Round 1

August 26, 2020

Dear Editorial Board Members,

Thank you for your comments on our manuscript submission entitled, "Assessing the yield and safety of endoscopy in acute GVHD after HSCT". We would like to address each of the points raised by the reviewers.

<u>*Reviewer #1*</u>:

1. *"Patients who did not have tissue biopsied during endoscopy were excluded; it would be crucial to know the reasons why no biopsies were performed in them (selection bias?)."*

In total, there were only 6 instances in which biopsy was not performed during endoscopy. In three of these cases, the procedures were aborted prematurely due to insufficient preparation and/or retching of the patient during upper endoscopy. In two cases, endoscopy was performed solely for PEG tube placement. In one case, endoscopy was performed to place a hemoclip for bleeding that occurred following initial endoscopy. Because the number of patients excluded for lack of tissue biopsy is small, selection bias is unlikely.

2. *"Current medication of the included patients (e.g., Mycophenolate)?"*

Table 1 has been updated to show the five most common immunosuppressants used within our study population.

3. *"A potential limitation for the yield of endoscopy is that pathological classification is subject to interobserver variability; illustrative images would be important."*

We have included sample endoscopic and histological images in Figure 2. Pathological classification of tissue involved by aGVHD at our institution follows recommendations from the 2014 NIH Consensus Development Project on Criteria for Clinical Trials in Graft Versus Host Disease (Shulman et al.). In this consensus report, minimum criteria for acute/active GVHD was defined as "Variable apoptotic criteria (≥1/piece) in crypts." The report also states that if an institution chooses to use a grading system for severity as we have, the site with the highest histological grade should be noted because of inherent variability in injury. Further, the report specifies that additional morphologic features that correlate with disease severity or non-relapse mortality included "the loss of Paneth cells within the small intestines and crypt loss within the colon", and the authors state that they "would recommend investigation into grading schemes based on the degree of apoptotic activity independent of the stage of crypt or mucosal destruction." We have clarified this issue for potential readers by adding this information in our methods section.

4. *"Some numbers are not clear; e.g., Table 1: hematologic disorders n=195 (AML 80 + B-ALL 34 + MDS 30 + Myelofibrosis 13?)"*

Only the four most common hematologic malignancies diagnosed in our population were included in the table. A caption has been added to the table to clarify this.

5. *"The text (and especially the abstract) should be more concise."*

The abstract has been revised to be more concise.

6. *"Reference list: Some references are incomplete/the format does not follow the guidelines of the journal."*

References have been edited to follow journal guidelines.

Reviewer #2:

1. *"The abstract is lengthy; should be shortened"*

The abstract has been revised and overall length shortened.

2. *"Is the histological classification of the severity of GVHD arbitrary? If not, please give reference"*

Please see our previous explanation. The classification is hospital-wide standard at City of Hope Medical Center. It follows the NIH Consensus Criteria as elaborated upon above.

3. *"Inclusion of representative pictures would largely enrich the manuscript"*

Illustrative endoscopic and histologic images have been added as separate figures.

Editorial Office:

1. *"The authors need to fill out the STROBE checklist with page numbers."*

We have completed the STROBE checklist and it will be included with this submission.

2. *"I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor"*

We have included the figures in PowerPoint format as requested.

3. *"I found the authors did not add the PMID and DOI in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout"*

We have revised the references to include the PMID and DOI.

4. *"I found the authors did not write the "article highlight" section. Please write the "article highlights" section at the end of the main text"*

We have written the section and included it at the end of our manuscript.

5. *"The author should number the references in Arabic numerals according to the citation order in the text. The reference numbers will be superscripted in square brackets at the end of the sentence with the citation content or after the cited author's name, with no spaces."*

We have adjusted the format of our references.

In addition to addressing the Reviewers' concerns, we also made some minor edits throughout for clarity. Thank you for providing us the opportunity to re-submit to your journal. We believe that the changes we made as a result of the reviewer's comments have made our manuscript much stronger.

Sincerely and on behalf of my co-authors,

Anand Rajan, MD

Round 2

Dear Editor, We have shortened the abstract even further. We will attach the manuscript with shortened abstract. We will also attach separate table files, and have revised the STROBE form with page numbers. Unfortunately we can only upload one file to this reply, is there a way we can give you the rest? Thank you, Anand Rajan, MD