

12 July 2018

Dear Dr. Kong

Please find enclosed our revised submission of the manuscript 33493 entitled "**Remission Status and Graft vs. Host Disease Impact Overall Survival Post Allogeneic Hematopoietic Stem Cell Transplantation for Acute Lymphoblastic Leukemia / Lymphoma**"

The following cover letter is in response to the comments raised by the reviewers during the peer review process. The responses to the reviewers comments are below and the corresponding changes in the manuscript were made using track changes.

Reviewer #1:

This is an interesting study on the use of HSC transplantation in Acute Lymphoblastic Leukemia and in Lymphoma. The study is interesting and as the aim to clarify the different results and guidelines between US and Europe. The results are good in term of survival and relapse free. The principal limitation is the retrospective nature of the study.

- 1. As the treatment is very complex, did all patients receive the same treatment in the different phases.**

The majority (>90%) of patients received HyperCVAD regimen in a uniform fashion in terms of intensity and timing of chemotherapy. Furthermore, the use of intrathecal chemotherapy prophylaxis was uniform. The details of the treatment protocol are outlined in the methods section under the "Treatment protocol and indications for transplant" section.

- 2. Additionally, for a better understanding the abbreviation should written in full also in the abstract.**

Agree, and have expanded all the abbreviations within the abstract and changes highlighted in track changes.

- 3. Moreover, the use of abbreviations should be limited as possible**

Agree, we have attempted to restrict abbreviations to only those directly related to allogeneic transplantation as much as possible. Thank you

Reviewer #2:

This original manuscript shows the result of retrospective cohort study in Saudi Arabia. The main original finding of this cohort study is that relatively younger age than the other large, multi-center trials give lower NRM rate. Interestingly, Philadelphia chromosomal status did not significantly affect the outcomes possibly because of TKI regimen. This cohort also showed positive effect on OS in cGVHD group. The authors claim that CR1 status was the sole determinant of relapse in this cohort. Major comment

- 1. Although the conclusion emphasize promising remising and early referral for allogeneic HCT for high-risk young and fit high-risk ALL-LBL patients**

Correct, there are two main messages from this manuscript; first that the overall outcome in high risk ALL patients is favorable which is likely in part due to lower non relapse mortality rate in our younger patient cohort; second, we identified predictors of outcome for overall survival and other important endpoints. For further clarity, we have amended the conclusion to highlight both of these conclusions.

2. **Insignificance of Philadelphia chromosomal status (pages 9~10 “Interestingly in our cohort, present of Ph chromosome...likely due to the use of TKI therapy...”). I do want to make sure that the authors tried to mention TKI (tyrosine kinase inhibitor) regimen or this is a typo of TBI. I am asking because I cannot find any description of TKI regimens in the method section – the use of some typical TKI such as imatinib. Please clarify. I guess it may also be very helpful to show the data of Philadelphia chromosome +/- comparison as graphs.**

All patients with Philadelphia positive chromosomal status received TKI in the form of dasatinib 100 mg daily during HyperCVAD therapy followed by maintenance post-transplant. We have indicated this within the methods section under “Treatment Protocol and Indications for Allogeneic HCT”. As we did not identify a prognostic factor of Ph chromosome status in the cox regression model, we did not submit a comparative graph to that effect.

3. **Page 10 ‘...cGVHD is a surrogate for such GVL effect.”. I agree with that. Maybe a little more explanation about GVL effect would be great.**

We agree, this is an important point. We have added to that paragraph “Such effect is felt to be mediated by a number of donor factors but perhaps largely T-lymphocytes that exhibit their role by identifying any residual leukemia cells and prolonging patient’s remission”.

4. **4. CR1 is the sole factor determining relapse – does the graph in Figure 1 compare non-relapse versus relapse based on CR1 yes/no? I think it does not. Please clarify. If not, I think it is very important to show the graph comparing the incidence of relapse based on CR1 status.**

In figure 1, we presented transplant outcomes for the entire cohort without stratifying. However, stratification based on remission status was presented in figure 2 as overall survival as this is the more sought out after outcome. Given that CR1 status was significant at the multivariable model we have presented the data for overall survival only.

- 5. Minor comments 1. I am not sure if the authors stated what aGVHD and cGVHD stand for in the text (I can see in the table). Please check it again. Also please make sure that all abbreviations are spelled out at their first appearance in the text.**

Thank you for this comment. We have now ensured that all abbreviations were expanded at first mention including within the abstract.

- 6. Labeling in Figure 1 would be too small to read if once the manuscript is published. The authors should make sure to use larger font size. 3. Formatting of reference – very hard to read for reviewers. Also make sure to follow the journal’s guideline (font, etc.).**

We agree with this comment and have edited figure 1 for larger font. With regards to the reference list, we have used the WJT format for reference list generation using Endnote.

Reviewer #3:

I have read with great interest the manuscript entitled, “Remission status and graft vs. host disease impact overall survival post allogeneic hematopoietic stem cell transplantation for acute lymphoblastic leukemia / lymphoma” by Damlaj and colleagues. There are several points that the authors should address in order to improve the manuscript.

- 1. I found that there are many factors which are not significant in univariate analysis but become statistically significant in multivariate analysis in table II (CR1 vs other for IR, aGVHD for PFS, B-cell vs T-cell for OS, and CR1 vs other for OS). This is called a suppression effect, and there may be unbalanced sample size, missing data and presence of interaction, etc in this data set. The authors should thoroughly elaborate this issue.**

This is a very important issue. It is true that this phenomenon can be explained by a suppressor effect, such scenario is seen where a variable of unknown significance can “boost” the significance of another variable. However, in our case we have only examined factors that were thought to be important predictors for outcome thus representing potential confounders; furthermore, we did not include all the factors in the table at the univariable stage to the next level but rather only those with a p-value of < 0.2 as it commonly practiced in the transplant literature, and is indicated in the methods section under the statistical analysis. That said, we recognize the limitations of this study and ideally the findings should be further confirmed in a larger cohort of patients with more events.

2. Abstract should stand alone. All abbreviations should be spelled out when used first.

We agree with this comment and have elaborated all abbreviations including those in the abstract.

3. Introduction section: Lymphoblastic Lymphoma. There is no need for capital Ls.

Noted and changed. Thank you.

4. Patient selection subsection: “Data were collected retrospectively from patient’s electronic medical records”. The authors already state this (2nd sentence, line 2 from top).

Thank you for this comment, we have changed accordingly and highlighted in track changes.

5. Treatment protocol and indication for allogeneic HCT subsection: What is “mesa dose”?

Thank you for identifying this typo. This is in fact meant to indicate “mesna” which is used for bladder protection from toxic metabolites of cyclophosphamide. This has been changed accordingly.

6. Statistical analysis section: the authors should not use the future tense.



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Noted and changed with highlights using track changes. Thank you.

We hope you find the responses above and the revised manuscript to be acceptable for publication.

Thank you for your consideration.

Moussab Damlaj, MD (on behalf of the co-authors)

7 Sept 2018

Dear Dr. Kong

Please find enclosed our revised submission of the manuscript 33493 entitled "**Graft vs. Host Disease Impact Overall Survival Post Allogeneic Hematopoietic Stem Cell Transplantation for Acute Lymphoblastic Leukemia / Lymphoma**"

The following cover letter is in response to the comment raised by the reviewer during the peer review process. The corresponding changes in the manuscript were made using track changes.

Further review comments (ID: 00504150)

The authors addressed most of my concerns. However, the authors did not address my major concern regarding statistical analysis (item #1 I pointed out). I highly recommend you to invite bio-statistical reviewer(s).

Response: We thank you for your feedback. We have rerun the multivariable analysis again with more stringent criteria inputting only variables with p value of ≤ 0.05 at the univariable stage to the multivariable level. We observed with such cutoffs, only aGVHD and cGVHD were prognostic at the multivariable stage for overall survival. Consequently, we have amended the manuscript to reflect this change (text of manuscript including results section and tables, as well as the audio recording).

We hope you find the changes above acceptable for publication. Thank you for your consideration.

Moussab Damlaj, MD (on behalf of the co-authors)