Peer Review File

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Reviewer A Comments

The authors report a retrospective, single center study in which they compared use of one of three FLT-3 mutation inhibitors versus no maintenance after allogeneic hematopoietic cell transplantation in AML patients.

1. Major limitations of this report are the heterogeneity for patient-, disease status- and treatment-related factors as well as the assignment of whether a patient would or would not receive one of 3 FLT-3 inhibitors post-transplant. There is significant imbalance in donor type (MUD: 28% vs 4% for no maintenance vs maintenance; and Haplo-cord: 32% vs 61% for no maintenance vs maintenance) and conditioning regimen intensity (myeloablative: 30% vs 61%, and reduced-intensity: 70% vs 39%). The authors must discuss these limitations in more detail.

***Thank you for this suggestion. We have added clarifying statements on page 8.

2. The authors have chosen to retrospectively identify those patients who fared better with the maintenance therapy such as the myeloablative conditioning group. This unorthodox strategy is flawed and should be justified.

***Thank you reviewer. We believe we have acknowledged these limitations and presented all FLT3 positive patients in our database in the defined time period. We did not select patients, and adjusted all the variables during the analysis to try to overcome the imbalance of patient characteristics. We have added a few more details in the methods section to try and clarify this.

3. Did all patients receive a FLT-3 inhibitor before transplant? Was the same agent given post-transplant?

***Thank you reviewer for this comment. We did not capture this data prior to stem cell transplantation.

4. The authors should indicate minimal (measurable) residual disease status at time of transplant as such has been noted to be an important factor for risk of relapse and likelihood of the FLT-3 inhibitor being useful.

***Thank you reviewer. We are also interested in this information but unfortunately do not have that data available since MRD testing is not standard of care for FLT3-mutated AML at our center or at most centers.

5. The authors conclude with a paragraph discussing the non-targeted agent selinexor as a maintenance therapy. Their paper focuses on using FLT-3 inhibitors as maintenance as this treatment is a targeted therapy. The authors would be much better served by focusing on how to reduce adverse events and keep patient on such therapy, and discussing potential improvements in FLT-3 inhibitor therapies.

***Thank you reviewer for this suggestion. We omitted the paragraph on selinexor and included a discussion on resistance patterns, and added several references.

6. The authors incorrectly use the term “donor status” throughout the text and table. They should use the term “donor type” or “graft type”.

***Thank you reviewer, we made this correction.

7. On page 9 line 5 the authors mean “awaiting”, not “pending”.

***Thank you reviewer, we made the correction to page 9

8. In Table 1, line 47, what does “haplo-cord” mean, i.e. a combined haplo-identical graft plus an UCB graft in the same patient, or are they listing those patients who received a haplo-identical graft along with those who received an UCB graft together?

***Thank you reviewer, we have clarified this in the footnotes and added a reference.

Reviewer B Comments

The article describes the outcomes of patients who received FLT3i following alloHSCT or did not receive FLT3i. There is a need for articles reporting on outcomes of patients with FLT3 mutations of all types (ITD, TKD, etc.). However, I wish to make several observations:

Major:

1. Please clarify in sentence 53 (page 4) whether you used the terms "FLT3, midostaurin, sorafenib, gilterininib") in combination (FLT3 and midostaurin) or not (FLT3, midostaurin,

sorafenib, or gilterininib). In the former scenario, the search might have limited to patients receiving FLT3i, and patients with FLT3 mutated AML who didn't receive FLT3i may have been excluded.

***Thank you reviewer for this suggestion. We clarified these in the method section on page 4.

2. According to the study, there is no OS advantage between the groups. However, after adjusting for conditioning regimen and donor type, survival is improved. This benefit was not clearly defined (was this seen in the MAC group, in the cord-blood group, or in the cord group that received MAC?), as it is not explained in the body of the article or demonstrated in a table. I recommend adding the univariate analysis table and mentioning in the body of the manuscript which group benefited from FLT3i, always emphasizing (as you did) the caveats of a retrospective study.

***Thank you reviewer for this helpful comment. We have added text to the end of the first paragraph of the results section. Overall, our sample size made it impossible to make a definitive conclusion, thus highlighting the need for large, randomized studies.

3. GVHD section: According to the authors, "Patients on FLT3i maintenance had a nonsignificant increased risk of developing acute GVHD", however in the following paragraph they say that "FLT3i maintenance was generally well tolerated and did not increase the risk of acute GVHD nor chronic GVHD" which contradicts their prior statement. It is important that they clearly state there was a difference in GVDH, but that it was not statistically significant.

***Thank you reviewer, we made the recommended changes on page 6.

Minor:

1. I would recommend adding the percentage of relapse in FLT3-mutated AML to sentences 1-2 (page 4).

***Thank you reviewer, we had added a brief comment regarding EFS in FLT3-ITD mutated patients compared to wild type on page 3.

2. In sentences 12-16 (page 4): "Some studies suggest that maintenance therapy with FLT3i can improve post-HSCT outcomes by eliminating minimal residual disease (MRD) during consolidation therapy". However, they only refer to one study that does not appear in the Quizartinib article. References to the other trials should be included.

***Thank you reviewer, we have added additional references.

3. Dosing: Ensure that all your patients receiving sorafenib received it only at the prescribed dose. Sorafenib can be poorly tolerated and is frequently started at a lower dose or lowered at some point. If so, please include the range (e.g. 200 - 400 mg BID).

***Thank you reviewer, we have updated the dose range for sorafenib.

4. Safety: It is recommended that the authors list the side effects of each drug separately. Furthermore, their patients received maintenance treatment for a median period of 287 days, while in randomized trials, therapy is typically administered for 12-24 months if tolerated. If these therapies were stopped earlier due to low tolerance, this must be stated.

***Thank you reviewer, we have updated this section to make it more clear.

5. Add references to sentences 5-9, 9-12, 39-44 on page 3.

***Thank you reviewer, we have updated these references.

Reviewer C Comments

1. The authors report an observational/retrospective single center study of comparing outcomes for patients who have FLT3 mutations and receive FLT3 inhibitors posttransplant as maintenance treatment versus those who do not. Total sample size is 80 patients. Overall, the study is well structured and well written and adds to the current literature as there is limited real world data available on the use of maintenance FLT3 inhibitors post allogeneic stem cell transplant.

***Thank you reviewer for these comments.

2. There are some limitations of the study such as variable time of initiation of FLT3 inhibitors, use of different donor types and conditioning regimens as well as utilization of different FLT3 inhibitors including sorafenib which is not utilized much in current clinical practice. These have been addressed by the authors.

***Thank you reviewer for these comments.

3. Other issues to address is that it is important to note that in the BMT-CTN 0901 trial, overall survival was statistically significant for MAC versus reduced intensity however it was not

statistically significant in the subgroup analysis of MDS and AML separately. Please clarify that in the discussion.

***Thank you reviewer for the suggestion. The BMT-CTN 0901 trial was stopped early after not reaching the planned enrollment. When the MDS and AML patients were analyzed separately, the patient number further decreased and was not powered enough to detect the difference. Our retrospective analysis faced a similar issue of small sample size. Thus, our analysis was limited, and we believe only large, randomized trials may provide more definitive conclusions.

4.Also recommend spelling numbers when used at the start of the sentence.

***Thank you reviewer for the suggestion, we have made these changes.