Second Salvage Hematopoietic Cell Transplant in a Sickle Cell Disease Presenting with Acquired Hypoplastic Anemia of Donor Marrow

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To The Editor:

Sickle cell disease (SCD) is the commonest hemoglobinopathy globally. Awaiting optimal gene manipulation strategy, hematopoietic cell transplant (HCT) remains the only possible cure for symptomatic SCD non-responsive to hydroxyurea.11Ribeil JA, Hacein-Bey-Abina S, Payen E, et al. Gene therapy in a patient with sickle cell disease. New England Journal of Medicine. 2017 Mar 2;376(9):848-55.·22Gluckman E, Cappelli B, Bernaudin F, et al. Sickle cell disease: an international survey of results of HLA-identical sibling hematopoietic stem cell transplantation. Blood, The Journal of the American Society of Hematology. 2017 Mar 16;129(11):1548-56.·33Thornburg CD, Files BA, Luo Z, et al. Impact of hydroxyurea on clinical events in the BABY HUG trial. Blood, The Journal of the American Society of Hematology. 2012 Nov 22;120(22):4304-10. Human leukocyte antigen (HLA) identical related donor transplant remains standard of care with outcomes approaching 85-95%, whereas HLA identical unrelated donor or haploidentical family donor (HFD-HCT) are valid clinical options with >80% survival at experienced centres[2,·44Kharya G, Bakane A, Agarwal S, Rauthan A. Pre-transplant myeloid and immune suppression, upfront plerixafor mobilization and post-transplant cyclophosphamide: novel strategy for haploidentical transplant in sickle cell disease. Bone Marrow Transplantation. 2021 Feb;56(2):492-504.. Although improving but graft failure (primary/Secondary) and graft vs host disease (GvHD) are common complications post HSCT followed by rare complications such as secondary malignancies or bone marrow hypoplasia/aplasia.55Bernaudin F, Socie G, Kuentz M, et al. Long-term results of related myeloablative stem-cell transplantation to cure sickle cell disease. Blood, The Journal of the American Society of Hematology. 2007 Oct 1;110(7):2749-56.·66Dallas MH, Triplett B, Shook DR, et al. Long-term outcome and evaluation of organ function in pediatric patients undergoing haploidentical and matched related hematopoietic cell transplantation for sickle cell disease. Biology of Blood and Marrow Transplantation. 2013 May 1;19(5):820-30. We report a child who underwent HFD-HCT for SCD and subsequently presented 1.5 years later with hypoplastic bone marrow requiring a second salvage HCT.

A seven-year-old east African boy diagnosed as SCD at the age of one year presented to us with multiple SCD related complications since infancy for a possible HFD-HCT in absence of HLA identical donor. He underwent HFD-HCT with elder sister (10-years-old, 6/10 HLA match) as donor using APOLLO protocol.[4] His post-transplant course was complicated by fungal pneumonia and BK virus induced hemorrhagic cystitis which were managed as per unit protocol. His MMF was tapered after 30 days post-transplant over 2 weeks, sirolimus was tapered 9 months onwards, and he was off immunosuppression by 12 months post HCT.

Post HCT Day + 538 he presented with complains of fever for 3 weeks associated with oral candidiasis

and poor feeding. His complete blood counts revealed pancytopenia (Absolute neutrophil count: 300/mm^3, Platelet count 8,000/mm^3), bone marrow biopsy suggestive of hypo-cellular marrow with significantly decreased cellularity and 100% donor chimerism. He required multiple transfusions and extended use of antibiotics and antifungals for management of bacterial sepsis and fungal pneumonia. In view of his symptomatology, parents were counselled regarding the need for second salvage transplant. After taking informed consent he underwent a 2nd salvage HCT using same donor. The transplant details during 1st and 2nd HCT are highlighted in Table 1. He tolerated conditioning well and had neutrophil and platelet engraftment on day 14 and 15 respectively. His post-transplant course was complicated by klebsiella sepsis, cytokine release syndrome (CRS) Gr II, engraftment fever (EF) and drug induced hemorrhagic cystitis. All the complications were managed as per unit protocols. As of 25/01/22, he is 140 days post HCT, doing well clinically with no evidence of acute or chronic GvHD, 100% donor chimerism and good immune reconstitution (absolute CD4 and CD19, 443 and 831 cells/mm3 respectively at day 100).

The definitive incidence and treatment of aplasia post HCT for SCD is still not clear. It has been rarely documented and treated with 2nd HCT.[5] The etiology of aplasia and donor chimerism have not been documented clearly in previous reports. Our patient had 100% donor chimerism at the time of presentation with marrow hypoplasia. There is no clear-cut understanding and guidelines for choice of conditioning chemotherapy in such scenario. We decided to go with reduced toxicity conditioning with low dose of serotherapy.

We report successful 2nd salvage HCT in a child with acquired hypoplastic anemia of donor marrow. Our experience suggests that 2nd HCT using same donor and reduced toxicity conditioning is a viable clinical option in a rare clinical setting where previous literature is sparse.

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AUTHOR CONTRIBUTIONS

Gaurav Kharya conceptualized the protocol. Sudhir Sapkota drafted the initial paper. Gaurav Kharya and Atish Bakane edited and finalized the draft. Sudhir Sapkota, Neeraj Teotia and Sakchham Singh compiled the data. All the authors were involved in clinical care of the patient, and read and approved the final version of the manuscript.

CONFLICT OF INTEREST

All the authors declare that there is no conflict of interest.

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Supporting information:

Table 1: Transplant details

REFRENCES

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`Table 1 Transplant details.docx` available at https://authorea.com/users/740722/articles/713442-second-salvage-hematopoietic-cell-transplant-in-a-sickle-cell-disease-presenting-with-acquired-hypoplastic-anemia-of-donor-marrow