November 15, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5319-review.doc).

Title: Optimal stem cell source for allogeneic stem cell transplantation for hematological malignancies

Author: Daniel Ka Leung Cheuk

Name of Journal: *World Journal of Transplantation*

ESPS Manuscript NO: 5319

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated.

2 Revision has been made according to the suggestions of the reviewers
(1) Reviewer 00504800

1. Comment: I would like to see a little more detail about double cord transplants and haploidentical transplants, as these are becoming more attractive options.

More details are added for double cord blood transplants and haploidentical transplants in the revised manuscript (page 10-14).

2. Comment: Please make sure that, when discussing double cord transplants, it is stated that the two cords be at least 4/6 HLA matched to the patient as well as to each other.

This is stated in the revised manuscript (page 10, 2nd paragraph).

3. Comment: Last paragraph, first sentence on p. 9, discussing the meta analysis of ref. #29: I think the statement that "disease free survival was significantly lower in the PBSC group" is incorrect. To my reading of the referenced paper, DFS was better in the PBSC group.

The mistake is corrected in the revised manuscript (page 7, last paragraph).

4. Comment: Please provide a little more detail on the pros and cons of haploidentical transplants (e.g., worse GVHD and engraftment failure if T cell replete; increased relapse rate and delayed immune reconstitution if T cell depleted). This is an area of growing interest due to the greater availability of haplo donors, if some of these problems can be overcome. There are several good recent reviews which can be cited in the interest of brevity.

More detail about haploidentical transplant is given in the revised manuscript (page 12-14). It is difficult to make generalization of pros and cons of different methods and modifications in terms of relapse risk, engraftment failure and GVHD, because of different disease status and risks of relapse, different conditioning and GVHD prophylactic strategies, different T cell dosing and graft constituents, etc.

5. Comment: In the author's center 8 antigen HLA matching may be performed, but in many centers 10 antigen matching is used. I would ask the author to consider changing (or adding) that 10/10 or 9/10 HLA matches are optimal.

The use of 9/10 or 10/10 HLA matched donor is mentioned in the revised manuscript (page 5, 2nd paragraph). The NMDP guideline recommends matching at A, B, C and DRB1 (8/8 matched) while British Transplantation Society recommends matching at DQB1 in addition (10/10 matched). However, there is still much controversy regarding necessity of matching at DQB1.

(2) Reviewer 00074323

1. Comment: The paragraph entitled "Selection among different stem cell sources" could be improved by a tentative flow-chart presenting a point-to-point approach to HSCT in hematologic malignancies, e.g.: 1) matched sibling donor (MSD) available > when BM, PBSC, UCB; 2) if MSD not available > if not urgency > matched unrelated donor (MUD); 3) if MUD not available …

A flow chart of suggested selection of donor and stem cells was made in the revised manuscript (Figure 1).

2. Comment: A brief paragraph could be worth, discussing how the major differences in blood cell composition among the three sources of stem could impact the outcome of HSCT, in terms of engraftment, GvHD and, possibly graft versus tumor.

A brief paragraph was written about the major differences in blood cell composition among the sources of stem cells in the revised manuscript (page 3, last paragraph).

3. Comment: The following paragraphs (page 5 – 13) report relevant data from RCT and meta-analyses that would assist hematologists in choosing the appropriate source of stem cells in different conditions. However, the structure is a bit repetitive and can slow the reading. To improve readability, most of data from RCT could be reported in a table and the text of the manuscript could be reserved to a more articulated discussion of results.

The section was largely rewritten (page 6-7) and a table (Table 2) summarizing the RCT findings is created in the revised manuscript.

4. Comment: The practice of HSCT is continuously evolving. In the last paragraph (conclusions), it could be advisable to briefly discuss how novel procedures may impact on the choice of SC source. In particular, manipulation of cells (stem cell enrichment, depletion of lymphocytes subsets or allo-reactive cells), mesenchymal stem cells, novel treatments of GvHD have recently been used to improve haploidentical SCT.

Brief discussion about these was given in the Conclusion of the revised manuscript accordingly.

5. Comment: page 5, 6th row from the bottom: please check data with ref 8 and make more clear what group percentages are referring to.

The data were given clearly in a newly created table (Table 2) instead of the text in the revised manuscript.

(3) Reviewer 00742009

1. Comment: Most of the discussions go around the choice of stem cells from the patients' perspective, there are, however, important considerations looking from the donors' perspective. Potential complications, time to off work, and donors' discomfort post-harvest are different with respect to BM harvest and PBSC collection. This deserves a separate column for discussion.

The donor's perspective was discussed more in the revised manuscript accordingly (page 4, last paragraph).

2. Comment: Leukemia patients who require stem cell transplantation are by nature having high risk disease. When the author mentions about "high risk" leukemia patients in the manuscript, he is actually referring to a subset of patients. He might want to elaborate how this "high risk" group is defined.

Different studies defined "high risk" hematological malignancies differently. In general, patients with acute leukemia in first complete remission or CML in chronic phase are defined as "low risk" and patients with acute leukemia in >= second remission, CML in blastic transformation, refractory anemia with excess of blasts in transformation, and lymphoma heavily pretreated with chemotherapy or autologous transplants are defined as "high risk". These are mentioned in the revised manuscript (page 6, last paragraph).

3. Comment: Given the complex interplay between stem cell source, disease characteristics, and graft-versus-host disease (GVHD), how does the choice of stem source affect the approach to GVHD prophylaxis?

PBSC has the highest risk of GVHD and therefore might require more intensive GVHD prophylaxis. This was mentioned in the revised manuscript (page 9, 1st paragraph).

4. Comment: To what extent is recipient's cytomegalovirus status determining in the choice of stem cells source?

If the recipient is CMV seronegative, Cord blood transplant might be preferred as it is less likely to transmit CMV infection and CMV seronegative donor might not be easily available (page 5, last paragraph).

5. Comment: When choosing the appropriate stem cell source from unrelated donors, the transplant physician has to take into consideration of other important factors such as cost and ABO mismatch. For instance, if a cord blood is found locally and a walking donor is found in an overseas country, the price tags for the procurement of the 2 sources of stem cells are substantially different. In the case of major ABO mismatch, obtaining PBSC from the donor can be more convenient as the small amount of red cells in the final product can obviate the need for red cell depletion whereas bone marrow obtained from the same donor needs to be processed, which takes time and there will be some loss in stem cells. Randomized studies are not needed.

ABO matching and location of donor are certainly other simple yet important considerations. These are mentioned in the revised manuscript (page 5, last paragraph).

6. Comment: Table 1 is not very informative. I would suggest the author to re-organize it so as to focus on unrelated donor transplantation for leukemia patients. "Availability" to be replaced by "typical time frame" from initiation of search to transplantation. To specify the actual volume in "Volume" so that the risk of volume overload can be appreciated. To specify the "speed of engraftment" in terms of neutrophils and platelet in figures. With this information, "stem cell proliferation rate" becomes unimportant. "Amount of stem cell" to be replaced by "optimal or minimum cell doses for transplant". "Freshness of stem cell" is not an important feature but potential "exposure to dimethyl sulfoxide" is. "Collection process", "Duration of collection process", and "Age of stem cell" are irrelevant in clinical practice. The author may also want to include a certain subset of patients (high risk), red cell content, CMV status for comparison among the different sources of stem cells. The resultant Table will be useful for the transplant physician to put it side by side with the patient and see which source of stem cell has the most advantages.

Table 1 was revised accordingly.

3 References and typesetting were corrected.

Thank you again for publishing our manuscript in the *World Journal of Transplantation*.

Sincerely yours,

Daniel KL Cheuk
Department of Paediatrics and Adolescent Medicine
The University of Hong Kong
Queen Mary Hospital
Pokfulam Road
Hong Kong
Fax: +852-22551523
E-mail: cheukkld@hkuss.hku.hk