Reviewer's report

Title: Is Symptom Reduction by Angiogenesis Inhibitors in GBM Patients Without a Price?

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Reviewer: Jeremy Rich

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This manuscript provides a summary of concepts regarding the use of bevacizumab for the treatment of glioblastomas. As bevacizumab has undergone a number of recent clinical trials with some indication of efficacy, critical analysis is indicated. This research group includes an important group of contributors to Neuro-Oncology but I do not think that the manuscript is currently ready for publication. With additional revision, this manuscript may have benefit.

Major Compulsory Revisions

1. The manuscript as written is a combination of review, conjecture, clinical anecdote, and brief histopathologic analysis. The authors are correct that definitive statements as to the benefit of bevacizumab require systematic analysis. It is therefore suboptimal to include undeveloped remarks from the authors’ clinical experience (e.g. “Typically, several of our patients return to normal activities of daily living shortly after bevacizumab therapy, while being severely impaired before, even under corticosteroid therapy.”). I would ask the authors to report more formally their clinical experience with number of patients, diagnosis, status, side effect profile, and outcome.

2. In a similar fashion, the pathologic analysis should be better presented. Figure 2 is not controlled and does not directly measure the patency of the neurovascular unit. The authors show Figure 3 with tumor cells distant from the original site after bevacizumab treatment. This is difficult to interpret as distant tumor cells are commonly detected in glioma patients independent from bevacizumab treatment. I agree with the authors that the work by several groups (most notably by Du et al. in Cancer Cell 2008 which should be referenced) that VEGF blockade may promote invasion is a concern. The authors may speculate that this is a problem but they should either provide controlled data or leave it for future study.

3. The title and running title are overly speculative. First, the authors have not discussed some of the biggest potential problems with bevacizumab (e.g. cost and risk of hemorrhage). Second, such bold questions deserve either a better answer or should be toned down.

4. The authors are incorrect that overall survival has not been reported. Vredenburgh et al. (J Clin Oncol. 2007) reported overall survival as has the very recent NCI report (Kreisl et al. J Clinl Oncol. 2008) and Norden et al. (J Neurooncol. 2008). The authors should also consider including discussion of the
abstracts presented at the annual ASCO meetings, including more fully the multi-institutional trial of bevacizumab vs. bevacizumab and irinotecan that was briefly discussed.

5. I would advocate a discussion of anti-angiogenics in a more sophisticated manner. Bevacizumab and AZD2171 have shown dramatically different clinical results that suggest ligand neutralizing antibodies and low molecular weight receptor antagonists are not phenotypically identical.

6. The discussion of bevacizumab’s effects on chemotherapy delivery is important but the literature should be approached with caution. The authors own study (Ref. 50) is performed with xenografts that do not invade or develop the neurovascular unit (e.g. the BBB) like human gliomas. Also, Mathieu et al. (Neoplasia 2008) directly test bevacizumab and temozolomide with different effects (Jahnke et al. with carboplatin). The bigger question may be whether irinotecan has benefit or not in the regimen with bevacizumab.

7. The authors start with the discussion of how tumor vasculature in brain tumors differs from systemic cancers but then they reference those tumor types for conclusions while missing a number of bevacizumab trials (12 to be exact) in the brain [Kreisl et al. 2008; Zuniga et al. 2009; Lai et al. 2008; Norden et al (J. Neurooncol) 2008; Poulsen 2009; Desjardins 2008; Fischer. 2008; Ali 2008; Kang 2008; Bokstein 2008; Benesch 2008; Vredenburgh (Clin Cancer Res.) 2007]. These trials deserve greater attention as the cumulative effect suggests that there is some biological effect of bevacizumab but the degree is uncertain.

8. A double blinded placebo controlled study would be great but this is unrealistic with an intravenous therapy in the brain tumor population (also the radiographic effects are commonly obvious). The many patients who have no effective therapy upon tumor progression deserve consideration even if the clinical trials are not optimally performed.

This review is one of many in the area (I count at least 17 published). My enthusiasm would increase with a greater systematic review of the current literature and/or inclusion of more rigorous studies from this group.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.