Open access • Journal Article • DOI:10.1200/JCO.2009.26.9027

Bevacizumab and recurrent malignant gliomas: a European perspective.

Wolfgang Wick, Michael Weller, Martin J. van den Bent, Roger Stupp

Institutions: University of Zurich, Erasmus University Rotterdam, University of Lausanne

Published on: 20 Apr 2010 - Journal of Clinical Oncology (American Society of Clinical Oncology)

Topics: Bevacizumab

Bevacizumab and recurrent malignant gliomas: a European perspective

Wick, W; Weller, M; van den Bent, M; Stupp, R

Letter to the Editor

to Friedman et al. J Clin Oncol 27:4733-4740, 2009

Avastin and recurrent malignant gliomas: a European perspective

Wolfgang Wick[1], Michael Weller[2], Martin van den Bent[3], Roger Stupp[4]

[1]Department of Neurooncology, National Center for Tumor Disease and German Cancer Research Center, Heidelberg, Germany, [2]Department of Neurology, University Hospital Zurich, Switzerland, [3]Department of Neuro-Oncology, Daniel den Hoed Cancer Center/Erasmus University Hospital Rotterdam, Rotterdam, The Netherlands, [4]Centre Hospitalier Universitaire Vaudois and University of Lausanne, Departments of Oncology and Neurosurgery

Correspondence:

Roger Stupp, MD
Department of Neurosurgery
University Hospital (CHUV)
Rue du Bugnon 46
CH-1011 Lausanne / Switzerland

Phone: +41-21-314-0156
Fax: +41-21-314-0737
Email: Roger.Stupp@chuv.ch

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 Food and Drug Administration (FDA) for the treatment of recurrent glioblastoma. The basis for this accelerated approval were 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 upfront treatment with the combination of bevacizumab and irinotecan.[2] Even prior to FDA approval bevacizumab was widely used in this indication in the US, and variably in European countries and is currently given on an off-label protocol for newly diagnosed high-grade glioma patients. The marketing application to European Medicines Agency (EMEA) is still under review.

It is remarkable that over the three years since the first report on efficacy of bevacizumab in recurrent glioblastoma only a few hundred recurrent glioblastoma patients were accrued into reported prospective clinical trials, while already thousands of patients have been treated off-label. Despite the rapid FDA 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 glioma patients.

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

First, was the right endpoint used? The primary endpoint was the rate of patients being alive and free of progression at 6 months (PFS6), a surrogate endpoint 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.[3,4] VEGF was initially also referred to as vascular permeability factor (VPF)[5] and it is well recognized that VEGF is a major mediator of blood brain barrier disturbance. Inhibiting VEGF signalling decreases tumor enhancement even without an intrinsic anti-tumor effect. Indeed, clinical progression has been observed in the absence of evident tumor progression on T1-gadolinium-enhanced magnetic resonance imaging (MRI) with T2-weighted sequences showing tumor extension without disruption of the blood-brain

barrier.[6] 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 radiological review (28% and 38%)[1] and finally by the FDA (20% and 26%)[7] illustrate the difficulties and limitations of objective response as the primary endpoint for outcome to treatment with anti-angiogenic agents. Of note, an international panel is currently revisiting the response criteria for brain tumors[8], and has judged response rate for anti-VEGF signaling treatments inappropriate.[3]

Secondly, does treatment with bevacizumab increase survival? The reported survival times of 8-9 months correspond to what had been reported as median survival after progression for patients treated with radiotherapy alone, or radiotherapy and concomitant temozolomide[9] before the availability of bevacizumab and needs to be compared to 6-7 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 at best modest survival benefit may be partly explained a 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 'pseudo-response'.[3] The duration of a response and ultimately overall survival are to be considered more accurate indicators of the therapeutic activity of a compound. The data reported in this *Journal*[1] remains 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, two years before publication (!). No update has been made available yet.

Thirdly, do we know the optimal bevacizumab dose? Stark-Vance's initial experience on of high response rates in recurrent glioma with bevacizumab used a dose of 5 mg/kg every 2 weeks[12], 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.

Fourthly, should bevacizumab be given as a single agent or in combination ? In most indications anti-VEGF agents are to be combined with classical cytotoxic drugs. Based on overall survival, the current trial shows little added benefit of irinotecan when looking at overall survival, and a marginal improvement in response rate. Yet, irinotecan adds to the toxicity of the regimen.[1] Anti-VEGF signaling drugs may increase the penetration of co-medication into tumors by reducing the intratumoral pressure and through normalization of abnormal and non-functional capillary

networks, or is drug penetration decreased by restoring the blood-brain barrier ? [12] Examples of the importance of well-designed trials can be derived from the experience in colorectal cancer, where the use of bevacizumab in the adjuvant setting did not translate into improved outcome, and the simultaneous administration of both bevacizumab and cetuximab seems to even be detrimental.[13]

Fifthly, 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, no drug or regimen either alone or in combination with bevacizumab has demonstrated activity.[14] Should other treatments therefore be applied prior to initiating bevacizumab while withholding bevacizumab as long as possible? This will also impact the design of future trials in recurrent glioblastoma.

Sixth, 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.[6,14]

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, pre-registration wide-spread clinical use rather than conclusive phase III trials.

There is no one generally agreed standard of care in recurrent glioblastoma, but an array of treatment options largely based on level III evidence. Ideally patients are enrolled into clinical trials. The numerous ongoing uncontrolled bevacizumab combination trials are unlikely to answer 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 how to best and most economically use the agent. The widespread use of bevacizumab even prior to the registration impedes on 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 (see above).

References

1. 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

2. 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

3. 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

4. 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

5. 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

6. Norden AD, Young GS, Setayesh K, et al: Bevacizumab for recurrent malignant gliomas: efficacy, toxicity, and patterns of recurrence. Neurology 70:779-787, 2008

7. Summary Minutes of the Oncologic Drugs Advisory Committee March 31, 2009. In: Center for Drug Evaluation and Research ed. Washington: Food and Drug Administration; 2009

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 in press

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. 2005;7:369 {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