Author's response to reviews

Title: Concerns about anti-angiogenic treatment in GBM patients

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Author's response to reviews: see over
To the Editor in Chief of BMC Cancer
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Dear Editor,

First of all we would like to thank you for the opportunity to improve our manuscript previously entitled “Is Symptom Reduction by Angiogenesis Inhibitors in GBM Patients Without a Price?” which we submitted for possible publication in the BMC Cancer, as a Debate article.

Following the reviewers’ comments we have changed the title to: “Concerns about anti-angiogenic treatment in GBM patients”.

Attached please find a detailed response to each of the reviewers’ comments and suggestions. The revised version of the manuscript is attached with changes marked with yellow. As requested, we have now strictly followed the journal style. In addition, this revised paper has been checked by a native English speaker.

Yours sincerely,
On behalf of all authors,

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Original Title: Is Symptom Reduction by Angiogenesis Inhibitors in GBM Patients Without a Price?
NEW TITLE: Concerns about anti-angiogenic treatment in GBM patients

Reviewer: Jeremy Rich

Reviewer’s report and authors’ responses:

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.

   a. Thank you for this valid comment. For the revised paper we decided to delete our own clinical data; these will be published in a separate paper.

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.

   a. As suggested, we have now included reference to Du et al. and use the figures as a clinical illustration to this reference.

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.

   a. As suggested, the title has been changed.
   b. Issues regarding costs and toxicity have been added to the revised Discussion section (please see page 11, lines 8 to 10).

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 Clin 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.
a. As advised, we have re-written the part about clinical data, have added recent literature, and have discussed in more detail the outcome data including survival. See also response 7 with respect to selection of papers included in this paper.

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.

a. Most clinical data are available for bevacizumab, only the Batchelor study studied AZD2171. Certainly, it is likely that small drugs act differently than large antibodies on these tumours as these are totally different agents with very different mechanisms of action. This is an interesting subject, but outside the scope of our paper. On the other hand, their effect on the permeability and therefore impact on MRI response in patients, which is of key importance to our discussion, does not appear to be very different.

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.

a. In fact the xenografts used in our own studies do invade into the brain; in particular the E98 nicely shows the invasive character of human glioma. On the other hand, the results of the two recent papers mentioned by the reviewer are in contrast to our own. Therefore, it is not possible to draw firm conclusions but we have added these references and have now addressed the apparent conflicting results in our revised Discussion section (please see page 10, lines 7 to 19).

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.

a. Thank you for these comments. The topic of our paper focuses on GBM. Several studies included both grade III and IV patients. In our paper we have included only studies with separate data on the results in GBM patients. The papers of Kreisl, Norden, Poulsen, Kang have been added to our revised paper.

b. In contrast, Benesch reported the results of a comp use program in children; Lai reported the results of combined radiotherapy with bevacizumab; Desjardins
reported only data on grade III patients; and Fischer reported data on PA findings after bevacizumab treatment. For the clarity of our message we have not included these latter papers. However, we think that the data of these latter studies do support our view that overall survival is not improved by angiogenesis inhibitors.

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.

a. We agree that a placebo controlled trial is not realistic, but a randomized trial without placebo is possible. A phase III study in first line is planned with bevacizumab. The present paper does not intend to be a systemic review but focuses mainly on preliminary conclusions from non-randomized trials with doubtful endpoints, this in the light of what is known about tumour biology in animal models. We believe this will help to fuel the necessary discussion on this subject and hopefully change the mindset of the neuro-oncology community.
Reviewer: Reviewer: Eric Wong

Reviewer's report and authors’ responses:

1. Verhoeff et al wrote this manuscript as a review of bevacizumab antiangiogenesis therapy for glioblastomas. They argue that bevacizumab decreased vascular permeability and has essentially no impact on the underlying glioblastoma cells. This is incorrect based on Cloughesy et al's report that was presented in the 2008 American Society of Clinical Oncologists: A phase II, randomized, non-comparative clinical trial of the effect of bevacizumab (BV) alone or in combination with irinotecan (CPT) on 6-month progression free survival (PFS6) in recurrent, treatment-refractory glioblastoma (GBM)" (Proceed ASCO 2008;26:2010b; May 20 Supplement). The trial showed that bevacizumab alone improves response and, more importantly, prolongs the PFS of patients. The prolongation of PFS suggests that there is impact on the underlying glioblastoma even though it cannot be visualized. I do agree with the authors that decreased vascular permeability after bevacizumab treatment impairs our ability to visualize the tumor, and migration of tumor cells by co-option of blood vessel is a major mechanism of resistance.

   a. Thank you for your comment that decreased vascular permeability after bevacizumab treatment impairs our ability to visualize the tumour, and that migration of tumour cells by co-option of blood vessel is a major mechanism of resistance. Consequently, this seems to imply that the prolongation of PFS can be an artefact caused by this inability. The recent exploratory survival analysis of Norden et al. (2008) shows comparable overall survival of AI treated patients compared to chemotherapy treated patients. This underscores the idea that PFS is probably not an optimal endpoint for anti-angiogenic agents in recurrent GBM. This discussion has now been added to the revised text (please see page 5, lines 15 to 24)
Reviewer: Andrew D. Norden

Reviewer’s report and authors’ responses:

General Comments:
This debate concerns an important, unresolved issue in contemporary neuro-oncology: whether anti-angiogenic therapy achieves true anti-tumor efficacy. This is a topic that should be of general interest to the oncology community because anti-angiogenic therapies are now being evaluated in nearly every known tumor type.

Major Compulsory Revisions:

1. Further editing for grammar and style is necessary to increase the clarity of the argument.
   a. As requested, the revised paper has been corrected by a native English speaker who has experience in checking scientific manuscripts.

2. In referring to the results of phase II trials on page 4 (line 9), the authors should cite the Cloughesy data (reference 19). Overall survival of 8-9 months was reported in Cloughesy’s study, and this should be discussed and compared to historical data.
   a. As requested, we have included these data in the revised Discussion (please see page 5, lines 18 to 19)

3. The Macdonald criteria, which are used widely as the authors note on page 6 (line 5), should be defined and explained in further detail. Further discussion of alternatives to Macdonald criteria is needed.
   a. As requested, we have discussed the criteria for tumour progression in more detail (please see page 6, lines 10 to 16).

4. On page 6 (line 12), the authors comment on the shift to an invasive tumor phenotype; citations 25 and 26 do not sufficiently support this claim in glioma.
   a. The reviewer correctly refers to our results obtained in the preclinical models used in (previous) references 25 and 26. Based on these results, we think that it is justified to conclude that “the impressive decreases of contrast enhancement in these tumours on bevacizumab treatment (Figure 1A-E) are not necessarily synonymous with anti-tumour effects” (see page 6 line 22 to 24). We do not claim that this shift to invasive phenotype always occurs, but want to point out that there is a great risk that this phenomenon will occur.

5. The section entitled Vascularisation and vessel normalization (page 7) is insufficiently detailed to be convincing.
a. As suggested, in the revised paper we have provided additional details to support our debate (please see page 8, lines 15 to 16).

6. Is there other literature that could be discussed in the section on Blood Brain Barrier and chemotherapy (page 9)? This brief section is not persuasive, as it cites a single study as evidence that anti-angiogenic therapy may reduce chemotherapy penetration. The authors’ argument may be correct, but a fair amount of published literature supports the counter-argument, that anti-angiogenic therapy promotes chemotherapy penetration.

   a. Indeed, two recent studies have now been included (please also see our response to point 7 from reviewer Dr. Jeremy Rich).

7. Other literature that supports the vascular co-option hypothesis should be reviewed and discussed; see Lamszus et al. Acta Neurochir Suppl 2003;88:169-77.

   a. Although the above-mentioned article was referred to (as Ref 52) in the first version of the paper, we have now included also Rubinstein et al. (2000) and Martens et al. (2007).

Minor Essential Revisions:

1. Bevacizumab is FDA-approved for lung and breast cancers, in addition to colorectal cancer as noted by the authors.

   a. We have made this addition in the revised manuscript.
   (please see page 4, line 1)

2. On page 5 (lines 3-4), the authors note that anti-angiogenic drugs reduce the need for corticosteroids. This has been reported in a number of recent studies that should be cited here.

   a. As advised, we have added these studies to the revised manuscript
   (please see refs. 19 - 24; page 5, line 7)
3. In Figure 1, ADC sequences are included. The potential significance of ADC must be discussed. Additionally, the size of the contrast-enhancing lesion in (c) appears to be larger (as opposed to smaller than baseline).

   a. In the revised paper we have added a reference concerning ADC (ref 42.) Indeed, the size of the lesion is larger than baseline, but its enhancement is decreased; we have added this information to the legend of Fig. 1.

4. The implication in Figure 2 is that bevacizumab treatment has increased invasion and co-option. Perhaps a non-bevacizumab treated sample could be provided as a comparison.

   a. We have included reference to Du et al. and use the figures as a clinical illustration to this reference. (please see page 9, lines 6 to 11)
Additional comments from the editors and authors’ responses:

1. If you want to use the images, you have to provide written permission from the publishers for us to reproduce them. Otherwise you will have to remove them and just cite the work.
   a. None of the images have ever been published before; all images are provided by courtesy of our own group.

2. We recommend that you copyedit the paper to improve the style of written English. If this is not possible, you may need to use a professional copyediting service. Examples are those provided by the Manuscript Presentation Service (www.biomedes.co.uk), International Science Editing (http://www.internationalscienceediting.com/) and English Manager Science Editing (http://www.sciencemanager.com/). BioMed Central has no first-hand experience of these companies and can take no responsibility for the quality of their service.
   a. We have followed your recommendation: this revised paper has been checked by a native English speaker who has experience in correcting scientific papers.

3. Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted.
   a. As requested, the revised paper now conforms to the journal style.