression levels of these markers were not correlated with survival in their cohort of bevacizumab-treated patients. Furthermore, they showed that the expression levels of VEGF and its receptors were not correlated with patient survival in a second large cohort of patients who were largely not treated with antiangiogenic treatments. The main limitation of this study is the relatively small number of patients in the group treated with bevacizumab. Acknowledging this limitation, however, this study did not find evidence that these plausible biomarkers helped decide which patient should be treated with bevacizumab. Furthermore, a group from the Netherlands, who used circulating endothelial cells as a marker for vascular damage from bevacizumab therapy,[7] found that vascular injury was increased during antiangiogenic treatment, but the amount of circulating endothelial cells did not predict the response to bevacizumab. Together with the results of the current study, it is likely that the amount of VEGF receptor-positive vasculature and the damage through antiangiogenic therapy do not predict survival after treatment with bevacizumab.

Is there a biological marker to identify glioblastoma patients who might benefit from bevacizumab treatment, or do we have trouble assessing these circulating biomarkers? A recent study from Marseille suggested that in patients with recurrent high-grade glioma high matrix metalloproteinase (MMP)2 plasma levels demonstrated prolonged tumor control and survival when bevacizumab—but not cytotoxic agents—was used.[8] The same authors recently provided evidence for relevant changes in the plasma levels of MMP during the course of therapy that were related to progression, thus making a prospective, well-planned analysis necessary.[9]

In the tumor tissue, an analysis from the AVAglio trial biomarker cohort by Sandmann et al suggested that bevacizumab might confer a survival benefit for patients with proneural *IDH* wild-type tumors.[10,11] Of note, this generally poorly performing *IDH* wild-type proneural group had the shortest survival of all groups in the AVAglio trial. These data need confirmation, possibly by analyzing data from the RTOG-0825 trial or preferably from a prospective study.

A different analysis of the RTOG-0825 trial, which found a multigene predictor model that defines a subgroup with a mesenchymal differentiation, was presented as an abstract at the American Society of Clinical Oncology in 2013. Patients in this subgroup showed worse survival when treated with bevacizumab as compared with the placebo group.[12]

Other studies suggest that the expression patterns of VEGF receptors are more complex and are not restricted to the tumor vasculature. An increasing number of groups have reported the expression of VEGFR-2 directly on glioblastoma cells.[13,14] Analyses from our group support the idea that VEGFR-2 expression on the glioblastoma tumor cells, rather than expression on the tumor-associated vessels, might play a role in identifying subgroups that show a differential response to bevacizumab treatment.[15] One subgroup with adverse outcome after treatment with bevacizumab was defined by inactivating *PTEN* mutations and coexistent VEGFR-2 expression on glioblastoma tumor cells.

In conclusion, finding a population of glioblastoma patients who benefit from bevacizumab treatment has been very challenging and should probably focus more on expression patterns of the tumor cells themselves rather than the tumor-associated

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endothelial cells. Up to now, there have been only a few studies in all cancers suggesting specific, molecularly defined groups that might benefit from bevacizumab treatment. If we can define a validated subgroup that benefits from bevacizumab treatment, however, this will change how we treat glioblastoma patients and improve the personalization of therapy for specific patients.

Conflict of interest statement. No conflicts of interest to disclose.

References

1. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*. 2004;350(23):2335–2342.
2. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol*. 2009;27(28):4733–4740.
3. Kreisl TN, Kim L, Moore K, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. *J Clin Oncol*. 2009;27(5): 740–745.
4. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N Engl J Med*. 2014;370(8):709–722.
5. Gilbert MR, Sulman EP, Mehta MP. Bevacizumab for newly diagnosed glioblastoma. *N Engl J Med*. 2014;370(21):2048–2049.
6. Baumgarten P, Blank A, Franz K, et al. Differential expression of vascular endothelial growth factor (VEGF)-A, its receptors VEGFR-1, -2 and -3 and co-receptors Neuropilin (NRP)-1 and -2 does not predict bevacizumab response in human astrocytomas. *Neuro Oncol*. 2016;18(2):173–183.
7. Beije N, Kraan J, Taal W, et al. Prognostic value and kinetics of circulating endothelial cells in patients with recurrent glioblastoma randomised to bevacizumab plus lomustine, bevacizumab single agent or lomustine single agent. A report from the Dutch Neuro-Oncology Group BELOB trial. *Br J Cancer*. 2015;113(2):226–231.
8. Tabouret E, Boudouresque F, Barrie M, et al. Association of matrix metalloproteinase 2 plasma level with response and survival in patients treated with bevacizumab for recurrent high-grade glioma. *Neuro Oncol*. 2014;16(3):392–399.
9. Tabouret E, Boudouresque F, Farina P, et al. MMP2 and MMP9 as candidate biomarkers to monitor bevacizumab therapy in high-grade glioma. *Neuro Oncol*. 2015;17(8):1174–1176.
10. Phillips HS, Kharbanda S, Chen R, et al. Molecular subclasses of high-grade glioma predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis. *Cancer Cell*. 2006;9(3):157–173.
11. Sandmann T, Bourgon R, Garcia J, et al. Patients With Proneural Glioblastoma May Derive Overall Survival Benefit From the Addition of Bevacizumab to First-Line Radiotherapy and Temozolomide: Retrospective Analysis of the AVAglio Trial. *J Clin Oncol*. 2015;33(25):2735–2744.
12. Sulman EP, Won M, Blumenthal DT, et al. Molecular predictors of outcome and response to bevacizumab (BEV) based on analysis of RTOG 0825, a phase III trial comparing chemoradiation (CRT) with and without BEV in patients with newly diagnosed glioblastoma (GBM). *J Clin Oncol*. (Meeting Abstracts) 2013;31:LBA2010.
13. Steiner HH, Karcher S, Mueller MM, Nalbantis E, Kunze S, Herold-Mende C. Autocrine pathways of the vascular endothelial growth factor (VEGF) in glioblastoma multiforme: clinical relevance of radiation-induced increase of VEGF levels. *J Neurooncol*. 2004; 66(1–2):129–138.
14. Hamerlik P, Lathia JD, Rasmussen R, et al. Autocrine VEGF-VEGFR2-Neuropilin-1 signaling promotes glioma stem-like cell viability and tumor growth. *J Exp Med*. 2012;209(3):507–520.
15. Kessler T, Sahm F, Blaes J, et al. Glioma cell VEGFR-2 confers resistance to chemotherapeutic and antiangiogenic treatments in PTEN-deficient glioblastoma. *Oncotarget*. 2015;6(31):31050–31068.