**Response to reviewers’ comments**

**Manuscript ID:** EJH-2020-0055

**Title:** Nonmyeloablative matched stem cell transplantation with optional reinforced stem cell infusion for hemoglobinopathies

Dear Editor,

We appreciate the editor and reviewers of “*European journal of Haematology*” for their effort and time in reviewing our manuscript. We have made some corrections and clarifications regarding the following points in the revised manuscript according to the reviewers’ comments. We are pleased that you are interested in our paper and hope that the revised manuscript will be suitable for publication in your journal. Again, we thank you for your constructive comments.

\*The numbers in the parentheses indicate the column in the marked-up version of the revised manuscript.

Sincerely,

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**Reviewer #1**

Q1. The dosage of total body irradiation for conditioning of NIH approach was 300 cGy. Please, clarify that why did you employed a range of 300–400 cGy total body irradiation? Furthermore, patients requiring additional optional reinforced stem cell infusion received an additional dose of 500 cGy. The cumulative toxicities of total body or total nodal irradiation, including hypothyroidism, hepatotoxicity, and cardiomyopathy, should be provided.

A1. Although the dosage of total body irradiation of NIH protocol was 300 cGy, we employed 300 cGy or 400 cGy total body irradiation. Conventionally, we have preferred 400 cGy total body irradiation in many conditioning regimens of various hematologic disease rather than 300 cGy. So, we admixed two dosages of 300 and 400 cGy total body irradiation. However, our results suggested that there were similar outcomes between patients receiving the dosage of 300 and 400 cGy, although a limited number of patients made the comparison very difficult.

On the other hand, currently available literatures of total body irradiation toxicities suggested the dose over 1200 cGy was associated with increased incidence of its late sequele, including neurologic complication, renal complication and secondary malignancies (Crit Rev Oncol Hematol. 2018 Mar;123:138-148). In addition, total nodal irradiation was generally accepted as modality with less toxicities than total body irradiation. Reflecting these findings, only small proportion of patients in our cohort experienced late complications followed by total body and total nodal irradiation. We have added corresponding sentences as follows:

Q2. Table 1 should provide additional information - e.g. for thalassemia major patients, which agents were used in cheating them? And, what was serum ferritin level before transplantation? For sickle cell anemia patients, which patients were on receiving hydroxyurea?

A2. According to your comment, we added more information for patients with β-thalassemia major to Table 1.

Q3. Gene therapy is another curative therapy for thalassemia and sickle disease. Therefore, the ‘only’ in sentence of ‘Allogeneic stem cell transplantation remains the only curative treatment option ~ hematologic disorders.’ (Page 3, Line 49) should be not correct.

A3. According to your comment, we have removed the ‘only’ in the corresponding sentence (Page 3; Line # 46).

Q4. Please, clarify that graft was unmanipulated in patients requiring optional reinforced stem cell infusion.

A4. We specified that initial and reinforced SC were infused without manipulation as follows: ‘Subsequently, peripheral blood (PB) stem cells ~ from MSD, and then administered to patients without manipulation.’ (Page 4; Line # 88–91) and ‘If whole blood (WB) PB donor T-cell chimerism declined to ~ reinforced infusion of unmanipulated SC from the same donors after total-nodal irradiation (TNI) at a single dose of 500 cGy.’

Q5. Please, clarify whether the same donor or another donor was used in this study when patients received optional reinforced stem cell infusion.

A5. We described used the same donor when patients received optional reinforced stem cell infusion as follows: ‘they were administered reinforced infusion of SC from the same donors after total-nodal irradiation (TNI) at a single dose of 500 cGy.’ (Page 4; Line # 97).

Q6. Please, provide detailed transfusion parameters (e.g. hemoglobin and platelet threshold to require transfusions). Also, did receive patients with sickle cell disease penicillin prophylaxis?

A6.

Q7. Lymphocyte count with being extremely low and peripheral blood donor T-cell chimerism at day 30 may not be valuable with your conditioning. Would you consider deleting corresponding sentences?

A7. According to your comment, we removed the sentences of lymphocyte count and peripheral blood donor T-cell chimerism at day 30.

**Reviewer #2**

Q1. Correct the number of patients experiencing graft-versus-host disease in the ‘ABSTRACT’, ‘RESULTS’, and ‘Figure 1’ sections.

A1.

Q2. The result that graft-versus-host disease occurred in three patients reinfused after one year, whereas two patients before 6 months did not (may be due to persistent alemtuzumab level) should be emphasized.

A2.

Q3. The paradigm considering that peripheral blood T cell chimerism > 50% should be reached before tapering immunosuppressive agent to avoid graft rejection should be confirmed by larger studies. In fact, several adult patients with sickle cell disease ceased sirolimus earlier than required and did not experience graft rejection with sustained peripheral blood donor chimerism after one year. It should be addressed.

A3.

Q4. Authors should discuss that these data suggest that optional reinforced stem cell infusion should be only proposed for patients with very early chimerism decline, because those who received the procedure had high risk of graft-versus-host disease, but low risk of graft rejection after one year.

Q4.