Haematopoietic stem cell transplantation: Prospects and Challenges in Nigeria

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SUMMARY

In developed economies, Haematopoietic Stem Cell Transplantation (HSCT) has come to stay as a last resort to salvage several patients suffering from various haematological and non-haematological diseases. However, it remains a dream for the majority of the patients who are either without health insurance or reside in developing nations as they are unable to afford its enormous costs. Technological inequalities, brain drain and lack of political will have also impeded effective transfer of the necessary expertise.

In Nigeria, the awareness of HSCT is limited. Our specialists are handicapped by the challenges posed by our poor infrastructure on the one hand and on the other hand; graft-versus-host disease (GVHD), post-transplant infections, relapse and organ toxicity. Sadly, because of these limitations, sickle cell anaemia, which is likely foremost beneficiary of HSCT in our environment, has not been able to attain the level of successes achieved with thalassemias in Europe and the USA. One must however point out quickly, that local opportunities at HSCT will go a long way to developing local expertise and innovation, boost confidence and ultimately improve management results. These benefits will all be lost if we continue to refer our patients to centres outside Nigeria. A major obstacle to obtaining HSCT in foreign countries by Nigerians is in compatible donor selection.

While we await the effective take-off of the National Health Insurance Scheme (NHIS), it is however instructive to note that a private-sector-driven HSCT initiative was recently started in India in spite of in order to ensure its affordability, acceptability and continuity. In this, the Federal Government should provide adequate funding.

INTRODUCTION

HSCT (or SCT) is the term currently used to describe the collection and transplantation of hematopoietic stem cells (HSC or SC). The procedure is performed either to replace an abnormal hematopoietic system with a normal one or treat non-hematopoietic malignancies by allowing the administration of myeloablative doses of chemo-radiotherapy (CRT). Beyond Nigeria, HSCT continues to be increasingly relevant, both because of its proven efficacy in several diseases and the increasing availability of donors. The European Group for Bone and Marrow Transplantation (EBMT) estimates that 19,203 and 20,207 transplants were performed in 2000 and 2002 respectively[1].

The Hematopoietic Stem Cell

The human HSC is capable of regenerating the entire lympho-hematopoietic system (LHS). This remarkable capacity for differentiation and proliferation in addition to its ability for cryopreservation and homing to the marrow has made HSCT clinically feasible. Transplantation of adequate donor HSC regularly results in complete and sustained replacement of the recipient's LHS; all red and white cells, platelets, as well as monocyte-

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macrophage population. The homing ability of the HSC following intravenous injection is mediated largely by the interaction between their integrins and the selectins on the bone marrow endothelial cells (EC). Human HSC can survive controlled freezing and thawing with minimal damage, making it possible to collect patient's marrow for later reinfusion following treatment with myeloablative therapy[2].

Brief History of HSCT

After the first infusion of a few milliliters of bone marrow was carried out on a patient with severe aplastic anemia in 1939[3], Bortin[4] reported on 203 allogeneic BMTs done between 1950 and 1962, all of which failed. Real progress was elusive until the late 1960s when the importance of the HLA system was recognized. In 1968, the first successful related allo-grafting was done[5]. In 1975, another review of the experimental background of marrow transplantation of 37 patients was published where some survivors were described[6]. The success of the first unrelated allo-grafting in 1979[7] stimulated the formation of the bone marrow donor registries worldwide.

The history of HSCT is incomplete without mention of the 1990 "Nobel Prize for Physiology and Medicine" shared by Dr. E. Donnall Thomas and Dr. J. Murray for work in the field of HSCT.

Types of HSCT

HSCT can be described according to the relationship between the patient and the donor and by the anatomic source of stem cells.

✦ Patient-Donor Relationship

1. *Syngeneic HSCT*: This is possible in about 1% of patients[8] i.e. those with identical twin donors. This is the best source of HSC; because there is no risk of contamination with tumor cells. With regards to "GVHD" however, that given sub-optimal peri-transplant immunotherapy, clinical conditions indistinguishable from aGVHD may develop[9].

2. *Autologous HSCT*: This involves the transplantation of self HSC; usually after high-dose

CRT. Engraftment is usually fast and host immunity is promptly recovered. However, auto-SCT lacks a graft-versus-tumor (GVT) effect, and the graft may be contaminated with tumor cells. The "GVHD" risk is similar to that in syngeneic SCT.

3. *Allogeneic HSCT (allo-SCT)*: This involves an immunologically different donor-recipient pair. After allo-SCT, T-cells arising from the graft may cause GVHD. Conversely, if pre-transplant immunosuppression is inadequate, host-versus-graft (HVG) reactions (rejection) may occur. The risks, direction and extent of these immunological sequellae are largely dependent on the degree of donor-recipient matching for the major (and recently too, the "minor"[10]) histocompatibility antigens.

✦ Stem Cell Sources

1. *Bone marrow stem cells*: Marrow is usually obtained from the donor's posterior iliac crest, under anesthesia; and filtered into anticoagulant solutions. Typically, a maximum of 10-15 ml/kg donor body weight (DBW) or 1.5L (whichever is smaller) are collected; which gives about 2-5 x 10^6 CD34$^+$ cells /kg recipient body weight (RBW)[11, 12]. Post-collection processing; such as red cell or T-cell depletion (TCD), or purging may then follow[12]. Marrow donation is a safe procedure, with only occasional mild complications reported.

2. *Peripheral blood stem cells*: Ordinarily, few HSCs circulate in the peripheral blood but the administration of hematopoietic growth factors (HGF) or chemotherapy (CT) mobilizes many more making it possible to harvest adequate HSCs for transplant. Donors are given 4-5 days of HGFs, following which HSCs are collected in one or two apheresis sessions[12]. For auto-SCT, at least 2.5 x 10^6 CD34$^+$ cells/kg body weight lead repeatedly to rapid and sustained engraftment[12]. Compared to the use of auto-BMSC, PBSC results in more rapid engraftment of neutrophils and platelets. While the use of PBSC reduces the morbidity of SCT, no studies have shown any improvement in survival in hematological malignancies. The initial reluctance to use PBSC for allo-SCT was because it contained

more T-cells than BMSC and may increase the incidence of GVHD[13]. Even though trials consistently show the use of HGF-mobilized PBSCs (from matched related donors) led to faster engraftment and only a trend towards increased incidence of aGVHD, however, no significant improvement in overall survival (OS) has been proved. Chronic GVHD (cGVHD) is significantly increased with PBSC, but this has been "balanced", at least in patients with malignancies, by reductions in relapse rates (RR) and non-relapse mortality[13]. This is because there is an increased likelihood of cGVHD after aGVHD, and grade I-II aGVHD (as compared to absence of aGVHD or grades IV aGVHD) have been clearly linked with reduced RR[13].

3. *Umbilical cord blood*: Cord blood (CB) contains a high concentration of HSCs and gives the advantage of immediate availability and significantly lower incidence of GVHD but slower engraftment compared to the other sources[14]. This is due largely to low numbers and immaturity of the T-cells in CB. However, the small dose of SCs obtainable has limited its use to the pediatric setting. In recent times, CB banking has developed in several countries. Nigeria definitely has an advantage in the availability of cord blood considering the high delivery rates; moreso as they are otherwise discarded.

Transplant Immunology
Exogenous or endogenous antigens are presented by antigen-presenting cells (APC) to T-cells. If unmatched for HLA antigens, T-cells from one individual will react with the mismatched "major" antigens, of the other. Between HLA-matched donor-recipient pairs, donor T-cells may react to differing "minor" antigens. Luckily though, reactions to minor antigens tend to be less intense. The MHC genes on chromosome 6p occupy code for HLA- A, B, C, DR, DQ and DP. On account of the rarity (~2%) of crossover events, they tend to be inherited en-bloc (haplotypes). Thus, the odds that any one patient will have an HLA-identical sibling is 0.25; defined by the equation; $\{p = 1-(0.75)^n\}$[8] where n equals the number of siblings. Consequently, an A/B/DR (6/6) in siblings as opposed to an A/B/C/DR/DQ (10/10) antigen match in unrelated donors, is sufficient to establish full HLA identity[15].

Bone Marrow Registries
The HLA genes are the most polymorphic of human genes, and thus the chances of any two unrelated persons being identical are in the order of 1 in 10,000. However, with increasing number of donors from various registries, HLA-matched unrelated grafting are now achievable for ~70% of patients of Caucasian stock and can now be found for over 50% within 3-4 months of search. The overall success rate has been put at 83% for all Caucasian patients[16]. In the absence of registries, it is only reasonable to assume that Nigeria's first transplants would be MRDs.

Purging techniques
A variety of techniques have been developed to rid auto-grafts of tumor cells.
1.   Antibodies (with or without complement) against tumor-specific antigens conjugated to toxins or to immuno-magnetic beads[17].
2.   In-vitro chemotherapy (CT) exposure and long-term culture[18].
3.   Positive selection of CD34$^+$ HSCs using antibodies, with subsequent column adherence or flow cytometry[17-19].

All these techniques can reduce the tumor load 3- to 5-logs. It may however be a while before they result in a significant decrease in relapse-free survival (RFS) or improvements in disease-free (DFS) or overall survival (OS).

THE TRANSPLANT CONDITIONING REGIMEN
The pre-transplant conditioning regimen achieves three main objectives;
a) Immunosuppression, to prevent the rejection of the transplanted marrow. This has emerged to be the most important reason for conditioning.
b) Anti-tumor effect, to eradicate the patient's underlying malignancy and
c) Myeloablation, the "marrow-space creating" function; which initially lost favour but appears to retain some relevance in the allo-transplant of patients with hemoglobinopathies, in whom there appears to

be a distinct place for creation of "marrow-space".

Different regimens have been developed for varying diseases, SC sources, whether related or otherwise and the extent of HLA-matching. Most include agents that have high activity against the primary disease and have myelosuppression as their predominant dose-limiting toxicity. Therefore, busulfan, cyclophosphamide, melphalan, thiotepa, carmustine, etoposide, and total-body irradiation (TBI) are commonly used in various combinations. Some examples will suffice here;

a)Acute lymphoblastic leukemia (ALL): TBI (fractionated, 14 Gy) and cyclophosphamide (Cy, 200 mg/kg BW, in divided doses over 4 days).

b)Thalassemia and sickle cell anemia: busulfan (14-16mg/kg BW, in divided doses over 4 days) and cyclophosphamide (200 mg/kg BW) are routinely used to eradicate the hyperplasic host haematopoiesis.

c)Severe aplastic anemia (SAA): Cy (200 mg/kg BW) and antithymocyte globulin (ATG) are sufficient to immunosuppress the patient's hypoplastic marrow.

THE TRANSPLANT PROCEDURE

The SC products are typically infused through a large-bore central venous catheter and are usually well tolerated. A few patients may develop fever, cough, or dyspnoea; symptoms which usually resolve with slowing of the infusion. If the product has been cryopreserved with dimethyl sulfoxide (DMSO), patients often experience short-lived nausea or vomiting due to its odour and taste.

ENGRAFTMENT

Clinically, engraftment is defined as the first appearance of an absolute neutrophil count of =500/uL at daily estimation over three consecutive days. However, the absolute definition of cellular engraftment is more rigorous and may entail fluorescence in situ hybridization (FISH) of sex chromosomes if donor and recipient are sex-mismatched, HLA-typing if HLA-mismatched, or restriction fragment length polymorphism (RFLP) analysis if sex- and HLA-matched[20].

Daily estimation of full blood counts (FBC) usually reveal progressive cytopenias with nadirs occurring by day 4 to 8 post-transplant due to the conditioning regimen, with donor cells appearing by day 10 to 18. The speed of engraftment depends on the HSC source, bone marrow, degree of HLA-match, use of post-transplant HGFs, the prophylactic regimen against GVHD and the presence or absence of GVHD[20].

When BMSC is used without HGF, engraftment occurs about day 20 while the use of PBSC may speed engraftment by as much as 5-7 days. Use of post-transplant HGF (usually G-CSF) can further accelerate engraftment by 3-5 days, whereas use of methotrexate delays engraftment by a similar period[8].

COMPLICATIONS FOLLOWING BONE MARROW TRANSPLANT
Chemoradiotoxicities[8, 21]

Early-onset complications include:
a) Nausea and vomiting.
b) Severe pancytopenia, hence patients are usually supported with several irradiated CMV-negative blood products.
c) Mild skin erythema.
d) Hemorrhagic cystitis from high-dose cyclophosphamide. This can be prevented by pre-hydration and administration of mercaptoethanesulfonate (MESNA).
e) Oral mucositis typically develops by day 5 to 7; for which narcotic analgesia and parenteral nutrition may be necessitated until engraftment has taken place.
f) Hair loss typically begins from day 5 to 6 onwards.
g) Venoocclusive disease (VOD) of the liver: This occurs in ~10% of patients with the peak incidence at day 16. It usually manifests as tender hepatomegaly, ascites, jaundice, and fluid retention; with a mortality of ~30%. Defibrotide, a new drug, has shown promising results in contrast to the use of tissue plasminogen activator (tPA), heparin and PG-E.

h) Interstitial pneumonia; develops in ~5% of patients from direct toxicity of the preparative regimen. Bronchoalveolar lavage (BAL) typically shows alveolar hemorrhage. High-dose glucocorticoids continue to be tried in randomized trials.

The heavily pretreated elderly patients tend to present with markedly reduced cardiac, pulmonary or renal reserves and dermatopathies associated with cumulative toxicities.

Late direct chemoradiotoxicities[22]

a) Decreased growth velocity in children and delayed development of secondary sex characteristics, hence growth and sex hormone replacement may be necessary.
b) Azoospermia in men and ovarian failure in post-pubertal women.
c) Thyroid dysfunction is sometimes seen.
d) Cataracts develop in 10-20% of patients; especially in those treated with TBI and high-dose glucocorticoids.
e) Aseptic necrosis of the femoral head may arise in ~10% of patients; particularly those receiving long term glucocorticoids therapy.

GRAFT-VERSUS-HOST DISEASE
Acute GVHD

GVHD results from allogeneic T-cells arising from the graft, reacting with host antigenic targets. By convention, GVHD developing before and after day 100 post-transplant are termed aGVHD and cGVHD respectively; but this concept is changing with the occurrence of severe aGVHD after day 100 after reduction of the intensity of the conditioning regimen [8, 13, 23]. Acute GVHD usually starts between day 10 and 28, and it is characterized by an erythematous rash, persistent anorexia or diarrhea, or both; and liver disease. Tissue biopsies may be needed for confirmation of GVHD. [13, 24]. Grade I aGVHD is mild and usually requires no treatment while grades II-IV are associated with poorer survival and are therefore treated aggressively[13]. The incidence of aGVHD is higher in patients who received inadequate prophylaxis, in recipients of SCs from unrelated or mismatched donors, and in older patients.

Prevention of GVHD may entail some or all of the following options[13];

a) Combinations of methotrexate and either cyclosporine or tacrolimus (FK 506) are most effective and are therefore popular.
b) Gut sterilization consists of sterile meals, daily metronidazole and adequate skin care.
c) Prednisone, anti-T cell antibodies, mycophenolate mofetil (MMF), and other immunosuppressive agents have also been studied in various combinations.
d) TCD (in-vivo or in-vitro) of the SC product is another approach. Though effective in preventing GVHD, is also associated with an increased risk of graft failure and of tumor relapse and is presently limited to settings where the odds for GVHD are greater than average, and for non-malignant diseases. .

Despite prophylaxis, aGVHD develops in ~30% and up to 60% of recipients of SC from matched siblings and unrelated donors respectively[13]. Treatment is usually with glucocorticoids, ATG, or monoclonal antibodies against T cells or its subsets.

GVHD would no doubt pose especial problems in our population and a high index of suspicion would be necessary. Pruritus, lip and palm erythematous changes should raise suspicion of GVHD; therefore skin biopsies should be carried out as early as possible. [25].

Chronic GVHD

Twenty to 45% of patients surviving >6 months after allo-HSCT develop cGVHD. It is commoner in those with a prior aGVHD; older patients, recipients of mismatched or unrelated grafts. cGVHD tends to resemble an autoimmune disorder with malar rash, sicca syndrome, arthritis, obliterative bronchiolitis, and bile duct degeneration and cholestasis[13]. High-dose prednisone and/or cyclosporine is standard therapy at present, although trials of other agents are ongoing[13, 23]. In most patients, cGVHD resolves, but it may

require 1-3 years before treatment withdrawal without recurrence. During this period, patients are susceptible to infections, and should receive prophylactic antibiotics. All suspected infections should be investigated and treated aggressively.

GRAFT FAILURE OR REJECTION

Occasionally marrow function is not regained or is lost soon after engraftment. This can be due to inadequate HSCs, damage during processing or storage, or post-transplant myelotoxic agents in addition to cytomegalovirus (CMV) or HHV6 infections. Graft failure after allo-SCT can also result from graft rejection especially following suboptimal immunosuppression; in TCD and HLA-mismatched donor transplants. However, only 1-3% of HLA-identical sibling grafts are rejected[8].

Even though survival following a one-antigen mismatched transplant is not markedly different in either the related or unrelated setting; unrelated transplants with >1 antigen mismatch are impaired and not advised.

Treatment of graft failure involves avoiding myelotoxic agents and the use of HGFs. Reinfusion of donor SCs is usually unhelpful unless preceded by further immunosuppression. Also, standard preparative regimens are poorly tolerated within 100 days of a first transplant because of cumulative toxicities[8]. However, milder regimens such as antibodies and glucocorticoids have resulted in engraftment in >50% of patients[23]. Recent trials with positively-selected CD34$^+$ HSCs have been able to achieve engraftment without GVHD, the results though early are promising[19].

INFECTION

The post-allo-SCT patients have a markedly increased risk of infection. Early profound neutropenia puts the post-transplant patient at risk for bacterial infections and most centers routinely begin antibiotherapy at granulocyte count <500/uL because of their immunocompromised status and a proactive approach is appropriate.

Fluconazole prophylaxis reduces the risk of candidal infections. Patients presenting with pulmonary mycosis usually require treatment throughout the transplant period[26]. Patients seropositive for herpes simplex would usually receive acyclovir prophylaxis. Despite prophylaxis and the development of simplified infection management protocols, most patients will develop infections, the management of which remains a challenge.

Patients with significant periods of stay in the tropics, such as Nigeria, usually undergo extensive parasitological work-up and/or prophylaxis (e.g. for malaria).

With engraftment, the rate and severity of bacterial infections drop; but patients, particularly allo-SC recipients, remain at significant risk of infection until full reconstitution of specific cellular immunity[26].

CMV disease arising from reactivation or new infection has stimulated the greatest research because of its high mortality. However, several preventive measures have now been adopted including the use of CMV-seronegative blood products, prophylactic Ganciclovir (or Foscarnet) beginning either at engraftment or with development of CMV antigenemia[26]. Pneumocystis carinii pneumonia has also been effectively curtailed by placing patients on oral trimethoprim-sulfamethoxazole (TMP-SMZ) for 1 week pretransplant and then after engraftment. The risk of infection is considerably reduced after 3 months post-transplant unless cGVHD develops (requiring immunosuppression), during which time it is advised that TMP-SMZ prophylaxis be continued and the patient carefully monitored for late CMV reactivation. In addition, varicella zoster prophylaxis is recommended, using acyclovir for 1 year post-transplant[26].

THE ROLE OF HSCT IN SPECIFIC DISEASES

NON-MALIGNANT DISEASES

Immunodeficiency disorders

Various immunodeficiency disorders can be cured by replacing abnormal HSC with normal donor HSCs. These include severe combined

immunodeficiency (SCID), Wiskott-Aldrich and Chediak-Higashi syndrome. By 1999, Europe had achieved 82% cure rate in SCID using HLA-identical donors with the best results in the B(+) forms[27].

Severe aplastic anemia

The EBMT recommends that allo-HSCT be offered to all children with SAA and adult patients <40 years with neutropenia =0.3 x 10^9/L. Patients >40 years do better with immunosuppressive therapy while the results remain equivocal for those aged between 10 and 40 with neutrophil counts >0.3 x 10^9/L[28]. Conditioning is with cyclophosphamide and ATG. SCT is however effective in all forms of SAA including, paroxysmal nocturnal hemoglobinuria and Fanconi's anemia. In Fanconi's anemia, patients are highly sensitive to CRT and so less intensive regimens are used, with good results.

Thalassemia major

HSCT is the only curative treatment for thalassemia. Arising from the work of Lucarrelli et al[29], it is now possible to achieve up to 90% cure rates in patients with thalassemia major (TM) using MRDs and a preparative regimen of busulfan and cyclophosphamide. He has also sub-classified TM into 3 prognostic groups. The best outcomes are from patients transplanted before the onset of hepatomegaly and/or portal fibrosis and if they have had adequate iron chelation therapy[29].

Sickle cell anemia

HSCT has been studied using the intention-to-treat model in patients with sickle cell anemia (SCA). An OS and DFS at 2 years of 90 and 80% respectively, have been reported following MRD-SCT[30]. Several studies in Europe, Canada and the USA have also reported similar findings[31-33]. The principal aims of these further studies were to define the risks and benefits of this therapy and to describe the natural history of survivors free of SCA. The results of SCT were best when performed in children with MRDs[30]. For adults however, SCT outcomes have been poor [34]. More carefully designed studies are urgently required in order to appraise the outcome. Even though many children

who received allo-SCT had significant complications, the DFS remains very good at 80-85% and thus holds a lot of promise. [30].

Other nonmalignant diseases

Theoretically, HSCT should cure any disease that results from an inborn error of the lymphohematopoietic system; congenital disorders of white blood cells, red cells or platelets and some storage disorders such as Kostmann's, Hurler's and Hunter's syndromes, chronic granulomatous disease, leukocyte adhesion deficiency, Blackfan-Diamond anemia, Gaucher's disease, and infantile malignant osteopetrosis and metachromatic leukodystrophy.

HAEMOPOIETIC MALIGNANCIES AND STEM CELL TRANSPLANTATION

Acute leukemia

Chemotherapy alone can achieve a DFS of 10-35% at 5 years. The best results for acute myeloid leukemia (AML) with allo-SCT are achieved in first complete remission (CR1), with average cure rates (DFS at 5 years) of 60- 65%[35]. However when patients are in second complete remission (CR2) or first relapse (R1), the DFS drops to 30-35%[8]. It is advised that all young, poor risk and relapsed patients with HLA-match donors be offered allo-SCT in CR1. Patients in CR1 lacking HLA-identical sibling are offered auto-SCT in several centers allowing much higher doses of CT while searching for an unrelated donor search. A better outcome is achieved when the harvest is done after 2-3 courses of CT. Nevertheless, RR is higher than in allo-SCT. For AML-M3 (APL) where cure rates of >70% can be achieved using standard CT alone, HSCT is only advised when CT has failed[35].

Allo-SCT is advised for all Philadelphia-positive (Ph+) and other high-risk ALL patients in CR1; when cure rates ~55% are expected[35]. Standard risk patients are expected to continue into consolidation and maintenance and most experts would only consider them for allo-SCT in CR1 or CR2; for which cure rates of 30-50% have been

reported. As with AML, auto-SCT is associated with higher RR and lower transplant-related mortality (TRM) compared to allo-SCT but OS is worse than in AML[36]. An OS of ~28% has recently been reported in patients with refractory disease with allo-SCT[37].

Chronic myeloid leukemia

Until 2003 when Imatinib (STI) came into trials, allo-HSCT was the only therapy that could reverse the Ph-positivity of patients with chronic myeloid leukemia (CML)[38]. Experts are still divided as to the first-line option for Ph+CML in chronic phase (CP). Most centers (including ours) however, commence such patients on STI and only consider them for grafting when treatment fails. Most experts agree that young patients with high risk disease (Sokal[39] or Hasford[40] score) and an MRD should have HSCT in CP[38]. The DFS rates at 5 years are 60-70%, 30-40% and 15-20% respectively for patients transplanted in CP, accelerated and in blast crisis. A niche has also been defined for auto-SCT.

Myelodysplasia

Long-term DFS of 40-50% has been achieved in myelodysplasia with allo-SCT. Results are better among younger patients and those with less advanced disease; even though SCT is advised only for patients with intermediate risk-I or higher according to the International Prognostic Scoring System[38].

Malignant lymphoma

Up to 40-50% of patients with intermediate- or high-grade non-Hodgkin's lymphoma (NHL) who fail CT and are transplanted in CR1 or CR2 can enjoy long-term DFS[41]. Most experts favor auto- rather than allo-HSCT because fewer complications occur and survival appears equivalent. The role of HSCT in patients with indolent NHL and chronic lymphocytic leukemia (CLL) is less clear due largely to advanced age and the indolent nature of this group of NHL. Moreover, TRM has been substantial, and further studies are needed[41].

The role of HSCT in Hodgkin's lymphoma (HL) is similar to that in NHL with 5-year DFS ranging from 20-30% in patients who never achieved CR1 with CT and up to 60% for those transplanted in CR2. However HSCT has no clear role in HL in patients with stable CR1.

Myeloma

Except for recent works from Arkansas and Hamburg, patients with myeloma who have failed CT have not received significant benefits from SCT. Barlogie compared "tandem auto" (several courses of high-dose thalidomide-containing CT supported by auto-SCT) with "tandem auto/allo" (tandem auto followed by RIC allo-SCT)[42, 43] while Kröger compared single-auto/allo with allo-SCT[44, 45]. These approaches are still in the trial phases but early results are promising.

Solid Tumors

HSCT has been tried with varying degrees of success in breast cancer, testicular cancer, ovarian cancer, small-cell lung cancer, neuroblastoma and pediatric sarcomas[46]. As usual, results are best with chemo-sensitive tumors and low disease bulk.

MANAGEMENT OF RELAPSE AFTER ALLO-HSCT

Among the options[47] open to patients who relapse post-HSCT, donor lymphocytes infusion (DLI) has generated intense interest because of its success in CML and the promises it holds for post-SCT immunotherapy in RIC-HSCT. As high as 75% CR has been achieved in CML, 40% in MDS, but only 25% in AML, and 15% in myeloma. Major complications of DLI include transient myelosuppression and GVHD[48].

Post-SCT relapses may also respond to discontinuation of immunosuppression, second or tandem transplants, further cytotoxic CT, Interferon-alpha, interleukin-2, G-CSF, Imatinib, irradiation, palliation[47] and lately CD34+ SC boosting[19].

PROSPECTS AND CHALENGES OF HSCT IN NIGERIA

Being the most populous black nation in the world, Nigeria is uniquely placed to set up the largest

stem cell and cord blood bank/registry to cater for Nigerians and ultimately, black people worldwide. The immense potential for foreign exchange earnings can only presently be imagined. .

However, we must first have regular power supply which will ensure apheresis and cryopreservation activities, develop our molecular biology services, overhaul our tissue donation policies. Consequently this will improve patient/donor data collection and the storage and retrieval systems for a more practical national health insurance (in this regard). By these, we will be honed for international best practices in our healthcare management.

In the absence of these, transplantation activities are likely to be taken over by the private-sector and thus be profit-driven, and consequently would be beyond the reach of the average Nigerian patient.

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