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Bevacizumab and Recurrent Malignant Gliomas: A European Perspective

TO THE EDITOR: Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF; Avastin, Genentech, South San Francisco, CA, and Roche, Basel, Switzerland), was approved in 2009 by the US Food and Drug Administration for the treatment of recurrent glioblastoma. The basis for this accelerated approval was uncontrolled phase II trials with a total of 215 patients; a single-arm phase II trial of bevacizumab with irinotecan added at progression and a randomized phase II trial of the same regimen or first-line treatment with the combination of bevacizumab and irinotecan.[1] Even before US Food and Drug Administration approval, bevacizumab was widely used in this indication in the United States and in some European countries, and is currently given off-label for patients with newly diagnosed high-grade glioma. The marketing application to the European Medicines Agency was rejected November 2009. European Medicines Agency felt that the still existing question about activity in recurrent glioblastoma prevented registration with the given data.

It is remarkable that over the 3 years since the first report on the efficacy of bevacizumab in recurrent glioblastoma only a few hundred patients with recurrent glioblastoma were accrued into reported prospective clinical trials, while already thousands of patients have been treated off-label. Despite the rapid US Food and Drug Administration approval, numerous questions with regard to dosing, timing, and efficacy remain. Opportunities to adequately test this promising agent were missed or avoided. This has already led to considerable national differences with respect to access and reimbursement of bevacizumab for patients with glioma.

Based on these reports and our own clinical experience, bevacizumab is without doubt a useful drug in recurrent glioma. However, the uncontrolled trials that evaluated bevacizumab and irinotecan versus bevacizumab alone (and the addition of irinotecan at progression) leave many questions unanswered.

Was the right end point used? The primary end point was the rate of patients alive and free of progression at 6 months, a surrogate end point that had been considered valuable for cytotoxic agents, but is inappropriate when studying antiangiogenic agents that will modify vascular permeability and thus the imaging response assessment based on contrast enhancement.[2,3] VEGF was initially also referred to as vascular permeability factor[4] and it is well recognized that VEGF is a major mediator of blood-brain barrier disturbance. Inhibiting VEGF signaling decreases tumor enhancement even without an intrinsic antitumor effect. Indeed, clinical progression has been observed in the absence of evident tumor progression on T1-gadolinium–enhanced magnetic resonance imaging with T2-weighted sequences showing tumor extension without disruption of the blood-brain barrier.[5] The substantial differences in response rates when independently assessed by the investigators (39% and 46% for bevacizumab and bevacizumab with irinotecan, respectively), by a sponsor-mandated central radiologic review (28% and 38%),[6] and finally by the US Food and Drug Administration (20% and 26%),[7] illustrate the difficulties and limitations of objective response as the primary end point for outcome to treatment with antiangiogenic agents. Of note, an international panel is currently revisiting the response criteria for brain tumors,[8] and has judged the response rate and progression-free survival inappropriate end points for anti-VEGF signaling treatments.[2]

Does treatment with bevacizumab increase survival? The reported survival times of 8 to 9 months correspond to what had been reported as median survival after progression for patients treated with radiotherapy alone,[9] or radiotherapy and concomitant temozolomide before the availability of bevacizumab, and needs to be compared with 6 to 7 months in many bluntly negative trials on recurrent glioblastoma.[10] The disappointing disparity between the high response rates reported for bevacizumab in recurrent glioblastoma and the modest at best survival benefit may partly be explained by the limited effect on the tumor mass itself.[11] The obvious question is whether the effects of bevacizumab by and large resemble that of dexamethasone and should therefore be named pseudoresponse.[2] The duration of a response, and ultimately overall survival, are probably more accurate indicators of the therapeutic activity of a compound. The data reported in *Journal of Clinical Oncology*[6] remain immature, with a minimum follow-up of only 6 months and just half of the patients having died at the time of analysis in September 2007, 2 years before publication. No update has been made available yet.

Do we know the optimal bevacizumab dose? Stark-Vance's[12] initial experience of high response rates in recurrent glioma with bevacizumab used a dose of 5 mg/kg every 2 weeks; nevertheless, the dose of bevacizumab in subsequent trials was doubled without further investigations or justification. One cannot rule out that the higher dose of bevacizumab actually increases toxicity and complication rate, this not even considering the economical impact.

Should bevacizumab be given as a single agent or in combination? In most indications, anti-VEGF agents had to be combined with classical cytotoxic drugs to demonstrate activity. Based on overall survival, this trial shows no added benefit of irinotecan when looking at overall survival, and a marginal improvement in response rate. Yet, irinotecan is largely responsible for the toxicity of the regimen.[6] Anti-VEGF signaling drugs may increase the penetration of co-medication into tumors by reducing the intratumoral pressure and through normalization of abnormal and nonfunctional capillary networks. As a severe unwanted effect, drug penetration might be decreased by restoring the blood-brain barrier.[12] Examples of the importance of well-designed trials included Randomized Phase III Study of Capecitabine, Oxaliplatin, and Bevacizumab With or Without Cetuximab in Advanced Colorectal Cancer (CAIRO 2), where the use of bevacizumab in the adjuvant setting did not translate into improved outcome, and the simultaneous administration of both bevacizumab and cetuximab even seemed to be detrimental.[13]

Do we know the best timing of bevacizumab? A source of concern is the rebound edema after discontinuation of bevacizumab. Because of this, salvage therapy after failure of bevacizumab has been particularly challenging, and no drug or regimen either alone or in

combination with bevacizumab has demonstrated activity.[14] Should other treatments therefore be applied before initiating bevacizumab while withholding bevacizumab as long as possible? This will also impact the design of future trials in recurrent glioblastoma.

What is the significance of the gliomatosis cerebri like pattern of recurrence that has been observed in some of the bevacizumab and other VEGF signaling pathway interfering agents? Recent experience suggests induction of a more aggressive and diffusely invasive tumor phenotype as a mechanism of escape to anti-VEGF therapy.[5,14] The clinical impact of this is yet unclear, but at least some patients show cognitive deterioration.

Lastly, the accelerated approval of bevacizumab is likely to influence future drug development. It encourages cheap(er) drug development strategies based on phase II protocols, promoting pre-registration widespread clinical use rather than conclusive phase III trials with well-considered end points showing clear clinical benefit.

There is no one generally agreed standard of care in recurrent glioblastoma but there are an array of treatment options largely based on level III evidence or expert opinion. Although ideally patients are enrolled into clinical trials, the numerous ongoing uncontrolled bevacizumab combination trials are unlikely to answer any of the most burning questions. From the patient's perspective, any clinical improvement leading to improved quality of life and with the least toxicity is of benefit. Such an effect is observed with bevacizumab in particular in patients with symptomatic peritumoral edema causing deficits and requiring steroids. But we lack properly designed trials to determine how to best and most economically use the agent. The widespread use of bevacizumab even before the registration impedes the possibility to conduct the appropriate trials that would answer these questions. Instead of conducting yet another uncontrolled study, attempts should be made to develop well-designed protocols that give answers to pertinent clinical questions outlined above.

Wolfgang Wick
Department of Neurooncology, National Center for Tumor Disease and German Cancer Research Center, Heidelberg, Germany

Michael Weller
Department of Neurology, University Hospital Zurich, Switzerland

Martin van den Bent
Department of Neuro-Oncology, Daniel den Hoed Cancer Center/Erasmus University Hospital Rotterdam, Rotterdam, the Netherlands

Roger Stupp
Centre Hospitalier Universitaire Vaudois and University of Lausanne, Departments of Oncology and Neurosurgery, Lausanne, Switzerland

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REFERENCES

1. 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 27:740-745, 2009
2. van den Bent MJ, Vogelbaum MA, Wen PY, et al: End point assessment in gliomas: Novel treatments limit usefulness of classical Macdonald's criteria. J Clin Oncol 27:2905-2908, 2009
3. Chen W, Delaloye S, Silverman DH, et al: Predicting treatment response of malignant gliomas to bevacizumab and irinotecan by imaging proliferation with [18F] fluorothymidine positron emission tomography: A pilot study. J Clin Oncol 25:4714-4721, 2007
4. Senger DR, Galli SJ, Dvorak AM, et al: Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. Science 219:983-985, 1983
5. Norden AD, Young GS, Setayesh K, et al: Bevacizumab for recurrent malignant gliomas: Efficacy, toxicity, and patterns of recurrence. Neurology 70:779-787, 2008
6. Friedman HS, Prados MD, Wen PY, et al: Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol 27:4733-4740, 2009
7. Center for Drug Evaluation and Research: Summary Minutes of the Oncologic Drugs Advisory Committee March 31, 2009. Washington, DC, US Food and Drug Administration, 2009 http://www.fda.gov/ohrms/dockets/ac/09/minutes/2009-4427m1-final.pdf
8. Macdonald DR, Cascino TL, Schold SC, et al: Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 8:1277-1280, 1990
9. Lamborn KR, Yung WK, Chang SJ, et al: Progression-free survival: An important end point in evaluating therapy for recurrent high-grade gliomas. Neuro-Oncol 10:162-170, 2008
10. Wick W, Puduvalli VK, Chamberlain M, et al: Enzastaurin versus lomustine in the treatment of recurrent intracranial glioblastoma: A phase III study. J Clin Oncol doi:10.1200/JCO.2009.23.2595
11. Kamoun WS, Ley CD, Farrar CT, et al: Edema control by cediranib, a vascular endothelial growth factor receptor-targeted kinase inhibitor, prolongs survival despite persistent brain tumor growth in mice. J Clin Oncol 27:2542-2552, 2009
12. Stark-Vance V: Bevacizumab and CPT-11 in the treatment of relapsed malignant glioma. Neuro-Oncol 7:369, 2005 (suppl; abstr 342)
13. Tol J, Koopman M, Rodenburg CJ, et al: A randomised phase III study on capecitabine, oxaliplatin and bevacizumab with or without cetuximab in first-line advanced colorectal cancer, the CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG): An interim analysis of toxicity. Ann Oncol 19:734-738, 2008
14. Norden AD, Drappatz J, Muzikansky A, et al: An exploratory survival analysis of anti-angiogenic therapy for recurrent malignant glioma. J Neurooncol 92:149-155, 2009

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