Author's response to reviews

Title: Induction therapy with bortezomib and dexamethasone followed by autologous stem cell transplantation versus autologous stem cell transplantation alone in the treatment of renal AL amyloidosis: a randomized controlled trial

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Author's response to reviews: see over
Dear Dr. Denyer,

Re: Manuscript “Induction therapy with bortezomib and dexamethasone followed by autologous stem cell transplantation versus autologous stem cell transplantation alone in the treatment of AL amyloidosis: a randomized controlled trial”

Please accept for your editorial consideration this submission of our revised manuscript to the BMC Medicine.

Thank you and the reviewers for their valuable comments on the previous version. We have revised the manuscript carefully according to your valuable suggestions. All revisions are highlighted in red font. We have also answered all the questions as listed below. This clinical trial was approved by the institutional ethical review board of Jinling Hospital in 2007 and registered in the clinical trial center of Jinling Hospital (the register number was JH2007011). However, at that time we didn’t well know the policy about clinical trials registration of the International Committee of Medical Journal Editors (ICMJE), and this clinical trial didn’t register online. We are very sorry about this. In addition, we have a professional English proofing company polished the language.

We hope this version answers all the questions raised by the reviewers, and get accepted for publication by the BMC Medicine. We have no conflict of interest to declare.

I look forward to hearing from you.

Yours sincerely,

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Replies to Dr. Vaishali Sanchorawala:

We want to thanks Dr. Sanchorawala for her detailed and professional comments. It is very important for us to promote the quality of our manuscript, and we have done our best to revise our paper as she suggested.

Major comments

1. Toxicity of 40 mg of dexamethasone in a twice a week fashion needs a mention. It is hard to believe that 100% of the patients with renal involvement and median serum albumin levels of < 3 g/dL, on this trial did not experience grade 3/4 edema with such high dose dexamethasone. Discussion about this specific side effect and reduction in dose to 20 mg needs to be detailed.

   **Answer:** It is our mistake to ignore this common toxicity. Actually, a small part of patients in BD induction group experienced grade 3/4 edema. As you know, 100% of the patients with renal involvement and median serum albumin levels of < 3 g/dL, with the support treatment of diuretics and serum albumin, most of patients can endure this toxicity of dexamethasone. 3 patients had reduction in dose to 20 mg for grade 3/4 edema and no one had a cessation of dexamethasone therapy. The detail for this toxicity was added in the results part and we also added discussion about this. (page 12, line 6-7; page 18, line 15-19)

2. 5 of 8 patients with infection during BD induction developed herpes zoster - were they not treated with acyclovir prophylaxis? This needs to be mentioned in the methods section as well as discussion section.

   **Answer:** Because all patients enrolled in this trial with renal involvement, to avoid the side effects (especially for acute kidney injury) of acyclovir, we haven’t use acyclovir prophylaxis for BD induction patients in this trial. This maybe leads to the relatively high incidence of herpes zoster. All patients with herpes zoster had recovered within 2 weeks after anti-virus therapy. We have mentioned this in the methods section as well as discussion section as suggested. (page 8, line 8-10; page 19, line 4-6)
3. 18% of patients developed grade 3 neuropathy during BD induction - this is different than CAN 2007 trial experience. Comment and a discussion about use of subcutaneous bortezomib vs weekly bortezomib.

**Answer:** The neuropathy during BD induction seems more frequent in our patients. The use of subcutaneous bortezomib or weekly bortezomib can reduce the incidence of neuropathy in other reports. We have added the comment and a discussion about use of subcutaneous bortezomib vs weekly bortezomib in the discussion part as suggested. (page 18, line 19-22; page 19, line 1-4)

**Minor comments:**

1. Are the nephrologists doing chemotherapy and stem cell transplants in China for this rare disease? There is no hematologist/oncologist as an author!

   **Answer:** As one of the largest nephrology center in China, we have more than 100 newly diagnosis AL amyloidosis patients per year, so we established the first stem cell transplantation center in nephrology department in China. Though there is no hematologist/oncologist as an author, all the authors have received chemotherapy and stem cell transplant training, and we also get the authorization for chemotherapy and stem cell transplant from the health department.

2. Background - line 3/4 - amyloid fibrils deposit in the tissues and not light chain fragments

   **Answer:** We have corrected it as suggested. (page 5, line 4)

3. Background - 2nd paragraph line 8 - Simple HDM/SCT therapy has many shortcomings, including a low hematologic complete response (CR) rate, a high TRM rate, and frequent relapse. This sentence does not belong in this paper of SCT for AL amyloidosis.

   **Answer:** Yes, that’s right. It has been deleted in the revised version. (page 5, line 22)

4. Background - 3rd paragraph - 1st line - lenalidomide reference needs an update:

**Answer:** Thanks. We have corrected it as suggested. (page 24, line 16-18)

5. Why were patients with creatinine > 2 mg/dL excluded?

**Answer:** From our limited experience before the trial begin, we found patients with creatinine > 2 mg/dL had higher treatment related mortality (over 10%) and at high risk of acute kidney injury during stem cell transplantation, so we don’t choose include those patients in this trial, and select the novel drugs chemotherapy regimen as first-line therapy for those patients.

6. Methods section - 1st paragraph - line 9 - should read Left Ventricular EF.

**Answer:** We have corrected it as suggested. Thanks. (page 7, line 14)

7. Study design - prophylaxis with antiviral and proton pump inhibitors given or not?

**Answer:** Omeprazole was given as prophylaxis to all patients who received BD induction, but they didn’t treat with anit-virus prophylaxis. We have added it in study design section. (page 8, line 8-10)

8. Hematologic and organ response criteria section of methods - 10th Annual International Symposium on Amyloid and AL amyloidosis - wrong title of the meeting!

**Answer:** Thanks. We have corrected this mistake. Since we have changed the criteria for hematologic and cardiac response (J Clin Oncol 2012; 30: 4541-9) according to the advice of professor Merlini, we delete this sentence in the manuscript. (page 8, line 15-16)

9. Results section - 1st paragraph - AL amyloidosis leads to nephrotic syndrome and not nephritic syndrome!

**Answer:** We have corrected it. Thanks. (page 11, line 18)

10. Page 12 - should read Mayo and not mayo
11. Reference 27 should be replaced with:

Answer: We have replaced reference 27 with the above reference. (page 25, line 24-27)

12. references 35 and 36 are the same.
Answer: We have deleted reference 35. (page 25)

13. Soften the conclusions - BD-HDM/SCT appears to be safer than HDM/SCT! Why? How did you reach that conclusion?
Answer: We realized that it not correct to make this conclusion. We have changed it as “the risk of the BD+HDM/SCT regimen is apparently comparable to that of HDM/SCT”. (page 20, line 5-6)

14. combine Table 1 and 2 as patient characteristics.
Answer: We have combined Table 1 and 2 as suggested. (page 28-30)

We hope that this revised version answers all the criticisms you made in you report, and that you could give the editor a favorable recommendation for the publication of our paper. Thank you very much.
Replies to Dr. Giampaolo Merlini:

We also want to thanks Dr. Merlini for his detailed and professional comments. It is very important for us to promote the quality of our manuscript, and we have done our best to revise our paper as she suggested.

Major comments

1. Selection bias. One hundred percent of patients had renal involvement. This is probably a selection bias since the study was conducted in a nephrology institution, and should be acknowledged and in the manuscript. I would also suggest to reflect this in the Title (e.g. “… in the treatment of renal AL amyloidosis …”).
   **Answer:** We have acknowledged as a limitation of this study in the discussion part, and we have changed the title as suggested. (page 1, line 4)

2. The sample size is too small to allow patients stratification based on known risk factors, as well as to allow a subgroup analysis.
   **Answer:** We also realized this question for this study, so the results for stratification based on known risk factors or subgroup analysis can’t match other studies’ results. We will continue this study and enroll more patients to make this stratification or subgroup analysis more clear.

3. In the introduction, the combination of melphalan and dexamethasone, besides treatment based on novel agents, should also be mentioned.
   **Answer:** We have added the combination of melphalan and dexamethasone regimen in the introduction part. Thanks. (page 5, line 14-18)

4. In the Methods section the Authors state that patients “who met the criteria for MM” were excluded. The criteria used to define multiple myeloma should be reported in detail. Were only
patients with symptomatic multiple myeloma excluded? If patients with “high” plasma cell infiltrate were excluded even if they did not have symptoms related to their tumor burden, this could have resulted in a relevant selection bias. Indeed, the median plasma cell infiltrate (3%) is significantly lower than expected.

**Answer:** We have added the criteria used to define multiple myeloma in the methods section and the reference for the criteria. We only excluded patients with symptomatic multiple myeloma, and the patients with “high” plasma cell infiltrate but cannot diagnosis MM were not excluded. The low plasma cell infiltrate maybe a feature of Chinese amyloidosis patients, the data from a large cohort of 245 patients in our center showed that the median plasma cell infiltrate is only 3.5% (unpublished data). (page 7, line 8-11)

5. Hematologic and cardiac response should be assessed according to the novel criteria of the International Society of Amyloidosis (J Clin Oncol 2012; 30: 4541-9).

**Answer:** We have renewed our data of hematologic and cardiac response according to the novel criteria of the International Society of Amyloidosis as suggested. (page 8, line 15-21)

6. The criteria used to define progression should be described in great detail, since there are no updated consensus criteria for progression in AL amyloidosis.

**Answer:** We have described the criteria used to define progression in the methods section. (page 8, line 21-22; page 9, line 1-3)

7. The response rate to BD, before SCT should be reported in the text in greater detail. The Authors should comment on the rationale for transplanting patients with AL amyloidosis without multiple myeloma, who achieve CR with BD.

**Answer:** We have reported the response rate to BD induction in detail in the results section and commented on the rationale for transplanting patients with AL amyloidosis without multiple myeloma, who achieve CR with BD in discussion section. (page 13, line 6-11; page 17, line 14-18)
8. The first paragraph of the Discussion repeats concepts and data already presented in the Introduction and could be significantly reduced.

**Answer:** We have significantly reduced the repeats concepts and data in the first paragraph of the Discussion section. Thanks. (page 16, line 2-16)

9. Previous experiences with adjuvant BD following ASCT should be mentioned, discussed, and compared with the approach proposed in this manuscript.

**Answer:** We have added the previous experiences with adjuvant BD following ASCT in the discussion section and compared with our approach. (page 16, 17-22, page 17, line 1-4)

10. Table 2. The proportion of patients (if any) with NT-proBNP >8500 ng/L (advanced stage III) should be reported, as well as that of subjects with dFLC >180 mg/L (a level known to affect prognosis).

**Answer:** We have added the data mentioned above in the Table 1 as suggested (the table 1 and table 2 was combined for the suggestion of professor Sanchorawala). (page 29-30)

11. Also, in Table 2, it is not clear how data are presented (median and range, mean and standard deviation or both?).

**Answer:** We have cleared it in Table 1. (page 29-30)

12. In Table 3, ITT response rates should be reported (i.e. calculated at 24 months in 20 and 23 patients for the BD-SCT and SCT arm, respectively).

**Answer:** We have reported the ITT response rates in Table 3. (page 12, line 19-21)

13. Univariate analysis. BNP and proteinuria should also be tested as dichotomized variables. NT-proBNP should be included. Cardiac stage III should be tested as a separate variable (there was no survival difference between stage I and II in this series). The use of MEL 140 should also be tested. The multivariate models should be changed accordingly.
Answer: We have updated the univariate and multivariate analysis data according to your suggestion and all data were presented in Table 3. (page 33)

Minor comments:

1. In the abstract the Authors should report the rate of hematologic response after BD and before SCT in the BD-SCT arm, as well as response rates at 3 and 6 months post transplant in both arms.
   Answer: We have added the rate of hematologic response after BD and before SCT in the BD-SCT arm, as well as response rates at 3 and 6 months post transplant in both arms in the abstract. Thanks. (page 3, line 15-18)

2. Results, line 8 from bottom. “Nephritic” should probably read “nephrotic”.
   Answer: We have corrected it. Thanks. (page 11, line 18)

3. Table 2. The upper reference limit for alkaline phosphatase should be reported.
   Answer: The upper reference limit for alkaline phosphatase in our hospital is 172 U/L. We have added it in Table 1. (page 30)

We hope that this revised version answers all the criticisms you made in your report, and that you could give the editor a favorable recommendation for the publication of our paper. Thank you very much.