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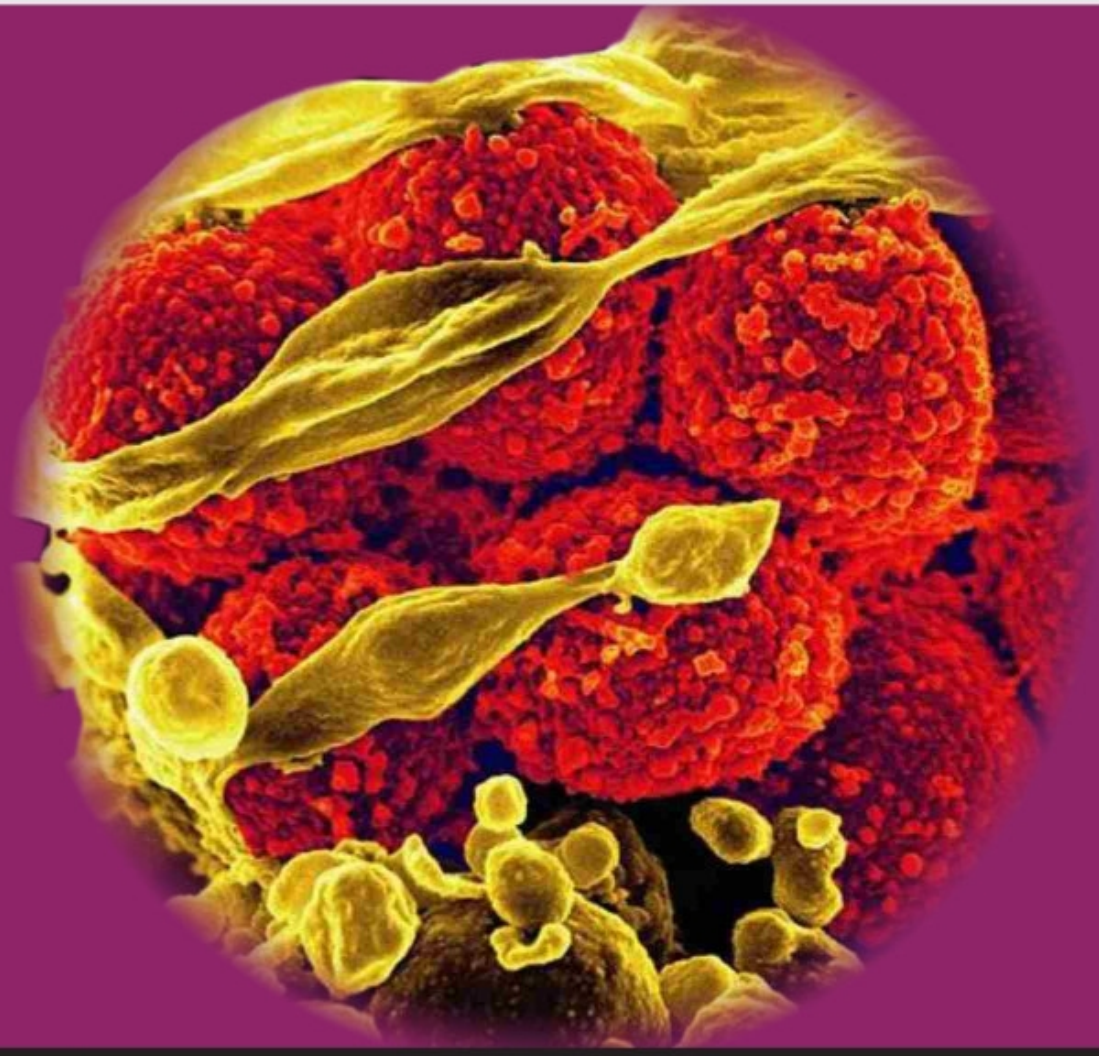

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The First Successful Haematopoietic Stem Cell Transplantation for a Patient with Sickle Cell Disease in a Private Hospital in a Low Resource Country, Nigeria: A Case Report

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ABSTRACT

Background:
Sickle cell disease (SCD) is a chronic debilitating disease and is highly prevalent in Nigeria. Despite documented challenges in setting up stem cell transplant centres in developing resource poor countries, the first successful haematopoietic stem cell transplant (HSCT) in Nigeria was performed at the University of Benin Teaching Hospital, Benin City (a Federal Centre) in 2011. Despite more challenges, we present the first successful HSCT in a private centre in Nigeria for a patient with SCD.

Case Report:
Patient was a 15 year old male with sickle cell anaemia (SCA) who had recurrent acute chest syndrome, stable haemoglobin (Hb) of 7g/dl and pentazocine addicted. The donor was an 18 year-old HLA matched (10/10) sister with haemoglobin phenotype AS. The patient had reduced intensity conditioning (RIC), fludarabine 160 mg/m^2, busulphan 14mg/kg (Flu/Bu) and anti-thymocyte globulin (ATG; ATGAM) 22.73 mg/kg. Graft versus host disease (GvHD) prophylaxis was with cyclosporin A and mycophenolate mofetil.

A total of 6.1 x 10^8/kg nucleated cells, i.e. stem cells from the bone marrow, were transfused on day 0. Neutrophil and platelet engraftment occurred on days +16 and +22 respectively. By day +30, donor chimerism was 68 % and there was no graft versus host disease (GvHD). The patient was clinically stable and was discharge on day +66. The full blood count result showed haemoglobin of 11.5 g/dl, white cell count of 6,200 /ul, platelet count of 113,000 /ul and haemoglobin phenotype was AS (as the donor). One year later, the patient had a 100 % donor chimerism and had not experienced any sickle cell crises.

Conclusion:
A private hospital in a low income country in collaboration with trained personnel from a Federal Teaching Hospital performed a successful HSCT for a patient with SCA despite several documented challenges. There is need for private public partnership to drive and sustain HSCT activities in low income countries like Nigeria.

Keywords: Sickle cell disease, haematopoietic stem cell transplantation (HSCT), private medical centre.

INTRODUCTION

Sickle cell disease (SCD) is the most important genetic disease in Nigeria with a prevalence of 2- 3% of her population of over 170 million persons.[1] Despite improved medical therapy for this chronic debilitating disease and improved life expectancy, complications in adult life are enormous.[2] Haematopoietic Stem Cell Transplantation (HSCT) remains the only cure for the disease and the first recorded stem cell transplantation was in 1984.[3,4] However, only 3% of the world's HSCT is currently performed in the whole of Africa and East Mediterranean.[5,6]

A review by Gluckman *et al* (2017) of a thousand HSCT matched related sibling donors (MRD) for SCD between 1986 and 2013 showed an overall survival (OS) and event free survival (EFS) of 91-100 % and 73-100 % respectively.[3] It also showed a better OS and EFS for younger age groups with OS lower in peripheral stem cell recipients than bone marrow.[3,7,8] Recent studies have shown promising results with the use of haplo-identical stem cell transplantation and gene therapy to cure SCD.[9,10]

Despite several documented challenges of setting up HSCT centres in developing and resource poor settings, the first successful HSCT for sickle cell anaemia (SCA) was performed in Nigeria in 2011 at the University of Benin Teaching Hospital (UBTH) for a seven year old boy with a history of cerebrovascular accident.[11-14] However only three stem cell transplants were performed for SCA from 2011 to 2014 at the UBTH.[15] From 2014 to November 2017, there was no HSCT activities in Nigeria as a result of documented challenges, especially funding, in sustaining established programmes in developing countries.[11-13] With more obvious challenges in private hospital settings, which include more difficulties in funding, fewer equipment and trained personnel, we present the first successful HSCT in a private stem cell transplant centre in Benin City, Nigeria, for a patient with SCA.

CASE REPORT

Patient was a 15 years old patient with SCA and the second of four children in a monogamous setting. The parents were separated as a result of his condition, frequent hospital admissions as well as lack of trust and quarrels with reference to their premarital haemoglobin phenotype results. The patient was referred to the transplant unit in Benin City, Nigeria, for HSCT on account of severe disease based on having over three episodes of acute chest syndrome within two years and a history of addiction to pentazocine.

His stable Hb was 7 g/dl, he had been on routine drugs and had commenced hydroxyurea three (3) months before presenting at the Facility. On examination, he was pale, icteric, no pedal oedema, no palpable lymphadenopathy and he weighed 54 kg. Central nervous system, renal, respiratory, cardiovascular, gastrointestinal and musculoskeletal systems were essentially normal. There were no obvious dental and ophthalmic abnormalities and no evidence of diabetes mellitus.

PRE-TRANSPLANT PREPARATION: The haemoglobin level of the patient was raised above 10 g/dl with transfusion of leucocyte depleted red cell concentrates before transplantation. Serum ferritin, Mantoux test and chest X-ray were normal. Viral screening for human immunodeficiency virus (HIV), hepatitis B and C were negative, but cytomegalovirus (CMV) was positive and his ABO/Rh D blood group was O/positive. The donor was his sister, who was clinically healthy with blood group O/positive, Hb phenotype AS and viral screening tests (HIV, CMV, hepatitis B and C) were all negative. Patient had a full dose of antimalarial therapy and anti-helminthic before the transplant.

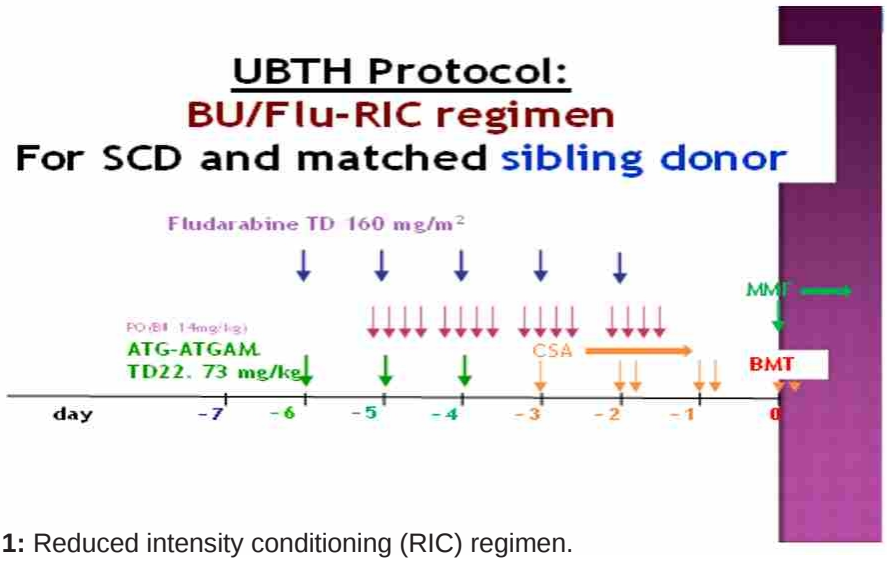

Figure 1: Reduced intensity conditioning (RIC) regimen.

(MMF: Mycophenolate mofetil, TD: Total dose, CSA: Cyclosporin, PO: Per oral, BU: Busulphan, ATG: Anti-thymocyte globulin, BMT: Bone marrow transplantation)

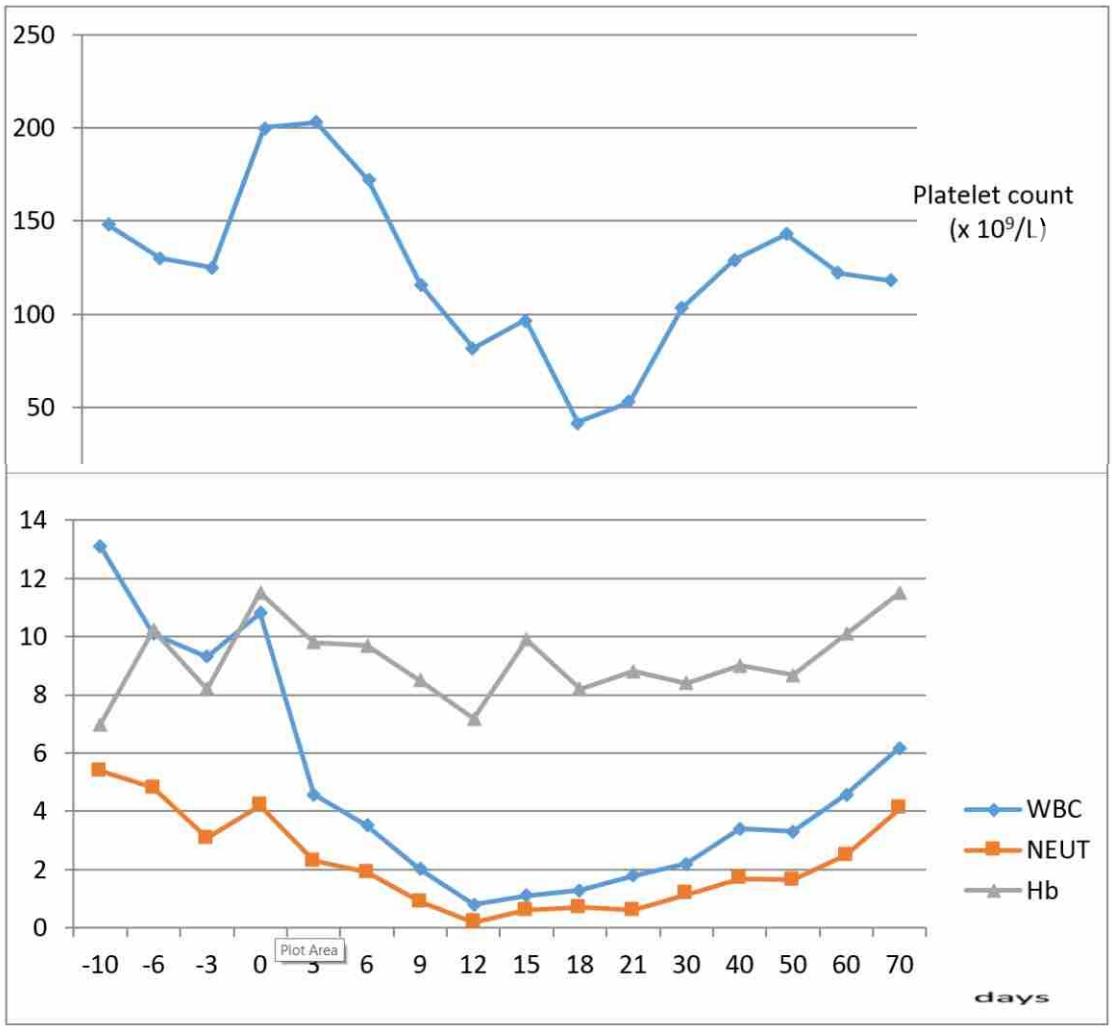

Figure 2: Blood parameters (Platelet count (x 10^9/L); WBC - white cell count (x 10^9/L); NEUT - absolute neutrophil count (x 10^9/L); and Hb – haemoglobin (g/dL)) of patient pre- and post-transplant.

CONDITIONING REGIMEN: The protocol was that of reduced intensity conditioning (RIC) regimen using fludarabine/bulsulphan (FLU/BU) at a dose of IV fludarabine 160 mg/m^{2}TD (days -6 to -2) and oral busulphan 14mg/kg (days -5 to -2; Figure 1). Anti-thymocytes globulin (ATGAM) 22.75 mg/kg and graft versus host disease (GvHD) prophylaxis with cyclosporin A (starting with 5 mg/kg from day -3 and mycophenolate mofetil (MMF) 2 x 500 mg/day from day 0) were given.[15] Other supportive therapy was gut decontamination with oral neomycin and gentamycin; fluconazole and acyclovir for antifungal and antiviral prophylaxis respectively were administered. Also the patient had prophylactic antibiotics throughout the duration of the transplant till the absolute granulocyte count was above 1500 /ul. Continuous heparin (100 IU/kg/day) infusion was administered to keep the central line patent and as a prophylaxis against veno-occlusive disease (VOD).

HAEMOPOIETIC STEM CELL

TRANSPLANTATION: The haemopoietic stem cell source was bone marrow, which was harvested on the 14th of December 2017 under spinal anaesthesia. A total of 1,200mls bone marrow extract was collected containing 120mls of anticoagulant. The extract was filtered and a nucleated cell dose of 6.1 x 10^8 /kg was transfused to the recipient through the central line. Engraftment of neutrophils and platelets occurred on days +16 and +22 respectively.

The patient had two units of platelet concentrates and one unit of packed red blood cell that were irradiated (using the routine radiotherapy machine to deliver 25Gy). There was no evidence of acute or chronic graft versus host disease (GvHD), donor chimerism was 68% at day +30 and patient was discharged home on day +66. At discharge, full blood count parameters were Hb of 11.5 g/dl, white blood cell count (WBC) of 6,200 /ul, and platelet count of 118,000 /ul. The changes in the blood parameters pre- and post-transplant are presented in Figure 2. The prophylaxis regimen used for GvHD was cyclosporin A and MMF, which were tailed off at 4 and 8 months respectively. The patient had immunization with non-live attenuated vaccines from 8 -10 months. At one year post transplant, the patient was clinically stable with no evidence of crisis, he had 100% donor chimerism, Hb phenotype was AS and was no longer on any routine medications for SCD.

DISCUSSION

Since the first recorded HSCT for SCD in 1984, the contribution of Africa and East Mediterranean to global HSCT data has been very low (3%).[4-6] Before 2011, Nigeria contributed no HSCT data to the world's registries. The first successfully recorded HSCT in Nigeria for sickle cell disease was in 2011 and between 2011 and 2013, only three successful HSCT for sickle cell disease were done at the Federal University Teaching Hospital.[15] Despite a 100% overall survival, the last recorded HSCT in Nigeria was in 2013 and there was no HSCT activity from 2014 to 2017. The explanation for this includes some documented challenges like, the huge financial cost of setting up and maintaining a transplant centre, lack of political will and inability of government to establish and sustain already established programmes. In order to sustain HSCT activities in Nigeria, there was the collaboration of a private hospital with trained personnel from the teaching hospital that was initiated in December 2017. There are more challenges in the private hospital, especially in a developing country, that include shortage of trained personnel, which was partly resolved by the collaboration with trained personnel from the teaching hospital and the cost of transplantation itself, as the patient had to pay out of pocket due to non-availability of Health Insurance that should cover transplantation and challenges of security etc.

The same RIC protocol (Figure 1) and prophylaxis reported in the previous HSCT performed at the University of Benin Teaching Hospital, Benin, Nigeria, was adopted for the index patient and this has been shown to be a

successful protocol with minimal complications when compared with full myeloablative conditioning regimen.[16] The haemopoietic stem cell source was bone marrow, which is associated with fewer incidences of GvHD compared to peripheral blood stem cells sources.[17] The central line was cared for using standard protocol and was changed every two to three weeks with no recorded significant catheter infection.

The index patient did well clinically, with full donor chimerism and no evidence of GvHD. Due to the lack of standard diagnostic tools, in developing countries like Nigeria, for viral and fungal infections, there was a need to administer prophylactic antiviral and antifungal agents throughout the transplant, which were stopped after day +200. Also blood components were irradiated by the old convention of using routine radiotherapy machine to irradiate the leucodepleted platelets and red cell concentrates. This method may not be as effective as the standard method of irradiation, but it is the only available method to irradiate blood components in a developing low resource country like Nigeria. However there was no recorded significant infection in this index patient who had the irradiated products.

He is currently clinically stable without any overt manifestation of SCD and we believe this outcome is a result of careful and meticulous patient/donor selection and the younger age of patient. Similarly, the use of a HLA-matched sibling donor as it was in this index donor has been shown to have a higher OS and DFS when compared with matched unrelated donors.[3] The patient was reviewed every two weeks for the first 3 months of discharge followed by monthly visits until 12 months post-transplant. There is need to explore the use of low dose total body irradiation with Alemtuzumab, especially for adults with SCD and haplo-idententical stem cell transplantation for those who do not have matched sibling donors.[18]

CONCLUSION

Patients with SCD have a very high chance of a disease free survival with HSCT, especially in children with matched sibling donors. Despite the challenges of performing HSCT in low income country like Nigeria, HSCT may be successfully performed in collaboration with experts in the private sector with adequate facilities and trained manpower. There is need for government in low income countries to play an active positive role in establishing and sustaining existing centres. Private public partnership (PPP) should be encouraged to make this, all-important procedure, readily available to the vast population with the high burden of SCD and other indications for stem cell transplantation.

Conflict of Interest:

No conflict of interest to declare.

Author's Contributions:

The study was designed by BGN and I-AYT; data was collected by all and interpreted by BGN. Data was analysed by BGN and OIN. The literature search and manuscript preparation by BGN.

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