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REVIEW ARTICLE

Challenges of bone marrow transplant for sickle cell disease in resource limited setting

[1]Chisara Sylvestina Okolo, [1]Ayodeji Olusola Dickson Olayanju

[1]Department of Medical Laboratory Science, Afe Babalola University, Ado-Ekiti, Ekiti State.

Corresponding Author:
Chisara Sylvestina Okolo

EMAIL:
okolocs@abuad.ed.ng
olayanjua@abuad.edu.ng

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Summary

Sickle cell disorders (SCD) are a group of inherited disorders that results from both parent being carriers, haemoglobin AS resulting in haemoglobin (SS), causing anemia, infections, pain, stroke, priapism, sequenstration crisis, multiple organ dysfunctions etc. There are several ways of managing sickle cell disorder but the best way, which is considered a gold standard cure for the disease is a successful bone marrow transplant of haematopoietic stem cells (HSCT). Bone marrow (BM), Peripheral blood (PBSC) and Umbilical cord blood (UCB) are rich in stem cells. In order to have a good bone marrow transplant, without graft rejection, the laboratory plays a vital role especially in compatibility testing of donor and recipients at the various stages of the transplant, which includes initial stage, during the transplant and follow up testing to ensure tolerance to the new graft and testing for chimerism. There are various types of transplant which include Autologous, Allogeneic (Sibling/ Unrelated Donor), Parent or relative, etc. The various pre transplant tests includes: Sickling test, High Performance Liquid Chromatograph (HPLC), Genetic studies, RBC Indices Hb – 6-9 gm/dL, Peripheral Smear, Retic count Reticulocytosis, ESR, Bone marrow analysis. Post-transplant test Includes Engraftment Analysis, Complete Blood counts, kidney function, liver function, Cholesterol, HIV, Hepatitis B, Hepatitis C, additional infectious studies (Endemic testing), Urinalysis etc. Haemopoietic transplantation challenges in a resource limited settings like Nigeria are enormous and they includes: Danger of serious illness associated with donor-to-patient stem cell transplant, lack of appropriate donors, Graft-versus-host disease (GVHD), Inadequate Human resource, Inadequate equipped facility, cost of the service, Corruption, Lack of political will, Leadership incompétence, Lack of

strategic planing, Policy inconsistency, Lack of qualified personnel, Poor healthcare administration, Conflict of interest among health workers. The cost of Bone Marrow Transplantation is highly exorbitant to Nigerians and government need to play vital role towards funding part of the cost and alleviating the pain of sickle cell. Effective implementation of National Health Insurance Scheme and address corruption are the most efficient ways the cost would be subsidized. Appropriate information campaigns largely championed by maternal and child health-care professionals would significantly contribute to raising the level of awareness and acceptance of Cord Blood donation. Training and re training of medical personnel cannot be over emphasized.

Keywords: Sickle cell, Haematopoietic Stem Cells, Resource Limited Setting

Introduction

Sickle cell disease (SCD) is an inherited disorder characterized by severe morbidity, impaired quality of life, pain crisis, organ failure, stunted growth (1). Sickle cell disease (SCD) and its variants are genetic blood disease caused by replacement of an adenine(A) for a thymine (T) in the sixth condon of the beta –globin gene on chromosome 11(2,3) this replacement results in hydrophilic glutamic acid being changed for hydrophobic valine and production of haemoglobin S(HbS) (3-5).

The burden of sickle cell disease is enormous in Nigeria that about every eight out of 100 infants die annually as a result of sickle cell (5,6) and 24% of adult are carriers of sickle cell disease and about two out of every 100 births are haemoglobin (SS), annual infant death of 100,000 representing 8% of infant mortality in the country(5,7,8).

Aside the pre mature death of sickle cell disease patients other burdens includes psychosocial challenges within the family, where other members of the family are being neglected, quarrels, huge financial burden(9), emotional stress, lifestyle disruption, denial of church wedding due to haemoglobin AS carriers (7,8,10,11). Therefore, Nigeria is considered to be the epic center of the disease and the government is not doing enough to tackle the disease.

The only permanent cure, which is considered a gold standard is haemopoietic stem cell transplant (HSCT) which is a very exorbitant venture in Nigeria. The cost of transplant in Nigeria in 2011, which was performed by Prof Bazuaye *et al*, cost about N5million(12) could be up to N10 to N15 million currently. Nigeria currently have just two bone marrow transplant centres, one in Benin, Edo state and, another one in Lagos University Teaching Hospital (LUTH) which was established in collaboration with Sickle Cell Foundation.

Who is eligible for HCT, in terms of both disease severity and psychosocial factors?

HB SS, HB SC and HB β^{0}children (<16years)

with matched HLA sibling donors should be encouraged to undergo HSCT having significant symptomatology(13). For HSCT, those SCD patients who are on hydroxyurea or other anti-sickling drugs yet were still having stroke, regular vaso-occlusive crisis greater than three times in a year are considered eligible for bone marrow transplant., acute chest syndrome(13,14). It has been documented that HLA-identical sibling donor HSCT offers about 95% cure, with minimum danger of major complications that could lead to death(13). Report has shown that elevated reticulocyte, and transcranial Doppler may later develop disease severity(13). Hereditary persistence of fetal hemoglobin (HPFH) children should not be bothered with HSCT because fetal haemoglobin protects the cells from sickling, therefore no serious health challenges(13).

Initial Diagnosis

A thorough family studies are extremely useful, and detailed haemoglobin evaluation is essential in the initial diagnosis of an individual suspected to be a carrier of haemoglobin S(15). Comprehensive hematologic evaluation, which includes haemoglobin electrophoresis, high-performance liquid chromatography (HPLC), examination of the peripheral blood smear, and qualitative sickle solubility assay, are a must. Other test such as pyruvate kinase (PK) deficiency that increase the likelihood of HbS polymerization should be carried out(15). Perform hemoglobin electrophoresis or High Performance Liquid Chromatography(HPLC) which separates the constituents of haemoglobin (16,17). Genetic testing shows heterozygosity for HbS(15).

Sources of Haematopoietic Stem Cells

The sources of haemopeitic stem cell includes Bone marrow (BM), Peripheral blood (PBSC) and Umbilical cord blood (UCB) which are very rich in stem cells(18). In order to have a good bone marrow transplant, without graft rejection, the laboratory plays a vital role especially in compatibility testing of donor and recipients at the various stages of the transplant (19,20), including initial stage, during the transplant and follow up testing to ensure tolerance to the new graft.

Donor Selection

HSCT donation involves aspiration of marrow cells from the hip bone mainly, and other sites of where stem cells are gotten such as the anti-cubital fossa for apheresis peripheral blood donation(18). The donation should be excluded when excessive risks for the donor are involved such post donation deaths due to cardiorespiratory arrest, pulmonary embolism, severe blood loss, wound infection, pain at the site of puncture, fatigue, low back pain, headaches, nausea, walking difficulties, and sleep disorders. Rarely, long-term adverse effects may occur, such as chronic pain at the donation site and the need of iron supplementation, blood transfusion in minors who donates for larger recipients(18). Granulocyte colony-stimulating factor (G-CSF) in peripheral blood (PB) transplantation donation may likely be related with bone pain. The risks of heterologous blood products, thrombocytopenia, and spleen rupture are likely to occur(21). Donors must receive a detailed information about the procedure, some adverse eventualities, health burdens involved, and informed consent, for the donation to be an altruistic act like donation and, the recipient's risks must be outweighed by the expected benefits(21). The use of HLA-identical sibling donor is the best and most preferred for HSCT, but on the other hand, unrelated donor. HSCT is a valid option for allogeneic bone marrow transplant of SCD patients who do not have an HLA-identical sibling donor '(20,22). During donor selection, all the classes (Class I: HLA-A,

HLA-B, HLA-C; Class II: HLA-DR, HLA-DQ; Class III: Complements and cytokines) of major histocompatibility is preferred to be 10/10 for better survival '(22). In matched Related Donor (siblings) 25% chance a sibling will be full match and the more siblings a patient has the better chance for a compatibility match.

Compatibility Testing

There are mainly three types of compatibility testing done to evaluate donors, these includes blood type, cross match, and HLA testing(23). For the purpose of transplantation HLA testing is inevitable. HLA which stands for Human leukocyte Antigen, are proteins clustered in the major histocompatibility complex (MHC), located on the short arm of chromosome 6(23,24). Essential for Allogeneic transplant are the Class I (HLA-A, HLA-B, HLA-C), Class II (HLA-DP, HLA-DR and HLA-DQ) and, Class III (Complements and cytokines)(23). Unrelated allogeneic hematopoietic stem cell HLA-A, -B, -C, -DRB1 and DQB1 loci match is done at high resolution typing of 10/10 between donor and recipient and it plays an important role in the outcome of HSCT(25). HLA compatibility of 10/10 usually have HLA DPB1 mismatches, due to the low LD **Types of Bone Marrow Transplant.**

between DPB1 and other HLA class II loci(26). Allogeneic HSCT HLA mismatch from unrelated donors will result in graft rejection and acute graft versus host disease (GvHD)(25). The only cure for sickle cell disease is HSCT which requires a matched donor(18,26,27). HSCT procedures takes precautions so that the entire donation/transplantation procedure is safe for both donors and recipients(18).

Allogeneic transplant

HLA-matched sibling donors

HSCT from HLA-Identical matched sibling donor gives normal erythropoiesis with stable long-term engraftment, ameliorates symptoms, stabilizes organ damage and has given excellent rates of survival(1,27).

Umbilical cord blood (UCB) transplantation

It is the supply line that connects the baby to the mother's placenta during embryogenesis. UCB is alternative hematopoietic stem cell source for patients with hematologic diseases who can be cured by allogeneic hematopoietic cell transplantation, it was limited to children, its low cell dose infused(28). Umbilical cord blood transplantation has improved tremendously, with greater emphasis on cord blood units of sufficient cell dose and human leukocyte antigen match and with the use of double umbilical cord blood units and improved supportive care techniques (28). HLA mismatch is tolerated even with haploidentical donors.Lack of awareness is a major limitation to harnessing the benefits of umbilical cord blood (UCB) in sub-Saharan Africa. Factors such as religion, education, information from health-care provider appear to influence awareness, and the decision to donate and use UCB(29).

Matched unrelated donor transplantation

Allogeneic HSCT remains the only curative therapy for SCD but its use is limited by lack of suitable HLA-matched donors (30). HLA-matched unrelated donor uses the most suitable HLA match at high resolution typing of 10/10 '(22).For patients without HLA-matched sibling donors, but who are eligible for transplant, fully allelic matched unrelated donor (8/8 HLA-A, B, C, DRB1) appears to be the next best option, there are high Graft versus

Host Disease(GvHD) rates and low engraftment rates in some of the unrelated donor transplant and, institutional expertise is needed for its use(31).

Haploidentical transplantation

This is half-matched transplantation; it could be from parent or relatives. The establishment of unrelated adult donor registries and cord blood banks has given those without HLA identical sibling donor the chance to find a suitable donor and cord blood units(18). The HLA-matched unrelated donors and haploidentical donors use has the ability to expand the applicability of HSCT for SCD(1). It is said to have less Graft versus Host Disease(GVHD) but, improvements are needed to increase the engraftment rate(31).

Autologous transplantation: Autologous stem-cell transplantation is transplantation in which stem cells are removed from a person, stored, and later reinfused back to that same person. It is easier to collect cells, more rapid hematopoietic recovery, cheap and mainly use for transplants in pediatrics.

Post transplantation testing and monitoring

After a successful HSCT, the following tests should be done to monitor the transplant:

Chimerism testing (engraftment analysis)

Chimerism analysis has become an important tool for the post-transplant observance engraftment. It indicates impending graft rejection, it monitors engraftment and treat imminent relapse by pre-emptive immunotherapy(32).

Other essential routine test are:

Bloodwork

- Complete Blood counts,
- kidney function
- liver function
- Cholesterol
- HIV
- Hep B
- Hepatitis C
- Urinalysis

Cost and other challenges of accessing bone marrow transplantation

In Nigeria, efforts worthy of commendation have been made by Bazuaye et al in 2011 at the University of Benin Teaching Hospital (UBTH), Benin City, Nigeria in pioneering the procedure in Nigeria(12). Currently, the procedure is available in only two centres in Nigeria: Igbenedion University, Ogada Edo State and National Sickle Cell Centre,Opp Lagos University Teaching Hospital(LUTH), Ishaga Road, Idi-Araba, Surulere, Lagos. Nigeria. (commissioned on 3rd of February, 2022).

Nigeria requires HSCT that will be affordable and available. In 2011, government paid for the first HSCT which was estimated at 5million naira (30,000 dollars) (12). Expensive drugs, power generation and expensive reagents contributes to the expensive procedure. The challenges of setting up a HSCT Unit in are enormous(12). Some of the challenges face includes : cost of the service, Corruption, Lack of political will by the government, Leadership incompetency, Lack of strategic planing, Policy inconsistency, Lack of qualified personnel, Poor healthcare administration, Conflict of interest among health workers(33).

Perfoming Bone Marrow Transplantation in Resource Limited Setting – Way Forward

Nigeria as a third world country lack the basic amenities for its citizens, carrying out an advanced technique like HSCT is a huge task that requires government intervention. Lack of infrastructure/Equipment, appropriate machine for segregating of stem cells after

harvesting, Selection of donor and patients, technical expertise on how to carryout HLA typing, there is no Supportive care in Nigeria like international standards, and blood donation is mainly commercial(27).

Challenges

Risk of serious illness associated with donor-to-patient stem cell transplant includes: lack of appropriate donors, Graft-versus-host disease (GVHD), Inadequate Human resource, Inadequate equipped facility(27).

Ways of reducing the high cost of transplant in Nigeria includes:

Private public partnership: private sector should partner with government in order to bring about quality health in Nigeria(12).

Government intervention: Government should subsidize healthcare to enable the down trodden and the not well to do to avoid quality health services in Nigeria.

National health insurance scheme(NHIS): HSCT should be included in the NHIS programme so that poor man can afford basic health intervention.

Faith based institution: Religious bodies should contribute in building a quality healthcare system for our citizens(33).

Government Efforts at reducing cost of BMT

Making policy: for any society to make move forward and progress there should be a robust and cost effective management system that is capable of utilizing the nation's scarce resources to the benefit of all. The cost of HSCT is high and should be reduced by the type of policy government placed on the table concerning healthcare system in Nigeria.

Subsidizing: government should make concerted efforts at making policies that would impact positively on the lives of her citizens. Subsidizing healthcare is one of such policies that has been waiting government nod(33).

Competing interests

The authors have declared no competing interests exist.

Authors' contributions

AOO designed the protocol, supervised the research and edited the first draft.

CSO performed literature search, editing and correspondence

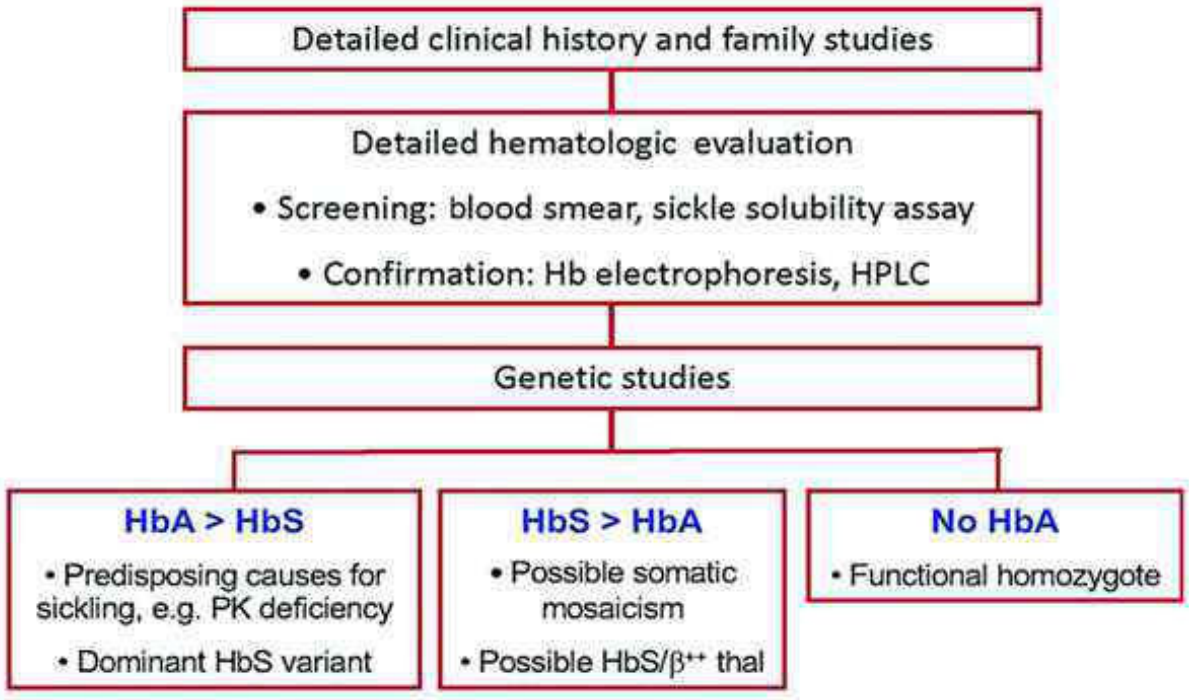

Figure 1: Initial Lab Test **(15)**

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