Author's response to reviews

Title: Bevacizumab plus irinotecan improves both response and survival in patients with recurrent malignant glioma: a survival gain analysis

Authors:

Tao Xu (xutao@smmu.edu.cn)
Juxiang Chen (juxiangchen@126.com)
Yicheng Lu (lyyc305@yahoo.cn)
Johannes E.A Wolff (jwolff@mdanderson.org)

Version: 2 Date: 24 March 2010

Author's response to reviews: see over
Dear editors,

Thank you for your kind help in the review process of our manuscript “Bevacizumab plus irinotecan improves both response and survival in patients with recurrent malignant glioma: a survival gain analysis”. The reviewers provided many informative and constructive suggestions for improvement of our paper. And we are very grateful for your detailed advices on writing skill and how to express our opinion in a more proper way.

We have revised the article according to the recommendations with ‘tracked changes’.

If there is any question, please do not hesitate to contact us.

We look forwards to hearing from you soon.

With kind regards

Juxiang Chen, M.D. PH.D
Department of Neurosurgery
Chang Zheng Hospital
415 Feng Yang Rd.
Shanghai 200003, P. R. China
Reviewer 1:
Xu et al. submit a manuscript on the survival gain of bevacizumab and irinotecan. The statistical analysis showing a survival gain is of interest and should be the main aspect of this manuscript. This interesting analysis aside the manuscript is too long and should be condensed to a brief report. The authors appears to want to use this analysis to show the a survival gain and A+I, but much of what is provides is a review of the literature.

Major comments:
1) Analysis should compare only recurrent malignant gliomas as that is the basis of the papers on A + I.
   Answer: Thank you for your suggestion, we had eliminated the parts in which comparison was made in overall HGG cohorts so as to make this manuscript more clear.
2) For comparative data, use only data extracted from malignant gliomas, not low grade, not newly diagnosed.
   Answer: Thank you for your advice. Actually, there are more than 2000 cohorts in our database, including LGG, HGG, newly diagnosed or recurrent cases. However, only 282 recurrent cohorts among 741 HGG cohorts were selected for analysis. No studies of low grade were included in the analysis. We believed that we might not declare it clearly in the manuscript so as to make this misunderstanding. We had modified this part in the manuscript. We also eliminated the parts in which comparison was made in overall HGG cohorts so as to make this manuscript more clear.
3) For response rates, what are those for recurrent GBM.
   Answer: Thank you for your advice. The response rates for recurrent HGG were measured by two consecutive MRI scans and the Macdonald criteria were used. Complete response and partial response were regarded as treatment response. The details were added these into the method part.
4) Would eliminate studies of children.
   Answer: Thank you for your advice. Actually, no studies of children were included in the analysis. We believed that we might not declare it clearly in the manuscript so as to make this misunderstanding. We had modified this part in the manuscript.
5) Focus on the 10 studies used for meta-analysis.

**Answer:** Thank you for your advice. We had eliminated some parts that mainly discussed the overall database, so as to make this manuscript more clear and focused.

6) Discussion is excessively long and is more a review of literature with diluting the analysis at hand.

**Answer:** Thank you for your suggestion. The question we are trying to answer is important but the data that are available in literature are from uncontrolled phase II studies. The method we used in our manuscript was created and proved by Professor Wolff. However, despite the statistical significance, we still cannot give a very confirm conclusion. In this revised manuscript, we changed the form of the paper to a systematic review (with all the phase II studies) and to include the pooled analysis data as secondary outcomes. In this way, the results would be expressed in a more precise way.

**Reviewer 2:**

This paper evaluates the role of bevacizumab plus irinotecan in recurrent malignant glioma by performing a survival gain meta-analysis of phase II studies. The authors have come up with the conclusion that the combination of those two regimens can improve the survival in patients with recurrent malignant glioma.

The question the authors are trying to answer is important but the data that are available in literature are from uncontrolled phase II studies. We cannot drive any implication for these uncontrolled data. In my opinion the data from this survival gain analysis are extremely weak, despite the statistical significance. I would suggest the authors to change the form of the paper to a systematic review (with all the phase II studies) and to include the pooled analysis data as secondary outcomes, underscoring that we cannot use these data to give any firm conclusion. Randomized controlled trial is mandatory.

**Answer:** Thank you for your kind suggestion, it’s true that we have no randomized controlled trials in this field. The novel method we used in this manuscript was created by Professor Wolff in order to assess the phase II trials, it was under the umbrella of meta-analysis and had been used in two published papers. In the database, patient cohorts were generated from more than 700 published papers. It provided us a way to
compare different treatment protocols (i.e., Bevacizumab+Irinotecan VS other protocol), then patients who received other treatment protocols were set as control groups. It was better than just pooled the results of 10 phase II studies together.

We totally believe that no firm conclusion can be drawn with these data, but we wanted to use a mathematic method to pool these phase II trials together, in order to make full use of these available data. We added these limitations into the discussion part. This manuscript was not a formal meta-analysis, and systematic review is a more proper form, we had modified it in our manuscript. Thank you again for your informative and constructive suggestions.

Specific comments

Major Compulsory Revisions:

1. The title of the article should be change. The data are too weak to support the title: “Bevacizumab plus irinotecan improves both response and survival in patients with recurrent malignant glioma: a survival gain analysis”.

Answer: Thank you for your suggestion. Yes, it’s true that our manuscript was not a formal meta-analysis, and no confirms conclusion can be drawn from phase II trials, despite statistical significance. Systematic review is a more proper form, we had modified it to “Effects of bevacizumab plus irinotecan on response and survival in patients with recurrent malignant glioma: a systematic review and survival-gain analysis”.

2. Abstract. In the conclusion of the abstract, the authors stated that: “The combination of bevacizumab and irinotecan can improve outcome in patients with recurrent malignant glioma”. The verb “can” is too “strong” for the available uncontrolled data and should be change.

Answer: Thank you for your suggestion, it’s true that the verb “can” was too strong for the conclusion. We had changed it into “might”, so that the results can be expressed more precisely.
3. Introduction section. In the last paragraph the authors stated: “Here we describe a second application of the same mathematical technology and its expansion to also analyze response to describe results from several phase II trials of bevacizumab and irinotecan for recurrent HGG”. This sentence should change so as to state more clear the aim of the study.

**Answer:** Thank you for your suggestion, we had modified this sentence in to “Here we did a systematic review of published phase II trials of bevacizumab plus irinotecan for recurrent HGG and used the previous mathematical technology to analyze the survival and response benefit of this treatment protocol.” We think it might be more proper to state the aim of our study.

4. Table 1 and 2 are important for the systematic review and authors should include those in the manuscript and they should pay more attention to discuss those tables in Results section.

**Answer:** Thank you for your kind suggestion. We had added a paragraph which mainly discusses the Table 1 and Table 2 in the Results part so as to make this part more substantial.

5. In Results section the authors describe the toxicity of the combination bevacizumab plus irinotecan but they do not include any numbers. A table with all the toxicities reported in phase II trials is necessary so as to justify the paragraphs in the Discussion section in which the authors adequately discuss that the toxicities may be a drawback for this combination of drugs.

**Answer:** Thank you for your informative and constructive suggestions, we had add an additional table (Table 3) in which all the toxicities reported in phase II trials were included.

Discretionary Revisions:

1. In both table 1 and 2, the list of the phase II studies are not in a specific order. Authors can choose a specific order to present their tables: number of patients included (e.g. from the study with the highest to the study with the lowest number of patients included or vice
versa) or alphabetical order etc.

**Answer:** Thank you for your advice, we had modified it in our manuscript, we ordered it using the alphabetical numbers of the references. It looks better in this way.

Minor Essential Revisions:

1. Page 7. Results section. Overall survival of the database subsection. “…13.7 months (SD 11.1 months).” There is a need for a space between 11.1 and months.
3. Page 17. Figure Legends. Figure 3. After the “… irinotecan group (b)” comma should be replaced with full stop.
4. Page 17. Figure Legends. Figure 4. After the “… irinotecan group (b)” comma should be replaced with full stop.
5. Reference section. Please write the full citation of references 9 and 23.
6. Reference section. Please correct the citation of reference 25.

**Answer:** We apologize for these mistakes. We have read the manuscript carefully again to correct these mistakes.

**Reviewer 3:**

In this interesting study, the authors performed a survival gain meta-analysis of phase II studies to evaluate the efficacy and safety of bevacizumab plus irinotecan using a preexisting database. They found that bevacizumab plus irinotecan improved response rates and had a possible moderate effect on overall survival.

The authors indicate in the introduction that the 6 month-progression free survival is less than 30% for recurrent glioblastomas. In fact this number is less than 9-16%; 30% would be considered an active agent.

There is controversy about the ability of irinotecan to pass through the blood-brain barrier.

**Answer:** Thank you for your advice, we had changed these two parts in the manuscript so as to make the words more precisely.
Major Compulsory Revisions

The definition of a patient cohort is not clear and should be clarified.

Answer: Thank you for your advice. Actually, the patient cohorts were generated from published papers. We had added the following sentences into the manuscript, in order to make it clearer and easier to understand. “Briefly, patient cohorts were generated into a database based on every published paper about HGG. Each patient cohort included more than 30 parameters, like general characteristics (mean age, sex, et al), pathological diagnosis, treatment response, survival time and so on. If there was more than one group of patients included in one paper, patient cohorts were generated separately depending on different groups.”

The study would be strengthened by somewhat more detailed description of the methods used and the benefits and limitations of these methods.

Answer: Thank you for your kind suggestion. As we know, there were no control groups in phase II trials. So the efficacy of a certain treatment protocol cannot be assessed properly, and phase III randomized controlled trial should be the best choice to draw a conclusion.

The novel method we used in this manuscript was created by Professor Wolff in order to assess the phase II trials, it was under the umbrella of meta-analysis and had been used in two published papers. In the database, patient cohorts were generated from more than 700 published papers. It provided us a way to compare different treatment protocols (i.e, Bevacizumab+Irinotecan VS other protocol), then patients who received other treatment protocols were set as control groups. It was better than just pooled the results of 10 phase II studies together.

However, we still believe that no firm conclusion can be drawn with these data, despite statistical significance, phase III randomized controlled trials are needed. Since this manuscript was not a formal meta-analysis, and systematic review might be a more proper form, we had modified these parts in our manuscript. Thank you again for your informative and constructive suggestions.