Sumerianz Journal of Medical and Healthcare, 2020, Vol. 3, No. 7, pp. 55-58
ISSN(e): 2663-421X, ISSN(p): 2706-8404
Website: https://www.sumerianz.com

Original Article Open Access

Successful Haplo – Haematopoietic Stem Cell Transplantation for Children with Sickle Cell Disease in a Low Resource Country Nigeria

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Article History
Received: June 5, 2020
Revised: June 29, 2020
Accepted: July 3, 2020
Published: July 10, 2020

Abstract

Background: Sickle cell disease is a chronic debilitating disease despite improved clinical management and improved survival. Stem cell transplantation and genetic engineering remains the only cure for the disease. Despite documented successful allogeneic HSCT in Nigeria, the paucity of full matched sibling donors have become a major challenge worldwide. We have successfully commenced Haplo HSCT in Nigeria making donors readily available for HSCT. Methods: Two children with ages 6 and 4years diagnosed with Sickle cell disease had their mothers as donors with HLA 5/10 matched .They had pre-transplant antimalarial, red cell exchange, anti-Helminthic and post- transplant day +7 Rituxamab for positive EBV . Conditioning regimen was with Fludarabin/Dexamethazone days -68 to -64 and days -40 to -36. Antithymocyte globulin(ATG) days -12 to -10, Fludarabin days -8 to -3 and Busulphan days -8 to -5. Both had post transplant Cyclosphosphamide on days +3 and +4.Immune suppression was with Tarcolimus and Mycophynolate mefortil. Results: Neutrophil engraftment for patient 1 and 2 were on days +18 and 17 respectively while for platelets it was day + 21 for both. Patients had 100% Chimerism on day +30 and were discharged on days + 38 and +42 respectively. Discharge parameters for first patient MP was total white cell count 3800/ ul, platelets 124,000 /ul and haemoglobin 10.8 g/dl while for the second patient UM the total white cell count was 3200 /ul, platelets 97,000 ul and haemoglobin 11.5 g/dl. Both patients are on follow up, immune suppression and are clinically stable. Conclusions: Stem cell transplantation remains a major therapeutic option for the cure of SCD. Successful haplo transplant in a private public collaboration in low resource countries will make HSCT readily available for patients who hitherto do not have sibling matched donors.

Keywords: Sickle cell disease; Haplo- transplant; Public private collaboration.

1. Introduction

Sickle Cell Disease is an inherited disorder of haemoglobin which requires the inheritance of two sickle cell genes (sickle cell anaemia) for the manifestation of various signs and symptoms typical of the disorder. Millions of individuals are affected worldwide especially people in the tropics and black Americans. The disease is associated with early mortality in most patients, with unfavourable outcome in the quality of life [1]. The patient is burdened with recurrent pain episodes and progressive damage to vital organs such as brain, lungs, kidney and spleen [2, 3]. There has been improvements in early survival, with advances in supportive care like usage of hydroxyurea, thereby

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creating a growing population of young adults with chronic health issues and complications of sickle cell disease [4, 5].

Nigeria has the highest pool of sickle cell patients in the world [6], about 2.3% of the Nigerian population suffer from sickle cell anaemia and about 25% of Nigerians are healthy carriers of the abnormal haemoglobin gene [7]. The only curative treatment modality for sickle cell disease is haematopoietic stem cell transplantation (HSCT) provided there is HLA-matched donor. In Nigeria, the first HSCT was performed in 2011 by Bazuaye et al at a Government Hospital for a 7 years old child with Sickle cell disease using full matched sibling donor HLA 10/10. As at 2017 a total of three HSCT for sickle cell with full matched sibling donor was done in the government facility while with a private collaboration with Celltek healthcare Medical center in Benin from 2017 to July 2019 a total of seven successful HSCT was done with full matched sibling donors. Activities of HSCT is low as HLA-matched donors are not readily available for most sickle cell disease patients [8, 9]. Celltek Healthcare Medical center has adopted and domesticated a protocol using partially HLA-matched (haploidentical donors). This novel approach has been used successfully in some centres in western countries [10, 11].

We hereby report two cases of patients with sickle cell disease who successfully had haplo HSCT at Celltek Healthcare, Benin City, Nigeria

2. CASE 1

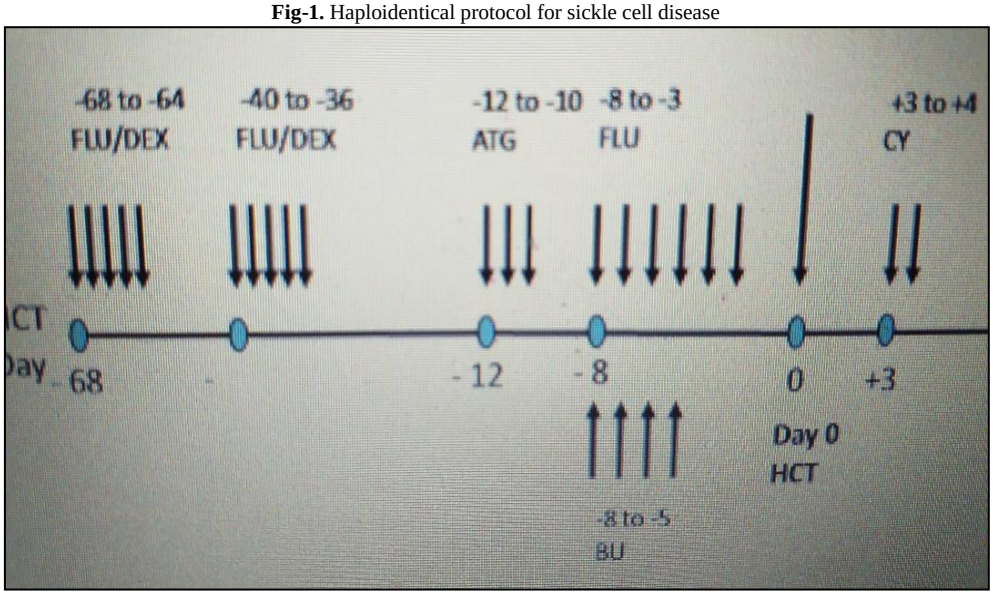
Patient MP was admitted for HSCT in Celltek Healthcare Benin City, Edo State of Nigeria on 27th May, 2019. She was a 6year old female and nursery school pupil who was diagnosed of sickle cell anaemia four years ago. She has had several hospital admissions on account of recurrent crises, acute abdomen, sepsis and malaria. She has had about 2-3 episodes of acute chest syndrome.

She was the second child of the parents in a monogamous setting. The donor was the mother, 42year old with Haemoglobin Phenotype AS and haploidentical with her child (HLA 5/10).Patient and mother had blood group of A Rhesus negative and O Rhesus positive respectively. She has never had blood transfusion in the past and no Donor Specific Antigen (DSA). Screening of Transfusion Transmissible Infections for both the mother and child were not reactive for Hepatitis B surface antigen, HCV, HIV and VDRL.

Her full blood count showed total white cell count of 10,600 /µl; Haemoglobin 10.1 g/dl and platelet 415,000 /ul. She has been on hydroxyurea six months before transplant. Physical examination showed a normal musculoskeletal, neurological, cardiovascular, respiratory and abdominal system. She weighed 23kg, height of 114cm and body surface area of 0.8 m^2. Patient had red cell exchange and Rituxamab to control her minor ABO blood mismatch.

Her conditioning regimen commenced on Day -65 with pulse doses of Fludarabine (FLU), Dexamethasone(Dexa), Bulsulphan(BU) and Antithymocyte globulin(ATG). She received these medications at various days (Fig.1) prior to 4th August, 2019 (Day 0) when she received allogeneic bone marrow stem cells earlier harvested from her mother. Volume of Harvested bone marrow was 879mls with anticoagulants (Heparin and ACD-A in Normal saline).Total nucleated cells was 9.17 x 108 cells/kg transfused over 5hrs with pre -medications of methylprednisolone, promethazine and furosemide. Also given was protamine sulphate (heparin antidote) through 150 mls of normal saline infusion over 5hrs.

Fig-1. Haploidentical protocol for sickle cell disease



In addition to the immune - suppressants, the child was on antibiotics, antifungal agents, antivirals and anti - malaria. She also had lots of supportive treatments especially irradiated blood components (red blood cells and platelet concentrates). He had Rituxamab on day + 7 for his positive Ebstein bar virus positivity.As at Day +57 the child was discharged home with a 100% chimerism, Hb of 10.8 g/dl, WBC of 3,800 /ul and platelets of 124,000 /ul.

3. CASE 2

UM was a 3year old male child who was seen at celltek on 9th June 2019 in preparation for haploidentical Haematopoietic Stem Cell Transplantation. He is a non-identical twin and known HbSS in a monogamous family. He has had several serious crises and an episode of enlarged lymph nodes the previous one month and was placed on acyclovir, antibiotics and steroids which regressed after two weeks. His blood group was O +ve and has never been transfused with blood or any blood products. His stable PCV was 25% and has been on hydroxyurea before HSCT.

Mother was 35year old and haploidentical(HLA 5/10) to the child. The blood group was O+ve and donor specific antigen was negative. Cytomegavirus (CMV), Ebstein Bar Virus (EBV), Retroviral screening (RVS), Hepatitis B surface antigen (HbSAg)/Hepatitis C Virus (HCV) and VDRL screening for mother and patient were negative. No history of addiction to analgesics and no history of any drug allergy. Physical examination revealed a pale child who was anicteric and not jaundiced. His body surface area was 0.64 m2, weight was 15kg, height 100cm and systems were essentially normal. He commenced conditioning regimen on Day -65 with Dexamethasone (Dexa) and Fludarabine (FLU). His Full Blood Count (FBC) was white cell count (WBC) was 17,900 /µl, haemoglobin 7.1 g/dl and platelet 258,000 /µl. He received stem transplantation on 18th August, 2019. He had post transplant cyclophosphamide day +3 and +4 with mycophynolate mefortil and tarcolimus as other immune suppression. His post transplant days had been significantly uneventful. He had good general supportive care especially blood and blood products support. He had 100% chimerism on day +42 and was discharged home with WBC of 3200 /ul, platelet 97,000 /ul, Hb 11.5 g/dl and a haemoglobin phenotype AS.

4. Discussion

There is no cure for sickle cell disease except allogeneic Haematopoietic Stem Cell Transplantation (HSCT) which remains one of the curative treatments of sickle cell disease [10]. However, lack of HLA_matched donor has been a major challenge to a successful HSCT and denying many prospective beneficiaries of the procedure [11]. To address this issue and offer more populations of Nigerians the opportunity of benefitting from HSCT, we devised a transplant protocol in line with published reports documenting successful outcome after haploidentical HSCT [12, 13].

The novel regimen involves post transplant cyclosphosphamide immunosuppression. This was the first time haploidentical (half-match) transplant was carried out in Nigeria, a country reputed to have the highest incidence of sickle cell disease patients in the world. The two patients had transplant without significant HSCT related morbidities as recorded in our full matched sibling donor HSCT.. Without the haploidentical HSCT these patients would still be looking for an HLA-matched donor. With this new method, many more patients stand the chance of being transplanted at very early age before complications of the disease set in.

These two patients tolerated HSCT well without severe toxicities. They were monitored closely for the complications of the regimen which include Fludarabine-related neurotoxicity and dexamethasone-induced hypertension. None of the patients developed any form of Graft-versus-Host-Disease which is the most dreaded acute complication of HSCT. We used bone marrow stem cells which has less GVHD compared to peripheral stem cells and post transplant cyclosphosphamide has been shown to be a potent immune suppressant for Haplo HSCT. There was no graft failure as the two patients demonstrated negative anti-HLA antibodies. Both patients had red cell exchange before transplant to reduce the levels of sickle cell and Rituxamab given to both for ABO mismatch and Ebstein Bar positivity respectively which has been shown to reduce immunological reactions and prevent lymphoproliferation from reactivated EBV.

In conclusion, we have shown that stem cells from related haploidentical donors can offer curative treatment for SCD in addition to increasing the stem cell donor pool. This provides an opportunity to spare many Nigerians the numerous chronic complications of sickle cell disease into adolescence and adulthood as many eligible patients will have asses to HSCT early in life

Acknowledgement

We acknowledge all the staff and management of Celltek Healthcare and Research Centre, Benin City, Edo State, Nigeria for their immense support during the management of these patients.

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