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PEER-REVIEW REPORT

Name of journal: *World Journal of Clinical Cases*

Manuscript NO: 80743

Title: Allogeneic stem cell transplantation in the treatment of acute myeloid leukemia: an overview of its obstacles and opportunities from the perspective of clinical immunology

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05196024
Position: Editorial Board
Academic degree: MD, PhD
Professional title: Associate Professor
Reviewer's Country/Territory: United States
Author's Country/Territory: Romania

Manuscript submission date: 2022-10-10

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-10-19 13:37

Reviewer performed review: 2022-10-27 21:17

Review time: 8 Days and 7 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection

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Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The article by Chen et al. is a comprehensive review of the strategies for treating AML by allogeneic SCT. Overall the manuscript is well written. I have a few recommendations for revision prior to acceptance for publication. The paragraph about homing starting on page 8 is very long. I recommend starting a new paragraph to help readability, perhaps starting with the section on MSCs in the middle of page 9. The section about MHC restriction and interaction between HSC and MSC on the top of page 9 seems out of date in light of the current use of haploidentical SCT. These references are quite old as well. Please revise this section, taking into consideration more modern insight from haplo SCT. The bottom 10-12 lines on page 9 are not clear. The statements about cell dose and reference 46 require clarification, as this paper specifically refers to reduced intensity and not myeloablative conditioning. After this, are the authors saying that TCD leads to higher cGVHD? That is how I read it, but I don't think that's what the authors mean (in contrast, on page 15 the authors provide a contrasting discussion of TCD, GVHD and GVL, which is much more clear). On page 10, the authors use the word "implantation" a number of times; "engraftment" would be more appropriate. I would be cautious in making statements about the superiority of one approach over another (page 10) especially when citing references like 53 which are not widely available and/or cited on Pubmed. The Beijing protocol has not been evaluated in much of the world. A statement like "the Beijing protocol may show some advantages to single cell source + PTCy transplant regimens" or something similar would be more appropriate. The Baumeister reference near the bottom of page 10 is a

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website link and not formatted. On page 11 the authors say HSCT is a dual transplantation of hematopoietic and immunocompetent cells. However, as they discuss in the following paragraphs, immune reconstitution comes from naïve or de novo immune cells from the donor. Perhaps immune cells would be a better term. On page 16 I recommend making a new paragraph starting with the word "Cytokines" after reference 121. Another reference at the bottom of this page is not formatted. Top of page 19: the discussion of DCL is thought provoking since this is not often considered. However, the references cited are quite old and should be updated. Also, does a reference exist for the statement that the number of DCL cases is surging? Similarly, on page 22, the reference given (170) for complications of DLI is quite old. Please update since there are many more recent publications on DLI for AML available. I recommend starting a new paragraph near the top of page 23, starting with "In recent years" after reference 171. Are any references for all the potential CAR T targets available at the bottom of page 23? Several references need formatting on the top of page 24. Reference 68 does not seem to be correct, please check.

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Language quality	[ ] Grade A: Priority publishing [ ] Grade B: Minor language polishing [Y] Grade C: A great deal of language polishing [ ] Grade D: Rejection
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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Although it is an invited article, the quality of this article is far less than my expectation. Some review work has been made on hematopoietic engraft failure, delayed immune reconstitution, and relapse. However, they focused more on basic studies, rather than the clinical applications. For a transplant doctor, there is not much novelty and attraction. I personally suggest rejection or major revision. 1. What strategies and new drugs are available for engraft failure or delayed engraftment? What clinical attempts have been made to separate GVL and GVHD? 2. For relapse after transplantation, DLI is not suitable for all types of leukemia. Besides DLI, what are those new clinical mechanisms and measures? HLA loss? New drugs? For relapsed patients, in addition to DLI, how about HMA, such as decitabine, the authors actually did not mention it! 4. The author mentioned novel cellular immunotherapies, such as CART, How about CAR-NK? Some complications were proposed at the end of the article, but they were not comprehensive, such as VOD, hemorrhagic disorders after transplantation, etc. Infections after transplantation (bacteria, viruses, fungi, etc.) should be covered in the article. 5. The article only mentioned the challenges or dilemmas of transplantation, but lacking new opportunities after transplantation, such as transplantation combined with CART, application of new drugs in conditioning regimens, ATG in combination with PTCY, etc. 6. The author mentioned MRD, whether it currently can predict the prognosis of AML patients after transplantation, whether MRD levels of different depth before transplantation can guide different transplantation model? 7. The author mentioned MSCs, MSCs were applied to HSCT, playing roles in promoting engraft and

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preventing GVHD, which should be reviewed in the paper. To sum up, the authors are seemed not experts in the field of allo-HSCT and do not have a better understanding and experience in HSCT. This article is not available for publication at this time.

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Provenance and peer review: Invited Manuscript; Externally peer reviewed

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Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
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Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Very well-written review articles that covers several aspects of HSCT in AML patients. I believe that several parts of this article can be also applied to other types of hematological malignancies that are treated with HSCT. Kindly find below the most important comments on this article: 1. Most of the article is focusing on the immune system. There is nothing about different treatment strategies, morbidity and mortality, clinical data, etc. I highly recommend to change the title accordingly. The clinical immunologists will be very happy to read this article while other clinicians (oncologists, hematologists, etc.) will be less interested. It is important that the title reflects the contents of the article. 2. The authors mentioned (in the abstract) some of the bottlenecks for the improvement of HSCT. Other bottlenecks should be, at list, listed in the article (such as conditioning and post-transplantation management). 3. The part entitled "HEMATOPOIETIC RECONSTITUTION AFTER BONE MARROW TRANSPLANTATION" is very long and basic. It is not that related to AML as well. Please shorten it or remove most of it. 4. The part entitled "INTERVENTION AND TREATMENT STRATEGIES FOR POST-ALLO-HSCT RELAPSE" is focusing only on immunotherapy. Either that title should be revised to clarify the contents or other treatment strategies should be added to this part. 5. The same previous title "INTERVENTION AND TREATMENT STRATEGIES FOR POST-ALLO-HSCT RELAPSE" is repeated twice. What should be the second one? If summary, it will be too ling summary and should be shorted as well.

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Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [ ] Grade B: Minor language polishing [Y] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [Y] Rejection

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

1. The manuscript is relatively confused and lacks the focus of discussion, and there should be detailed discussions on several hot issues. 2. The quantity and quality of the grafts and the age of donor also affect the reconstruction after allogeneic hematopoietic stem cell transplantation. 3. The survival of allo-HSCT also affected by the compatibility of specific HLA loci of the donor and recipient. 4. Maintenance therapy (demethylation, targeted drugs, etc.) to relapse after allo-HSCT for AML should be mentioned. 5. The relapse prediction models and the tests for HLA loss in haploidentical HSCT should be discussed.