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PEER-REVIEW REPORT

Reply to Company Editor-in-Chief

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

We are very thankful to you and to the peer-reviewers for the pertinent notes; we have carefully read the comments and have revised/completed the manuscript accordingly. Our responses are given in a point-by-point manner below. All the changes to the manuscript are highlighted in yellow. We hope that, in this new form, the manuscript will be suitable for publication in the *World Journal of Clinical Cases*.

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Answer: Thank you for pointing this out. The tables have been formatted according to your specifications.

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Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the RCA. RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com /.

Answer: Thank you for your suggestion. We have used your RCA database to supplement the reference list with newer and impactful titles.

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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: obstacles and opportunities

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)

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	[Y] Minor revision [ ] Major revision [ ] Rejection
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.

We are very thankful to you and to the peer-reviewers for the pertinent notes; we have carefully read the comments and have revised/completed the manuscript accordingly. Our responses are given in a point-by-point manner below. All the changes to the manuscript are highlighted in yellow. We hope that, in this new form, the manuscript will be suitable for publication in the *World Journal of Clinical Cases*.

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.

Answer: thank you for this suggestion. We have split this section into several paragraphs for clarity and to increase its readability.

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.

Answer: Thank you for this valuable suggestion. We have rewritten this paragraph

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based on newer references as indicated.

Histocompatibility is another consideration for allogeneic transplantation, as transplantation failure may also occur not only due to immune rejection but also to major histocompatibility complex (MHC) restriction between donor HSCs and recipient stromal cells and because recipient stromal cells do not support the proliferation and differentiation of donor HSCs. There is a complex interplay between MSCs and HSCs in HSCT, as MSCs are known to support HSCs and enhance their engraftment. Due to their properties, i.e., adherence to plastic and ability to be expanded *ex vivo*, as well as the lack of reported side effects after their administration, MSCs have been employed in clinical patient research and MSCs infusion have been co-administered with HSCs to enhance the engraftment of the latter, particularly in the setting of haploidentical alloHSCT with/without T-cell depletion. In addition, MSCs secrete soluble molecules (e.g., IFN-γ, cytokines, chemokines, etc.) and exhibit immunomodulatory actions, having already been employed successfully in the prevention and treatment of GVHD in individuals who had been subjected to alloHSCT. Several of the processes in which MSCs are involved include decrease in inflammation and in the proliferation of B-cells and T-cells, as well as an increase in tissue repair [34, 37-38].

The bottom 10-12 lines on page 9 are not clear.

Answer: The paragraph has been clarified.

The statements about cell dose and reference 46 require clarification, as this paper specifically refers to reduced intensity and not myeloablative conditioning.

Answer: thank you for raising this point. We were comparing and contrasting CD34+ cell dose in myeloablative vs RIC regimens. We have clarified the statement based on the ref. 46: "In contrast, individuals who are subjected to low-intensity preconditioning rather than myeloablative regimens may benefit from a higher dose of $CD34^+$ cells, as it has been shown that relapse and/or progression rates were significantly lower (9% vs 36%) in subjects who had received

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an elevated number of $CD34^+$ cells".

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).

Answer: Thank you for raising this point. We have deleted this statement to avoid any ambiguity.

On page 10, the authors use the word "implantation" a number of times; "engraftment" would be more appropriate.

Answer: Thank you for this suggestion. We have replaced the term implantation with the term engraftment as suggested.

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.

Answer: Thank you for your suggestion. We have amended this statement per your suggestion: "The Beijing Protocol and the posttransplant cyclophosphamide (PTCy) protocol are some of the most commonly used pretreatment protocols for HLA haploidentical transplantation worldwide. Recently, Tang et al. conducted a retrospective study and found that the Beijing Protocol exhibited some advantages versus single-cell source + the PTCy transplant regimens….."

The Baumeister reference near the bottom of page 10 is a website link and not formatted.

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Answer: thank you for pointing this out, we have corrected this issue.

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.

Answer: Thank you for this suggestion. We have replaced the term immunocompetent with the term immune as suggested.

On page 16 I recommend making a new paragraph starting with the word "Cytokines" after reference 121.

Answer: Thank you for this suggestion, we have performed this change.

Another reference at the bottom of this page is not formatted.

Answer: Thank you for raising this point, we have corrected this error.

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?

Answer: Thank you for this suggestion, we have rewritten this section based on newer references. Regarding the "surge" in DCL cases, what we wanted to convey is that

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more cases have been reported, not necessarily that there has been a surge of new cases. Yes, the references for the potential CAR-T targets were inserted as website links by mistake, we have corrected this error.

DCL was first recognized in 1971. Since then, few DCL cases have been reported. The molecular mechanisms involved in DCL occurrence seem to involve cytogenetic abnormalities (chromosome 7 monosomy has been depicted in more than one fifth of DCL cases) or genetic aberrations that arise in RUNX1, ASXL1, DNMT3A, IDH1/2, EZH2, JAK2, CEBPA, GATA2 and other genes. In addition, it has been hypothesized that leukemia cells could have been transferred from the donor during the alloHSCT procedure. Moreover, several theories support the fact that DCL can arise due to reduced immune surveillance following alloHSCT, the donor cells' genomic instability or due to an aberrant stromal niche that exhibits a pro-leukemia potential [138, 139].

Several references need formatting on the top of page 24. Reference 68 does not seem to be correct, please check.

Answer: Thank you for raising these points, we have corrected these errors.

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: obstacles and opportunities

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05262508

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Position: Peer Reviewer
Academic degree: MD, PhD
Professional title: Professor
Reviewer's Country/Territory: China
Author's Country/Territory: Romania
Manuscript submission date: 2022-10-10
Reviewer chosen by: AI Technique
Reviewer accepted review: 2022-10-17 12:08
Reviewer performed review: 2022-11-04 11:45
Review time: 17 Days and 23 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] 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 [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
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.

Answer: We are very thankful to you and to the peer-reviewers for the pertinent notes;

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we have carefully read the comments and have revised/completed the manuscript accordingly. Our responses are given in a point-by-point manner below. All the changes to the manuscript are highlighted in yellow. We hope that, in this new form, the manuscript will be suitable for publication in the *World Journal of Clinical Cases*. However, we must point out that this manuscript was not intended for a transplantology-related journal, therefore the manuscript might not seem novel or attractive to a specialist in alloHSCT, yet it might be of great interest to a clinical hematologist, oncologist, internal medicine specialist or even general practitioners.

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?

Answer: Thank you for raising this point. We have provided a brief overview of graft failure and delayed engraftment. The distinction between GVL and GVHD is reported in Table 3.

A serious complication of allo-HSCT is graft failure. Graft failure can be either primary, i.e., HSCs from the donor fail to engraft at all, or secondary, i.e., HSCs from the donor engraft successfully but a loss of donor cells occurs at some time point […]. In addition, poor graft function has also been identified as a complication of allo-HSCT, yet it must be differentiated from graft failure. In both graft failure and poor graft function, cytopenias are present, the bone marrow is hypocellular and there is no evidence of relapse. In terms of chimerism, poor graft function is associated with full-donor chimerism, whereas in graft failure it is either full-recipient or mixed. Initial donor engraftment is noted in both primary and secondary poor graft function, and also in secondary graft failure, but not in primary graft failure. However, initial hematological recovery only occurs in secondry graft failure and secondary poor graft function, whereas it is absent in both primary graft failure and primary poor graft function. Risk factors for graft failure include major ABO incompatibility, HLA mismatch, pre-transplantation MRD and disease type, stem cell source and dose, conditioning regimen, and

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others, whereas poor graft function seems to be influenced more by the presence of BM fibrosis, damage to HSCs or stromal cells caused by the selected conditioning regimen or other pharmacological agents, infections or GVHD, as well as a low infusion dose of HSCs. Graft failure, poor graft function and their management have been reviewed elsewhere […].

Table 3. Strategies to separate GVHD and GVL.

Separation strategies	Approaches	Brief description	Reference
GVHD risk prediction	GVHD biomarker testing	Contributes to GVHD diagnosis and provides evidence for the early use of anti-GVHD drugs.	[123]
	Cytokine gene polymorphism testing	Helps to identify patients with a high risk of severe GVHD and take preventive measures.	[124]
Modification of donor graft cells	Donor T-cell depletion	Donor T-cell depletion reduces GVHD while increasing the risk of infections, graft rejection, and disease relapse.	[109]
	Graft-specific cell population depletion	Removing specific cell populations such as naive T cells in the graft that consistently cause severe GVHD.	[118]
	DLI to treat relapse	DLI is very effective in the treatment of relapsed slow-growing hematopoietic malignancies such as CML; however, the mechanism is unknown.	[122]
	Application of chimeric antigen receptor (CAR) T-cell	The combination of single-chain variable fragment (scFv) that identifies leukemia-specific antigens and the activating domain of T cells enhances specific identification and killing of leukemia cells.	[125, 126]
	Suicide gene transduced donor lymphocyte infusion	A genetically modified suicide gene is introduced. Donor lymphocytes expressing this gene are sensitive to prodrugs, a feature that can be used when needed to regulate GVHD through the drug clearance of transduced cells.	[127]
	Selecting memory T cells	Memory T cells cause mild or no GVHD and have critical graft-versus-tumor functions.	[118]

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	Enhancing activated γδ T cells	γδ T cells have the ability to kill leukemic blasts, and allogeneic T-cell receptor (TCR) γδ T cells are not alloreactive and do not cause GVHD.	[128]
	Selecting Tregs	Tregs suppress the activation and proliferation of effector T cells and downregulate the body's response to foreign antigens or autoantigens.	[Jiang, 2010]
	Modifying/selecting other cells in the grafts	Selecting mesenchymal cells, NK cells, and manipulating dendritic cells and dendritic cell subsets.	[79, 122, 129]
Drug intervention	Application of immunosuppressants	Various immunosuppressants suppress T cells and reduce GVHD via different mechanisms.	[130]
	Application of histone deacetylase inhibitors (HDACis)	HDACis, such as vorinostat, downregulate inflammatory cytokines and increase the number of Tregs, thereby reducing the occurrence of GVHD, without effecting the GVL effect of donor CTLs.	[131, 132]
	Suppression of cytokines related to the occurrence of GVHD	Th1 cytokines such as TNF-α, IFN-γ, and IL-6 are related to aGVHD; Th2 cytokines such as IL-4, IL-5, and IL-10 are related to cGVHD. Appropriate regulation of these cytokines facilitates GVHD management.	[122]
	Enhancing cytokines that suppress GVHD	Various cytokines such as IL-11 and keratinocyte growth factor reduce GVHD while preserving the GVL effect.	[122]
	Targeting MiHAs on hematopoietic cells	CTLs targeting MiHAs such as HA-1 and HA-2 (expressed on hematopoietic cells only) promote the GVL effect.	[121]
	Development and application of tumor vaccines	Vaccines targeting MiHAs on hematopoietic cells and leukemia-specific antigens improve GVL specificity.	[133]

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!

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Answer: Thank you for raising this point. We have discussed others topics in this subsection, such as MRD, HLA loss, maintenance therapy as relapse prevention, pre-emptive therapy of relapse, novel agents used in the prevention/treatment or relapse (HMAs, FLT3 inhibitors or venetoclax) or which are currently being investigated in this setting.

Another incriminated mechanism involved in post-alloHSCT relapse is HLA loss which has been reported in HSCT from both unrelated donors as well as sibling donors. Loss of HLA antigens reduces the efficacy of the GvL effect and favors the immune escape of AML cells. In haploidentical HSCT, as there is no incompatible target to stimulate alloreactivity, the GvL effect remains low […]. Wu et al. analyzed nearly 800 cases of AML and ALL who were subjected, following an ATG T-cell-replete conditioning regimen, to haploidentical HSCT and delineated that relapse occurred faster in AML patients who experienced loss of HLA antigens versus those who did not (223 days vs 321 days, P=0.03). The factors linked with HLA loss in AML were acute GVHD (OR=4.84) and body mass index <18.5 kg/m² (OR=0.10) […]. Similarly, Jan et al. have evaluated HLA loss in the setting of haploidentical HSCT and concluded that minor HLA antigens might be involved in the process of immune recognition […].

&

Prevention and pre-emptive treatment of post-alloHSCT relapse remain major challenges for hematologists who manage individuals diagnosed with AML. The choice of therapy is dictated by measurable residual disease (MRD) levels. If MRD is undetectable, subjects should undergo maintenance therapy, whereas detectable MRD requires pre-emptive management strategies, e.g., DLIs […]. A recently published meta-analysis highlighted that FLT3 inhibitors are a safe and tolerable therapy option for individuals who have undergo alloHSCT for FLT3-mutated AML. The use of these pharmacological agents as maintenance therapy post-alloHSCT was associated with prolonged overall and relapse-free survival, with no significant differences between the treatment and control groups in terms of non-relapse mortality, GVHD or adverse events […]. Moreover,

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sorafenib maintenance therapy following alloHSCT for FLT3-mutated AML was linked with increased overall survival and reduced cumulative incidence of relapse in AML patients who were subjected to alloHSCT in the 1st complete remission […]. Similarly, Fathi et al. explored, in the setting of a clinical trial, the benefits of 100 mg/day enasidenib maintenance post-alloHSCT for IDH2-mutated AML. In their investigation, 2-year progression free survival was 69%, overall survival was 74%, and the cumulative incidence of moderate/severe GVHD and of relapse were 42% and 16%, respectively, with only one patient experiencing AML relapse while on enasidenib maintenance […]. Another attractive option for post-alloHSCT maintenance in the management of AML is represented by hypomethylating agents, namely azacitidine and decitabine. A meta-analysis of 14 studies delineated that the use of hypomethylating agents in this setting was correlated with reduced rates of cumulative incidence of relapse and GVHD, as well as higher rates of overall and relapse-free survival versus observation only […]. Similarly, the combination of low-dose decitabine and venetoclax, i.e., a BCL-2 inhibitor, was associated with lower lates of relapse in high-risk AML patients who received this combination as maintenance therapy post-alloHSCT […].

&

Apart from DLIs, other cell-based therapies, such as a second allo-HSCT, as well as CAR-T and CAR-NK cell-based treatments, have been developed. A second allo-HSCT can be tempted in younger patients, in whom relapse occurs at least 6 months after the first allo-HSCT and who already have a matched related donor following the first allo-HSCT. However, there is a current need to conduct prospective studies to assess the benefits and risk of a second allo-HSCT, as most data have been derived from retrospective investigations. Impressive overviews of a second allo-HSCT in the setting of relapsed AML post-allo-HSCT has been published elsewhere [KREIDIEH + ….].

Hypomethylating agents, i.e., azacitidine and decitabine, IDH1/2 inhibitors and venetoclax have been recognized as members of the therapeutic *armamentarium* in the setting of post-allo-HSCT AML relapse as well. In addition, immune checkpoint inhibitors (e.g., ipililumab, magrolimab),

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monoclonal antibodies (gemtuzumab ozogamicin and the anti-IL3 agent CLS360) and vaccines are displaying promising results. In addition, several novel targeted agents are currently being developed and/or investigated [Leota, krei…]:

- small-molecule inhibitors (apart from FLT3 inhibitors and the BCL-2 inhibitor venetoclax): trametinib (anti-MEK agent), glasdegib (a molecule that interacts with the Hedgehog pathway), uproleselan (anti-E-selectin agent)
- histone-deacetylase inhibitors: panobinostat
- IDH1/2 inhibitors: ivosidenib, enasidenib

3. 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.

Answer: Thank you for this valuable suggestion. CAR-NK therapy and others complications of allo-HSCT, e.g., VOD, hemorrhagic disorders, infection, have been now covered.

In addition, other cell-based therapies, such as CAR-NK therapies, have emerged from the drug pipeline landscape. Ureña-Bailén and collaborators have reported that NK-92 cells transduced with CD276-CAR constructs triple knocked-out for CBLB, NKG2A and TIGIT (inhibitory checkpoints of NK cells), CD276-CAR-NK-92 with CBLB knock-out, as well as CD276-CAR-NK-92 with TIGIT knock-out, exerted significant cytotoxicity against cellular models of AML [urena]. Similarly, CD123-CAR-NK constructs exhibited antileukemic potential and a satisfactory safety profile in a cellular model of CD123+ AML [caruso]. Similarly, NPM1-mutation-specific TCR-like CAR cytokine-induced memory-like NK constructs displayed significant antileukemic potential against a cellular model and patient-derived NMP1-mutated AML samples [Dong]. Thus, we may hypothesize

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that NK-CAR constructs might emerge as future therapies of AML.

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In addition, apart from chronic GVHD, allo-HSCT poses the threat and several late onset complications which can develop in the context of GVHD or accompany it. Late-onset complications of allo-HSCT can affect the skin and mucosa, eyes, gastrointestinal tract, lungs (e.g., bronchiolitis obliterans syndrome), muscles and connective tissue, endocrine system and the metabolism (hypogonadism, thyroid dysfunction, osteoporosis, diabetes), kidneys, nervous system, and/or the heart. In addition, infections (e.g., with viruses such as varicella-zoster virus, Epstein-Barr virus or cytomegalovirus reactivation, fungi or encapsulated bacteria) and the development of secondary malignancies in allo-HSCT recipients have emerged as "swords of Damocles" in the survival of AML patients in the post-allo-HSCT setting. These complications have been discussed in detail elsewhere […]. A recent investigation of over 40000 leukemia patients who were subjected to allo-HSCT revealed that the most frequent late-onset complications of this therapeutic procedure were azoospermia (~71%), chronic GVHD (5-year post-alloHSCT prevalence at ~43%), secondary malignancies (20-year post-alloHSCT prevalence at ~21%), depression (post-alloHSCT prevalence at ~18%), hypothyroidism (15-year post-alloHSCT prevalence at ~11%), bronchiolitis obliterans syndrome (4-month post-alloHSCT prevalence at ~10%), cardiovascular disease (15-year post-alloHSCT prevalence at ~7.5%) and avascular necrosis (10-year post-alloHSCT prevalence at ~5%) […]. However, future prospective studies are needed to clarify the exact epidemiology of late complications of allo-HSCT.

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.

Answer: Thank you for pointing this out. We have mentioned these novel strategies as future directions for research in the field of allo-HSCT.

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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?

Answer: Thank you for this valuable suggestion. We have stressed out the importance of MRD in the pre-transplantation and post-transplantation settings as suggested.

Prevention and pre-emptive treatment of post-alloHSCT relapse remain major challenges for hematologists who manage individuals diagnosed with AML. The choice of therapy is dictated by measurable residual disease (MRD) levels. If MRD is undetectable, subjects should undergo maintenance therapy, whereas detectable MRD requires pre-emptive management strategies, e.g., DLIs [….]. A recently published meta-analysis highlighted that FLT3 inhibitors are a safe and tolerable therapy option for individuals who have undergo alloHSCT for FLT3-mutated AML. The use of these pharmacological agents as maintenance therapy post-alloHSCT was associated with prolonged overall and relapse-free survival, with no significant differences between the treatment and control groups in terms of non-relapse mortality, GVHD or adverse events [….]. Moreover, sorafenib maintenance therapy following alloHSCT for FLT3-mutated AML was linked with increased overall survival and reduced cumulative incidence of relapse in AML patients who were subjected to alloHSCT in the 1st complete remission […]. Similarly, Fathi et al. explored, in the setting of a clinical trial, the benefits of 100 mg/day enasidenib maintenance post-alloHSCT for IDH2-mutated AML. In their investigation, 2-year progression free survival was 69%, overall survival was 74%, and the cumulative incidence of moderate/severe GVHD and of relapse were 42% and 16%, respectively, with only one patient experiencing AML relapse while on enasidenib maintenance […]. Another attractive option for post-alloHSCT maintenance in the management of AML is represented by hypomethylating agents, namely azacitidine and decitabine. A meta-analysis of 14 studies delineated that the use of hypomethylating agents in this setting was correlated with reduced rates of cumulative incidence of relapse and GVHD, as well as higher rates of overall and relapse-free

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survival versus observation only […]. Similarly, the combination of low-dose decitabine and venetoclax, i.e., a BCL-2 inhibitor, was associated with lower lates of relapse in high-risk AML patients who received this combination as maintenance therapy post-alloHSCT […].

7. The author mentioned MSCs, MSCs were applied to HSCT, playing roles in promoting engraft and preventing GVHD, which should be reviewed in the paper.

Answer: Thank you for your suggestion. This topic has been discussed as indicated:

Histocompatibility is another consideration for allogeneic transplantation, as transplantation failure may also occur not only due to immune rejection but also to major histocompatibility complex (MHC) restriction between donor HSCs and recipient stromal cells and because recipient stromal cells do not support the proliferation and differentiation of donor HSCs. There is a complex interplay between MSCs and HSCs in HSCT, as MSCs are known to support HSCs and enhance their engraftment. Due to their properties, i.e., adherence to plastic and ability to be expanded *ex vivo*, as well as the lack of reported side effects after their administration, MSCs have been employed in clinical patient research and MSCs infusion have been co-administered with HSCs to enhance the engraftment of the latter, particularly in the setting of haploidentical alloHSCT with/without T-cell depletion. In addition, MSCs secrete soluble molecules (e.g., IFN-γ, cytokines, chemokines, etc.) and exhibit immunomodulatory actions, having already been employed successfully in the prevention and treatment of GVHD in individuals who had been subjected to alloHSCT. Several of the processes in which MSCs are involved include decrease in inflammation and in the proliferation of B-cells and T-cells, as well as an increase in tissue repair [34, 37-38].

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.

Answer: Thank you for your comments. We must point out that this manuscript was

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not intended for a transplantology-related journal, therefore the manuscript might not seem novel or attractive to a specialist in alloHSCT, yet it might be of great interest to a clinical hematologist, oncologist, internal medicine specialist or even a general practitioner, thus, it was designed for a broader audience.

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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: obstacles and opportunities

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 04383865
Position: Peer Reviewer
Academic degree: MBChB, PhD
Professional title: Assistant Professor
Reviewer's Country/Territory: Sweden
Author's Country/Territory: Romania

Manuscript submission date: 2022-10-10
Reviewer chosen by: AI Technique
Reviewer accepted review: 2022-10-31 05:19
Reviewer performed review: 2022-11-11 09:46
Review time: 11 Days and 4 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] 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
Re-review	[ ] Yes [Y] No

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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:

Answer: We are very thankful to you and to the peer-reviewers for the pertinent notes; we have carefully read the comments and have revised/completed the manuscript accordingly. Our responses are given in a point-by-point manner below. All the changes to the manuscript are highlighted in yellow. We hope that, in this new form, the manuscript will be suitable for publication in the *World Journal of Clinical Cases*.

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.

Answer: Thank you for this suggestion. We have amended the article's title to reflect its contents: Allogeneic stem cell transplantation in the treatment of acute myeloid leukemia: an overview of its obstacles and opportunities from the perspective of clinical immunology

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).

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Answer: Thank you for raising this point, we have mentioned other bottlenecks of alloHSCT as suggested.

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.

Answer: Thank you for raising this point. We have shortened this section. We did not remove it because we believe it is an important overview for the readers of the World Journal of Clinical Cases many of whom might not be accustomed with alloHSCT.

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.

Answer: Thank you for raising this point. We have discussed others topics in this subsection, such as MRD, HLA loss, maintenance therapy as relapse prevention, pre-emptive therapy of relapse, novel agents used in relapse treatment (HMAs, FLT3 inhibitors, venetoclax) etc.

Another incriminated mechanism involved in post-alloHSCT relapse is HLA loss which has been reported in HSCT from both unrelated donors as well as sibling donors. Loss of HLA antigens reduces the efficacy of the GvL effect and favors the immune escape of AML cells. In haploidentical HSCT, as there is no incompatible target to stimulate alloreactivity, the GvL effect remains low […]. Wu et al. analyzed nearly 800 cases of AML and ALL who were subjected, following an ATG T-cell-replete conditioning regimen, to haploidentical HSCT and delineated that relapse occurred faster in AML patients who experienced loss of HLA antigens versus those who did not (223 days vs 321 days, P=0.03). The factors linked with HLA loss in AML were acute GVHD (OR=4.84) and body

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mass index <18.5 kg/m² (OR=0.10) [….]. Similarly, Jan et al. have evaluated HLA loss in the setting of haploidentical HSCT and concluded that minor HLA antigens might be involved in the process of immune recognition [….].

&

Prevention and pre-emptive treatment of post-alloHSCT relapse remain major challenges for hematologists who manage individuals diagnosed with AML. The choice of therapy is dictated by measurable residual disease (MRD) levels. If MRD is undetectable, subjects should undergo maintenance therapy, whereas detectable MRD requires pre-emptive management strategies, e.g., DLIs [….]. A recently published meta-analysis highlighted that FLT3 inhibitors are a safe and tolerable therapy option for individuals who have undergo alloHSCT for FLT3-mutated AML. The use of these pharmacological agents as maintenance therapy post-alloHSCT was associated with prolonged overall and relapse-free survival, with no significant differences between the treatment and control groups in terms of non-relapse mortality, GVHD or adverse events [….]. Moreover, sorafenib maintenance therapy following alloHSCT for FLT3-mutated AML was linked with increased overall survival and reduced cumulative incidence of relapse in AML patients who were subjected to alloHSCT in the 1st complete remission […]. Similarly, Fathi et al. explored, in the setting of a clinical trial, the benefits of 100 mg/day enasidenib maintenance post-alloHSCT for IDH2-mutated AML. In their investigation, 2-year progression free survival was 69%, overall survival was 74%, and the cumulative incidence of moderate/severe GVHD and of relapse were 42% and 16%, respectively, with only one patient experiencing AML relapse while on enasidenib maintenance […]. Another attractive option for post-alloHSCT maintenance in the management of AML is represented by hypomethylating agents, namely azacitidine and decitabine. A meta-analysis of 14 studies delineated that the use of hypomethylating agents in this setting was correlated with reduced rates of cumulative incidence of relapse and GVHD, as well as higher rates of overall and relapse-free survival versus observation only […]. Similarly, the combination of low-dose decitabine and venetoclax, i.e., a BCL-2 inhibitor, was associated with lower lates of relapse in high-risk AML

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patients who received this combination as maintenance therapy post-alloHSCT […].

&

Apart from DLIs, other cell-based therapies, such as a second allo-HSCT, as well as CAR-T and CAR-NK cell-based treatments, have been developed. A second allo-HSCT can be tempted in younger patients, in whom relapse occurs at least 6 months after the first allo-HSCT and who already have a matched related donor following the first allo-HSCT. However, there is a current need to conduct prospective studies to assess the benefits and risk of a second allo-HSCT, as most data have been derived from retrospective investigations. Impressive overviews of a second allo-HSCT in the setting of relapsed AML post-allo-HSCT has been published elsewhere [KREIDIEH + ….].

Hypomethylating agents, i.e., azacitidine and decitabine, IDH1/2 inhibitors and venetoclax have been recognized as members of the therapeutic *armamentarium* in the setting of post-allo-HSCT AML relapse as well. In addition, immune checkpoint inhibitors (e.g., ipililumab, magrolimab), monoclonal antibodies (gemtuzumab ozogamicin and the anti-IL3 agent CLS360) and vaccines are displaying promising results. In addition, several novel targeted agents are currently being developed and/or investigated [Leota, krei…]:

- small-molecule inhibitors (apart from FLT3 inhibitors and the BCL-2 inhibitor venetoclax): trametinib (anti-MEK agent), glasdegib (a molecule that interacts with the Hedgehog pathway), uproleselan (anti-E-selectin agent)
- histone-deacetylase inhibitors: panobinostat
- IDH1/2 inhibitors: ivosidenib, enasidenib

In addition, other cell-based therapies, such as CAR-NK therapies, have emerged from the drug pipeline landscape. Ureña-Bailén and collaborators have reported that NK-92 cells transduced with CD276-CAR constructs triple knocked-out for CBLB, NKG2A and TIGIT (inhibitory checkpoints of NK cells), CD276-CAR-NK-92 with CBLB knock-out, as well as CD276-CAR-NK-92 with TIGIT

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knock-out, exerted significant cytotoxicity against cellular models of AML [urena]. Similarly, CD123-CAR-NK constructs exhibited antileukemic potential and a satisfactory safety profile in a cellular model of CD123+ AML [caruso]. Similarly, NPM1-mutation-specific TCR-like CAR cytokine-induced memory-like NK constructs displayed significant antileukemic potential against a cellular model and patient-derived NMP1-mutated AML samples [Dong]. Thus, we may hypothesize that NK-CAR constructs might emerge as future therapies of AML.

&

In addition, apart from chronic GVHD, allo-HSCT poses the threat and several late onset complications which can develop in the context of GVHD or accompany it. Late-onset complications of allo-HSCT can affect the skin and mucosa, eyes, gastrointestinal tract, lungs (e.g., bronchiolitis obliterans syndrome), muscles and connective tissue, endocrine system and the metabolism (hypogonadism, thyroid dysfunction, osteoporosis, diabetes), kidneys, nervous system, and/or the heart. In addition, infections (e.g., with viruses such as varicella-zoster virus, Epstein-Barr virus or cytomegalovirus reactivation, fungi or encapsulated bacteria) and the development of secondary malignancies in allo-HSCT recipients have emerged as "swords of Damocles" in the survival of AML patients in the post-allo-HSCT setting. These complications have been discussed in detail elsewhere […]. A recent investigation of over 40000 leukemia patients who were subjected to allo-HSCT revealed that the most frequent late-onset complications of this therapeutic procedure were azoospermia (~71%), chronic GVHD (5-year post-alloHSCT prevalence at ~43%), secondary malignancies (20-year post-alloHSCT prevalence at ~21%), depression (post-alloHSCT prevalence at ~18%), hypothyroidism (15-year post-alloHSCT prevalence at ~11%), bronchiolitis obliterans syndrome (4-month post-alloHSCT prevalence at ~10%), cardiovascular disease (15-year post-alloHSCT prevalence at ~7.5%) and avascular necrosis (10-year post-alloHSCT prevalence at ~5%) […]. However, future prospective studies are needed to clarify the exact epidemiology of late complications of allo-HSCT.

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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.

Answer: Thank you for pointing this out. In fact, it was a conclusion/summary. We have shortened it as suggested.

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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: obstacles and opportunities

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06407858
Position: Peer Reviewer
Academic degree:

Professional title:

Reviewer's Country/Territory: Reviewer_Country

Author's Country/Territory: Romania

Manuscript submission date: 2022-10-10

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-11-03 07:51

Reviewer performed review: 2022-11-13 01:44

Review time: 9 Days and 17 Hours

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
Re-review	[ ] Yes [Y] No

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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.

We are very thankful to you and to the peer-reviewers for the pertinent notes; we have carefully read the comments and have revised/completed the manuscript accordingly. Our responses are given in a point-by-point manner below. All the changes to the manuscript are highlighted in yellow. We hope that, in this new form, the manuscript will be suitable for publication in the *World Journal of Clinical Cases*.

2. The quantity and quality of the grafts and the age of donor also affect the reconstruction after allogeneic hematopoietic stem cell transplantation.

Answer: Thank you for raising this point. We have mentioned this information in the revised manuscript.

"In addition, the quantity and quality of the grafts, as well as the age of donor, can also affect immune reconstruction after alloHSCT. For example, alloHSCT from donors aged >50 years has been linked with lower CD8+CD45RA+ naïve T-cells and CD19+ B-cells counts, reduced serum IgM and IgA concentrations, and higher EBV reactivation rates…"

3. The survival of allo-HSCT also affected by the compatibility of specific HLA loci of the donor and recipient.

Answer: Thank you for raising this point. We have mentioned this information in the revised manuscript.

In addition, the survival of individuals who have undergone alloHSCT is also affected by the

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compatibility of specific HLA loci of the donor and recipient. A recent publication has pointed out that HLA matching and the age of the recipient are simple factors that can accurately stratify subjects into prognostic groups, as well as predict overall survival and non-relapse mortality in alloHSCT […..]. However, a meta-analysis of 19 investigations with a patient sample of 3336 individuals concluded that mismatched alloHSCT from unrelated donors remains a safe procedure which is linked with favorable outcomes [….].

4. Maintenance therapy (demethylation, targeted drugs, etc.) to relapse after allo-HSCT for AML should be mentioned.

Answer: Thank you for this extremely valuable suggestion. We have discussed this topic in the revised version of the paper.

Prevention and pre-emptive treatment of post-alloHSCT relapse remain major challenges for hematologists who manage individuals diagnosed with AML. The choice of therapy is dictated by measurable residual disease (MRD) levels. If MRD is undetectable, subjects should undergo maintenance therapy, whereas detectable MRD requires pre-emptive management strategies, e.g., DLIs […]. A recently published meta-analysis highlighted that FLT3 inhibitors are a safe and tolerable therapy option for individuals who have undergo alloHSCT for FLT3-mutated AML. The use of these pharmacological agents as maintenance therapy post-alloHSCT was associated with prolonged overall and relapse-free survival, with no significant differences between the treatment and control groups in terms of non-relapse mortality, GVHD or adverse events […]. Moreover, sorafenib maintenance therapy following alloHSCT for FLT3-mutated AML was linked with increased overall survival and reduced cumulative incidence of relapse in AML patients who were subjected to alloHSCT in the 1st complete remission […]. Similarly, Fathi et al. explored, in the setting of a clinical trial, the benefits of 100 mg/day enasidenib maintenance post-alloHSCT for IDH2-mutated AML. In their investigation, 2-year progression free survival was 69%, overall survival was 74%, and the cumulative incidence of moderate/severe GVHD and of relapse were 42% and 16%,

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respectively, with only one patient experiencing AML relapse while on enasidenib maintenance […]. Another attractive option for post-alloHSCT maintenance in the management of AML is represented by hypomethylating agents, namely azacitidine and decitabine. A meta-analysis of 14 studies delineated that the use of hypomethylating agents in this setting was correlated with reduced rates of cumulative incidence of relapse and GVHD, as well as higher rates of overall and relapse-free survival versus observation only […]. Similarly, the combination of low-dose decitabine and venetoclax, i.e., a BCL-2 inhibitor, was associated with lower lates of relapse in high-risk AML patients who received this combination as maintenance therapy post-alloHSCT […].

5. The relapse prediction models and the tests for HLA loss in haploidentical HSCT should be discussed.

Answer: Thank you for this extremely valuable suggestion. We have discussed this topic in the revised version of the paper.

Another incriminated mechanism involved in post-alloHSCT relapse is HLA loss which has been reported in HSCT from both unrelated donors as well as sibling donors. Loss of HLA antigens reduces the efficacy of the GvL effect and favors the immune escape of AML cells. In haploidentical HSCT, as there is no incompatible target to stimulate alloreactivity, the GvL effect remains low […]. Wu et al. analyzed nearly 800 cases of AML and ALL who were subjected, following an ATG T-cell-replete conditioning regimen, to haploidentical HSCT and delineated that relapse occurred faster in AML patients who experienced loss of HLA antigens versus those who did not (223 days vs 321 days, P=0.03). The factors linked with HLA loss in AML were acute GVHD (OR=4.84) and body mass index <18.5 kg/m^2 (OR=0.10) […]. Similarly, Jan et al. have evaluated HLA loss in the setting of haploidentical HSCT and concluded that minor HLA antigens might be involved in the process of immune recognition […].