3-2020

Worldwide network for blood and marrow transplantation (WBMT) recommendations for establishing a hematopoietic stem cell transplantation program in countries with limited resources (Part II): Clinical, technical and socio-economic considerations

M Aljurf
King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia

D Weisdorf
University of Minnesota, Minneapolis, MN, USA.

S K. Hashmi
King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia

A Nassar
National Cancer Institute, Cairo University, Cairo, Egypt

E Gluckman
Eurocord Hôpital Saint-Louis and University Paris Diderot, France

Hematol Oncol Stem Cell Ther 13 (2020) 7–16

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/hemonc

Worldwide Network for Blood and Marrow Transplantation (WBMT) recommendations for establishing a hematopoietic stem cell transplantation program in countries with limited resources (Part II): Clinical, technical and socio-economic considerations ☆

M. Aljurf [a,*], D. Weisdorf [b], S.K. Hashmi [a,c], A. Nassar [d], E. Gluckman [e], M. Mohty [f], D. Rizzo [g], M. Pasquini [g], M. Hamadani [g], W. Saber [g], P. Hari [g], M. Kharfan-Dabaja [h], N. Majhail [i], U. Gerges [j], A. Ali Hamidieh [k], F. Hussain [a], A. Elhaddad [d], H.K. Mahmoud [d], A. Tbakhi [l], T.B. Othman [m], R.M. Hamladji [n], M.A. Bekadja [o], P. Ahmed [p], A. Bazarbachi [q], S. Adil [r], S. Alkindi [s], S. Ladeb [m], D. Dennison [s], M. Patel [t], P. Lu [u], A.E. Quessar [v], S. Okamoto [w], Y. Atsuta [x], A. Alhejazi [y], M. Ayas [a], S.O. Ahmed [a], N. Novitzky [z], A. Srivastava [aa], A. Seber [ab], H. Elsolh [a], A. Ghavamzadeh [k], D. Confer [g], Y. Kodera [ac], H. Greinix [ad], J. Szer [ae], M. Horowitz [g], D. Niederwieser [ac,af]

[a] *Hematology Department, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia*
[b] *University of Minnesota, Minneapolis, MN, USA*
[c] *Department of Medicine, Mayo Clinic, Rochester, MN, USA*
[d] *National Cancer Institute, Cairo University, Cairo, Egypt*
[e] *Eurocord Hôpital Saint-Louis and University Paris Diderot, Paris, France*
[f] *Hopital Saint-Antoine, Sorbonne University, Paris, France*
[g] *Center for International Blood and Marrow Transplant Research (CIBMTR), Milwaukee, WI, USA*
[h] *Department of Medicine, Division of Hematology-Oncology and Blood and Marrow Transplantation Program, Mayo Clinic, Jacksonville, FL, USA*
[i] *Blood and Marrow Transplant Program, Cleveland Clinic, Cleveland, OH, USA*

☆ These guidelines were developed by WBMT and are published jointly in Hematology/Oncology and Stem Cell Therapy and Biology of Blood and Marrow Transplantation.

https://doi.org/10.1016/j.hemonc.2019.08.002

[j] Hematologic Malignancies & Bone Marrow Transplant, Department of Medicial Oncology, New York-Presbyterian Hospital/Weill Cornell Medical Center, New York, USA
[k] Tehran University of Medical Sciences, Hematology, Oncology & SCT Research Ctr., Tehran, Iran
[l] King Hussein Cancer Center, Amman, Jordan
[m] Center National de Greffe de Moelle Osseuse de Tunis, Tunis, Tunisia
[n] Pierre and Marie Curie Center, Algiers, Algeria
[o] University Hospital Establishment 1st Nov, Oran, Algeria
[p] Armed Forces Institute of Transplantation, Rawalpindi, Pakistan
[q] Hematology/Oncology, American University of Beirut Medical Center, Beirut, Lebanon
[r] Aga Khan University Hospital, Karachi, Pakistan
[s] Sultan Qaboos University Hospital, Muscat, Oman
[t] University of the Witwatersrand, Johannesburg, South Africa
[u] Hebei Yanda Ludaopei Hospital, Langfang, China
[v] Hôpital 20 Août, Casablanca, Morocco
[w] Japanese Data Center for Hematopoietic Cell Transplantation, Nagoya, Japan
[x] Keio University School of Medicine, Tokyo, Japan
[y] King Abdulaziz Medical City, NGHA, Riyadh, Saudi Arabia
[z] African Blood & Marrow Transplantation Society (AFBMT), South Africa
[aa] Christian Medical College & Hospital, Bagayam, Vellore, India
[ab] Instituto de Oncologia Pediatrica, Sao Paulo, Brazil
[ac] Center for Hematopoietic Stem Cell Transplantation, Aichi Medical University Hospital, Nagakute, Japan
[ad] Medical University of Graz, LKH-Univ. Klinikum Graz, Austria
[ae] Department of Clinical Haematology, Royal Melbourne Hospital, VIC 3050, Australia
[af] Department of Hematology and Medical Oncology, University Hospital, Leipzig, Germany

Available online 20 August 2019

KEYWORDS
Bone marrow transplantation;
Developing countries;
Low income countries

Abstract
The development of hematopoietic stem cell transplantation (HSCT) programs can face significant challenges in most developing countries because such endeavors must compete with other government health care priorities, including the delivery of basic services. While this is may be a limiting factor, these countries should prioritize development of the needed expertise to offer state of the art treatments including transplantation, by providing financial, technological, legal, ethical and other needed support. This would prove beneficial in providing successful programs customized to the needs of their population, and potentially provide long-term cost-savings by circumventing the need for their citizens to seek care abroad. Costs of establishing HSCT program and the costs of the HSCT procedure itself can be substantial barriers in developing countries. Additionally, socioeconomic factors intrinsic to specific countries can influence access to HSCT, patient eligibility for HSCT and timely utilization of HSCT center capabilities. This report describes recommendations from the Worldwide Network for Blood and Marrow Transplantation (WBMT) for establishing HSCT programs with a specific focus on developing countries, and identifies challenges and opportunities for providing this specialized procedure in the resource constrained setting.

Introduction

The establishment of hematopoietic stem cell transplantation (HSCT) programs in developing countries can enhance and improve tertiary care health services. There are various positive attributes that favor the establishment of such a high-profile venture; however, there are also significant obstacles to be addressed.

Since the obvious issue in most economies is cost distribution and budget allocation for the populations' healthcare, public health measures take precedence over the non-communicable chronic diseases. However, over time, there has been increasing focus on chronic diseases particularly cancers as these have become leading cause of mortality in both developing and developed nations. Thus there has been an exponential growth of both prevalence and inci-

* Corresponding author at: Oncology Center, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia.
E-mail address: maljurf@kfshrc.edu.sa (M. Aljurf).

dence of the diseases which can be cured by HSCT including sickle cell anemia, thalassemia, leukemia, myeloma, lymphoma, immunodeficiencies and metabolic disorders. As a result, many new HSCT centers have been opening in the developing nations.

In most developing countries, a HSCT program has to compete for allocation of limited funds with other priorities for basic health care services such as food, sanitation, immunization, population control and prevention of communicable diseases. Developing countries should also have the expertise to offer 'state-of-the art' treatments, including HSCT which can provide treatment locally at a much lower cost than abroad.

The most important step would be to provide financial, technological, legal, ethical and other support for local individuals and institutions to proactively establish new HSCT program. The goal is to develop a customized local experience tailored to each developing country and also to allow local dissemination of this experience as it evolves [1].

While establishing a HSCT program in a developing country, one should take into consideration several difficulties. Financial, technologic, logistic, social, and the availability of skilled manpower are all potential difficulties. Given the exponential growth in both the numbers of HSCT worldwide and the establishment of new HSCT centers in the high and low income countries, the Worldwide Network for Blood and Marrow Transplantation (WBMT) has recognized the need to provide guidance to institutions and individuals who are considering start of a new HSCT center. Part I of this report describes the absolute minimum, minimum, preferred, and ideal requirements for the establishment of a new HSCT program. This part II of the series describes the clinical, technical and financial considerations for establishing a HSCT program in the resource constrained setting (typical for developing countries).

Financial issues and cost of establishing a transplantation program

HSCT remains a highly specialized, complex, resource intense and costly medical procedure. A 2009 report from the Agency for Healthcare Research and Quality (AHRQ) in the United States (US) showed that HSCT was among the top ten procedures with the greatest increase in hospital costs from 2004 to 2007. Total US national costs of HSCT hospitalization increased from $694 million to $1.3 billion over this time period [2].

Thus establishment of a dedicated center for this costly procedure requires a comprehensive understanding of economic indicators and challenges. There are four main economic evaluations that provide information to guide decision making on the basis of the value for money: cost minimization, cost benefit, cost effectiveness, and cost utility.

Cost minimization is commonly practiced in HSCT whenever lower cost, equally effective treatment is chosen over more expensive treatments. Cost benefit analysis is rarely used in procedures like transplant because it requires assignment of monetary costs to measure clinical benefits which are difficult to assign in this complex setting with potential for long-term cure for a proportion of recipients.

Cost utility analysis is a specific type of cost effectiveness analysis where outcomes are adjusted to consider health related quality of life, so that a cure without treatment sequelae is considered more valuable than a cure resulting continuing health disabilities [3].

In this paper we will emphasize HSCT interventions that focus primarily on cost-effectiveness or cost-utility. To develop a cost containment program, proof of both clinical and economic effectiveness is preferred before widespread adoption of new technologies [4].

It is critical to identify the exact drivers of cost before considering initiation of a HSCT program. Little available data to evaluate the exact drivers of HSCT costs in developing countries. A recent study of establishment of a cancer center in a developing country (Rwanda) indicated that $556,105 US dollars was the necessary start-up funding to implement the cancer program [5]. The annual operating cost of the cancer program was found to be $957,203 US$. Radiotherapy, labor, and chemotherapy were the most significant cost drivers, however radiotherapy required sending patients out of country because there were no radiation units in Rwanda. Labor accounted for 21%, whereas chemotherapy, supportive medications, and consumables accounted for 15% of the costs. While the radiation therapy is not routinely performed for HSCT, it is necessary part of certain preparative regimens and thus establishment of a radiation therapy unit is likely to significantly increase the costs.

The high costs of HSCT can be presumably attributed to various factors as discussed below (Fig. 1).

Patient related factors

When designing a national program for HSCT in a developing country, few patient related factors can be assessed for cost reduction. Although there is no consistent correlation between costs and patient age, sex, performance status, or disease risk, in some more recent studies, advanced risk disease was a significant predictor of higher costs [6—10].

In view of the limited resources in developing countries, health authorities should allocate available resources to the best priorities where low cost inputs yield high dividends. However, there are no clear recommendations and each country needs to adopt the policies that satisfy its population needs.

Considering the young median age in many developing countries, it would be prudent to initially make HSCT available to younger patients with curable diagnoses and longer lifespan benefit. Subsequently, expanding eligibility for HSCT to older and advanced disease subjects may be appropriate as the program's experience develops.

Transplant center experience

Cost reduction and clinical outcomes have been shown to improve with increasing institutional experience [11]. However, this economic advantage may be offset as the complexity of treated patients increases and more aggressive supportive interventions are applied, resulting in a plateau in the improvement curve [11—13]. Growing local expertise

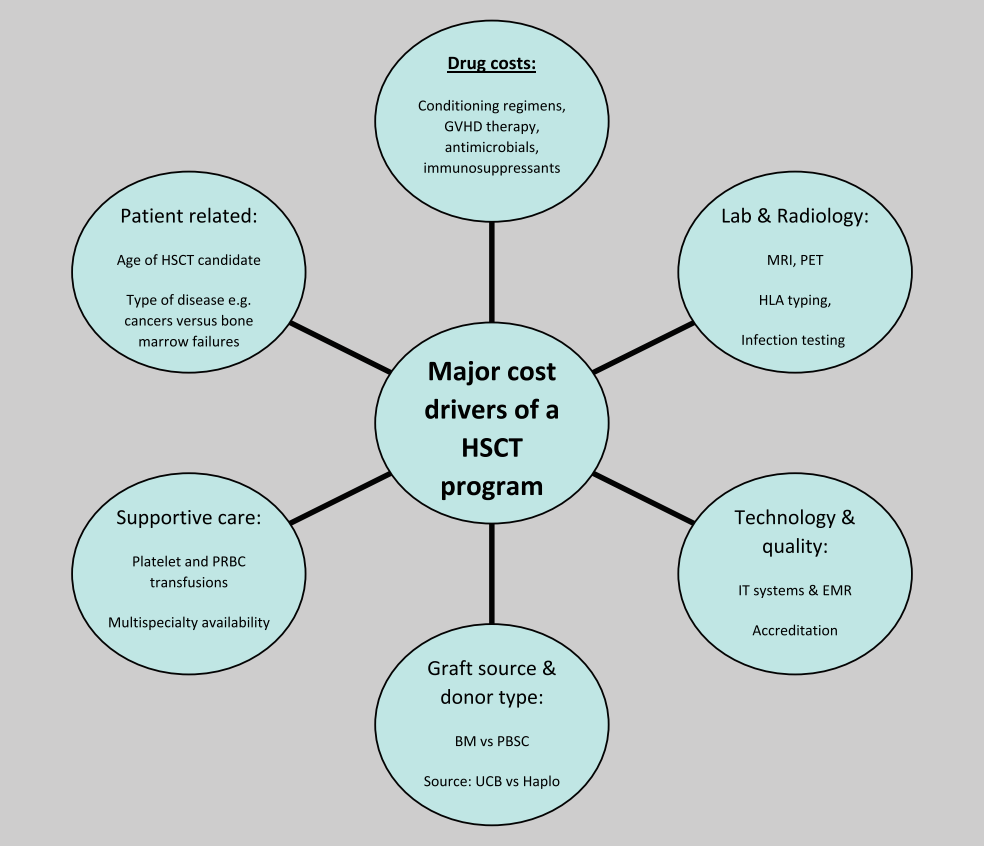

Fig. 1 Major determinants of costs in establishment of an HSCT program. HSCT: hematopoietic stem cell transplant; MRI: Magnetic resonance imaging; PET: positron emission tomogram; HLA: human leukocyte antigen; IT: information technology; EMR: electronic medical records; BM: bone marrow; PBSC: peripheral blood stem cells; PRBC: packed red blood cells; GVHD: graft-versus-host-disease; UCB: umbilical cord blood; haplo: haploidentical; RD: related donor; URD: unrelated donor.

and adopting cost effective practices can limit total costs and improve transplant outcomes.

Human resources and continuous training

Availability of well-trained staff at different steps of transplantation with continuous training and to advance their knowledge is a cornerstone of any successful transplant program. Migration of health care professionals from developing to developed countries deprives the developing world of valuable and essential human resources [14]. Countries should strengthen health system requirements, including physical infrastructure and skilled human resources to meet the multidisciplinary requirements of HSCT aiming for high quality and safety as fundamental principles. International cooperation and twinning with other institutions in developed countries could facilitate exchange of expertise across the globe. Adequate attention for neutropenic and hygienic precautions and any other measures to reduce infection should be considered.

Donor selection and HLA typing

With the advance in immunogenetics and transplantation immunology, particularly in the structure and function of the HLA system in the 1990s, new and efficient technologies for HLA typing emerged and progressed [15,16].

According to the guidelines of World Marrow Donor Association (WMDA) and European Federation for Immunogenetics (EFI), high-resolution HLA typing should be performed both for HSCT recipients and donors. HLA typing should also include the HLA-C locus due to the recognized role of this locus in graft rejection [17,18].

The technology for HLA typing has evolved from the serological level to the cellular level, and recently to the molecular level. Serotyping was the mainstream method for HLA typing and played a critical role in organ transplantation before the 1990s. However, most HLA antisera are polyclonal with lower specificity and variable sensitivity. Therefore, molecular methods to type HLA at the DNA level have replaced serologic and cellular typing.

Commonly used DNA based HLA typing methods include PCR based sequence specific primers (PCR-SSP), and PCR based restriction fragment length polymorphism (PCR-RFLP), single-strand conformation polymorphism (PCR-SSCP), sequence-specific oligonucleotide (PCR-SSO) and single nucleotide polymorphism (PCR-SNP). PCR-SSP genotyping was a commonly used method for HLA typing in clinical laboratories worldwide. PCR-SSP and PCR-SSO methods have a high cost and prolonged operation time, therefore are rarely used for HLA typing at present.

PCR-SNP is a simple and fast method with high resolution and will become more commonly used as the technology continues to improve. At present, PCR-sequence-based typing (PCR-SBT) technology has significant advantages over other HLA typing methods in terms of accuracy, efficiency and automation. In addition, the operational costs have been greatly reduced [15]. It is recommended that new programs in developing countries with limited resources should start by performing matched sibling transplantation, where high resolution typing may not be necessary and some risks are reduced.

Outsourcing HLA typing can be a cost-effective alternative in developing countries where laboratories with immunogenetic capabilities and expertise are not yet available. Many companies throughout the developed countries offer molecular-based HLA typing at very competitive prices, particularly for bulk contracts.

Conditioning intensity

Both the intensity and duration of conditioning affect the cost of HSCT. Large studies confirmed that the costs associated with reduced intensity regimens are lower, with fewer median hospital days within the first year of the transplant compared with high-dose or myeloablative regimens [8].

Myeloablative allogeneic HSCT is not only associated with a higher frequency and severity of short-term toxicities, but also late complications such as a higher likelihood of infertility, growth retardation in children and new primary malignancies. This may also increase on the use of blood products, risk of infections, transplant-related mortality, and length of hospital stay. Despite these advantages, lower-intensity regimens must be adapted for important patient and disease related variables as a recent multicenter trial showed a clear advantage in reducing relapse of AML using myeloablative regimens in younger fit patients [19].

Several recent studies had suggested that intermediate intensity regimens with a 20—30% reduction in dose intensity could reduce toxicity without causing significant increases in the risk of relapse or overall worse transplantation outcomes [20—22].

The cost and limited availability of radiation therapy in many developing countries should not be a major obstacle as non-radiation based conditioning regimens are available for nearly all diseases or conditions in which HSCT is indicated.

Blood product support

In adult recipients of autologous HSCT, two randomized trials have demonstrated similar rates of bleeding when therapeutic rather than prophylactic strategy for platelet transfusion was used [23,24]. Both American Society of Clinical Oncology and British Society of Haematology recommend that therapeutic platelet transfusion strategy could be used in autologous HSCT setting which will result in less platelet usage and substantial cost savings [25,26]. In allogenic HSCT, a randomized study subgroup analysis found similar rates of bleeding when low dose of platelet (1.1×10^{11}) was used compared to medium (2.2×10^{11}) or high dose (4.4×10^{11}). This led to a decreased number of platelets transfused per patient at doses between 1.1×10^{11} and 4.4×10^{11} platelets per m^2 with similar bleeding events [27]. Irradiated blood products should be utilized according to international guidelines.

Performing autologous stem cell transplant without stem cell cryopreservation

Cryopreservation of stem cells needs a relatively advanced stem cell processing laboratory with mechanical, controlled rate freezers. Several reports have described the feasibility of non-cryopreserved G-CSF mobilized whole blood or autologous bone marrow (with or without prior administration of G-CSF). Stem cell graft containing blood units or bone marrow can be briefly stored in a standard blood bank refrigerator at +4 °C until infusion [28—30].

The outcomes of autologous HSCT for multiple myeloma using non-cryopreserved stem cells and without G-CSF support has recently been described by several centers [31—34]. This technique depends on abbreviated conditioning, with one day of high dose melphalan for myeloma or short duration conditioning for lymphoma patients. This technique avoids the need for costly cryopreservation technology and also avoids the possible side effects described with infusion of dimethyl sulfoxide (DMSO) which is required for cryopreservation. These autologous transplantation techniques were reported to yield early engraftment and reduced hospital stay with significant cost savings. Outcomes were comparable to conventional conditioning with cryopreserved stem cells in multiple myeloma patients [31—34]. Two recent studies of non-cryopreserved autografts from developing countries utilizing post-HSCT G-CSF also indicate comparable engraftment rates to cryopreserved autografts [35,36].

Thus, for a new HSCT center, it may not be necessary to have mechanical freezers in place for autograft cryopreservation, as safety and efficacy of utilizing non-cryopreserved stem cells is evident.

Graft source

Peripheral blood stem cells (PBSC) are known to offer more rapid neutrophil and platelet recovery compared to bone marrow grafts with an early cost reduction of approximately 30% compared to bone marrow in some studies [37—39]. The use of PBSC can lead to specific resource saving in hospitalization, platelet transfusions and use of growth factors [40,41].

Unlike autologous transplantation, chronic GVHD is a serious late complication of allogeneic HSCT and results in serious morbidity and mortality. Most studies report a higher incidence of chronic GVHD with the use of allogeneic PBSCs, which may potentially offset the early cost savings. Appropriate selection of cases and developing well-informed indications for the use of PBSCs could reflect favorably on procedural costs and transplant outcomes [42].

In a recent study by the Center for International Blood and Marrow Transplant Research (CIBMTR), the use of PBSCs resulted in an acceptable alternative for transplanting patients with aplastic anemia in developing countries, as

PBSC grafts were associated with faster engraftment, lower frequency of infections, and a lower likelihood of graft rejection in heavily pretransfused patients [43].

However, in autologous HSCT there is strong evidence of clinical benefit and cost savings using PBSCs which has been consistently reported [44—47].

Alternative donors and graft manipulation:

The use of alternative donors, specifically HLA-compatible unrelated donors (URD), has emerged as a significant driver of costs, even beyond the costs of stem cell procurement [8,48,49]. Among the various sources of alternative donors, myeloablative umbilical cord blood (UCB) transplantation is associated with the highest costs, followed by matched URD. Accordingly, these donor sources should not be considered a priority in developing countries for a new HSCT program.

The preferred and most cost effective alternate donor transplantation modality in developing countries may be a related (family-member) haploidentical transplantation using post-transplant cyclophosphamide (PTCy) for GVHD prevention. The posttransplant course, however, might require more experience as conventional, URD HSCT.

Alternatives to PTCy for haploidentical transplantation use different methods of T-cell depletion (TCD) of the donor graft or other cellular manipulation which are complex and require advanced and costly stem cell processing technology [50].

Cost of supportive care medications:

Pharmacy costs range from 8% to 39% of the total expenditures in HSCT. Hematopoietic growth factors, GVHD prophylactic drugs and antimicrobials are the major contributors to pharmacy costs [51—53]. Several generic forms are now available for fluconazole and more recently for voriconazole as well [54]. This could help offset some costs, provided that these alternative products demonstrate similar efficacy. Pharmacy costs are expected to continuously rise given the changes in HSCT practice with increasing use of newer immunosuppressive regimens and the higher cost of new anti-infective agents [52]. The long-term excess pharmacy costs for patients with chronic GVHD who may require prolonged immunosuppressive treatments are unpredictable and may be large [52].

A biosimilar drug is a similar copy of an approved injectable original biologic substance, which may be available after the original patent protection has expired [55]. Since drugs are produced by cultured cells, small biological differences between original and biosimilars may exist. However, the use of well-established biosimilars should be considered for cost containment and for improved availability of drugs needed for HSCT provided that they are demonstrably as safe and efficacious as the originator product. If properly evaluated and clinical effectiveness is proven these biosimilars, their generally reduced costs may contribute to the long-term financial sustainability of HSCT programs [55—57]. Several biosimilars of G-CSF are less expensive alternatives to the original brand product. The European Medicines Agency (EMA) has recently approved several biosimilar versions after the patent of the original G-CSF brand expired in Europe in 2006 [55].

Several G-CSF biosimilars have been evaluated in the setting of stem cell mobilization for autologous HSCT. Results show similar mobilization yields with comparable safety profiles as the originator G-CSF. Moreover, both myeloid and platelet recovery times are similar to the originator G-CSF product [56—62]. This non-inferiority model could be extrapolated to other medications, ultimately leading to significant cost saving. Highly reputable pharmaceutical companies are already involved in the manufacturing process of several biosimilar medications essential for HSCT [63]. Table 1 presents several currently approved biosimilars which are used in the HSCT arena. The utilization of these biosimilars should be explored in developing countries when local approvals are in place.

However, the major problems encountered beyond the costs of certain drugs are reliable availability. The experience in different countries and continents underlines the need to check the availability and approval of the essential drugs to perform HSCT. In some countries cyclosporine is only available orally but not intravenously, Busulfan may not be available at all and the import of the drug is sometimes very difficult. The WBMT prepared a list for essential drugs, which should be available or for a successful program. Licensing of drugs in a country may depend on the demand and some drugs needed for HSCT may be used only for HSCT. Sometimes availability of drug needed for HSCT will also improve the treatment of the underling disease before HSCT. Close interaction with the health authorities of the country is recommended to guide informed policies for specific drug availabilities.

Post transplantation factors

Several post-transplant factors may greatly increase costs. Prolonged hospitalization and late complications are the most significant drivers of costs. Designing programs for post-transplant care including home health services and outpatient follow up systems allowing safe follow up at either their own homes or at a hostel where a well-trained and qualified nurse can monitor patients who need less aggressive intervention, have been found to reduce post-transplant costs [64].

Socioeconomic and other factors

In many developing countries, many acute leukemia patients die before referral to a national or regional HSCT center. This indirectly leads to a relatively larger proportion of HSCT being done for non-neoplastic indications such as bone marrow failure and hemoglobinopathies, diseases more permissive of delays until HSCT. The time from diagnosis to HSCT is likely to be longer in developing countries with the resulting unintended consequences of having sicker candidates present for HSCT due to advanced disease, poor performance status, more infections or transfusion alloimmunization. The consequences of delay may be higher costs of HSCT and poorer outcomes. Efforts to shorten the time from diagnosis to HSCT should be considered a priority in developing countries. Increasing public awareness and

Table 1 List of some Biosimilars approved in the United States and the European Union pertaining to HSCT*.

Generic/molecule	Biosimilar	Year approved	Use in HSCT
Filgrastim	Tevagrastim	2008 (EMA)	Mobilization of peripheral stem cells for autologous HSCT
	Ratiograstim	2008 (EMA)	
	Filgrastim Hexal	2009 (EMA)	
	Zarzio	2009 (EMA)	
	Accofil	2014 (EMA)	
	Zarxio	2015 (US-FDA)	
Rituximab	Truxima	2017 (EMA)	Treatment of chronic GVHD
	Rixathon	2017 (EMA)	
	Ritemvia	2017 (EMA)	
Infliximab	Inflectra	2013 (EMA); 2016 (US-FDA)	Treatment of acute GVHD
	Flixabi	2016 (EMA)	
Etanercept	Benepali	2016 (EMA)	Treatment of acute GVHD
	Erelzi	2016 (US-FDA); 2017 (EMA)	Treatment of BOS
			Treatment of IPS
Enoxaparin	Inhixa	2016 (EMA)	DVT prophylaxis
	Thorinane	2016 (EMA)	DVT treatment

EMA: European Medicines Agency; US-FDA: United States Food and Drug Administration; GVHD: Graft-versus-host-disease; BOS: Bronchiolitis obliterans syndrome; IPS: Idiopathic pulmonary syndrome; DVT: Deep venous thrombosis; HSCT: Hematopoietic stem cell transplantation.
*The table list only some of the approved biosimilars and not intended to be inclusive of all approved biosimilars. WBMT is working on a separate publication that will have a complete list of approved biosimilars.

patient education about essential hygienic and infection control measures as well as utilization of social services may also help educate patients and caregivers about recommendations that will increase HSCT success in developing countries.

The Human Development Index (HDI) is used by the United Nations Organization to evaluate a country's socioeconomic achievements based on three parameters: longevity, knowledge, and standard of living [65]. The number of transplants performed per unit population, as well as early and long-term outcomes are directly related to the HDI [66—70].

Information technology (IT) and quality benchmarks:

The most effective way to improve HSCT outcomes is to establish and maintain good quality programs in transplant centers. Established databases to define benchmarks for error reduction and improvement of outcomes. It is desirable for each HSCT center to have an internal database with experienced data managers and staff who can maintain the database and report the data to global registries (e.g. EBMT, CIBMTR or others). Developments in artificial intelligence (AI) for some aspects of tertiary care centers' management is predicted to lower costs. These may include machine learning algorithms in medical billing, supply chain management, scheduling efficiencies, virtual radiology (for image interpretation), and prevention of re-admissions [71—77]. Since many AI companies are currently originating in developing countries, it may be valuable to explore the application of AI systems at HSCT startup with the goal of cost-reduction.

Telemedicine in developing countries

Available techniques today allow intensive cooperation with experienced centers. Pilot programs are currently active across the world. This technique is particularly valuable where a very experienced HSCT program director is not available. Important guidelines for success involve training of the local senior physicians, suitable facilities and laboratory capabilities in place and regular communication with outside consultants.

Conclusions

Establishment of a HSCT center in countries with limited resources is a multistep endeavor requiring many financial, social, technical and human resources and involvement of physicians, health authorities, politicians, nurses and scientific societies. The main obstacle in some countries remains constrained resources and inexperience which may lead to high operating and maintenance costs, but may also complicate initial organization of a program. The WBMT has outlined the major drivers of costs for a HSCT program and presents general recommendations to help limit initial program costs. New cost-effectiveness studies from developing countries for each aspect of HSCT (conditioning type, GVHD management, IT systems implementation, graft source and donor choice, laboratory testing, drug costs [and biosimilar use], blood bank utilization [defined thresholds for PRBC

and platelet transfusion] may be of particular value in improving the safety and affordability of HSCT.

Declaration of Competing Interest

None of the authors declare any relevant conflict of interest.

References

[1] Thorsteinsdóttir H, Quach U, Martin DK, Daar AS, Singer PA. Introduction: promoting global health through biotechnology. Nat Biotechnol 2004;22:3—7.

[2] Stranges E, Russo CA, Friedman B. Procedures with the most rapidly increasing hospital costs, 2004—2007, HCUP Statistical Brief 82. December 2009. Agency for Healthcare Research and Quality: Rockville, MD. http://www.hcup-us.ahrq.gov/reports/statbriefs/ sb82.pdf.

[3] Khera N, Zeliadt SB, Lee SJ. Economics of hematopoietic cell transplantation. Blood 2012;120(8):1545—51.

[4] Welch HG. Valuing clinical strategies early in their development. Ann Int Med 1992;116:263—4.

[5] Neal C, Rusangwa C, Borg R, Tapela N, Mugunga JC, Pritchett N, et al. Cost of providing quality cancer care at the Butaro Cancer Center of Excellence in Rwanda. J Global Oncol 2018;4:1—7.

[6] Lee SJ, Klar N, Weeks JC, Antin JH. Predicting costs of stem-cell transplantation. J Clin Oncol 2000;18(1):64—71.

[7] Lin YF, Lairson DR, Chan W, Du XL, Leung KS, Kennedy-Nasser AA, et al. allogeneic peripheral blood stem cell transplantation versus bone marrow transplantation in pediatric patients with acute leukemia. Biol Blood Marrow Transplant 2010;16 (9):1272—81.

[8] Saito AM, Zahrieh D, Cutler C, Ho VT, Antin JH, Soiffer RJ, et al. Lower costs associated with hematopoietic cell transplantation using reduced intensity vs high-dose regimens for hematological malignancy. Bone Marrow Transplant 2007;40 (3):209—17.

[9] Saito AM, Cutler C, Zahrieh D, Soiffer RJ, Ho VT, Alyea EP, et al. Costs of allogeneic hematopoietic cell transplantation with high-dose regimens. Biol Blood Marrow Transplant 2008;14(2):197—207.

[10] Rizzo JD, Vogelsang GB, Krumm S, Frink B, Mock V, Bass EB. Outpatient-based bone marrow transplantation for hematologic malignancies: cost saving or cost shifting?. J Clin Oncol 1999;17(9):2811—8.

[11] Griffiths RI, Bass EB, Powe NR, Anderson GF, Goodman S, Wingard JR. Factors influencing third party payer costs for allogeneic BMT. Bone Marrow Transplant 1993;12(1): 43—8.

[12] Bennett CL, Armitage JL, Armitage GO, Vose JM, Bierman PJ, Armitage JO, et al. Costs of care and outcomes for high-dose therapy and autologous transplantation for lymphoid malignancies: results from the University of Nebraska 1987 through 1991. J Clin Oncol 1995;13(4):969—73.

[13] Majhail NS, Mothukuri JM, Macmillan ML, Verneris MR, Orchard PJ, Wagner JE, et al. Costs of pediatric allogeneic hematopoietic-cell transplantation. Pediatric Blood Cancer 2010;54 (1):138—43.

[14] Taylor AL, Hwenda L, Larsen BI, Daulaire N. Stemming the brain drain-a WHO global code of practice on international recruitment of health personnel. N Engl J Med 2011;365 (25):2348—51.

[15] De Santis D, Dinauer D, Duke J, Erlich HA, Holcomb CL, Lind C, et al. 16(th) IHIW : review of HLA typing by NGS. Int J Immunogenet 2013;40(1):72—6.

[16] Yuying S, Yongzhi X. The Advanced HLA Typing Strategies for Hematopoietic Stem Cell Transplantation. 2013. Innovations in Stem Cell Transplantation, Taner Demirer, IntechOpen. Available from: https://www.intechopen.com/books/innovations-in-stem-cell-transplantation/the-advanced-hla-typing-strategies-for-hematopoietic-stem-cell-transplantation.

[17] World Marrow Donor Association Standards [Internet]. WMDA. 2017 [Accessed 24 February, 2019]. Available from: https://www.wmda.info/professionals/quality-and-accreditation/wmda-standards/.

[18] European Federation for Immunogenetics [internet]. EFI. 2019 [Access Accessed 9 January 2019]. Available from: https://www.efi2019.org.

[19] Scott BL, Pasquini MC, Logan BR, Wu J, Devine SM, Porter DL, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. J Clin Oncol 2017;35(11):1154—61.

[20] Suh KJ, Kim I, Lim J, Ha H, Park S, Koh Y, et al. Total costs and clinical outcome of hematopoietic stem cell transplantation in adults with leukemia: comparison between reduced-intensity and myeloablative conditioning. Clin Transplant 2015;29 (2):124—33.

[21] Chen YB, Coughlin E, Kennedy KF, Alyea EP, Armand P, Attar EC, et al. Busulfan dose intensity and outcomes in reduced-intensity allogeneic peripheral blood stem cell transplantation for myelodysplastic syndrome or acute myeloid leukemia. Biol Blood Marrow Transplant 2013;19(6):981—7.

[22] Eom KS, Shin SH, Yoon JH, Yahng SA, Lee SE, Cho BS, et al. Comparable long-term outcomes after reduced-intensity conditioning versus myeloablative conditioning allogeneic stem cell transplantation for adult high-risk acute lymphoblastic leukemia in complete remission. Am J Hematol 2013;88 (8):634—41.

[23] Stanworth SJ, Estcourt LJ, Powter G, Kahan BC, Dyer C, Choo L, et al. A no-prophylaxis platelet-transfusion strategy for hematologic cancers. N Engl J Med 2013;368:1771—80.

[24] Wandt H, Schaefer-Eckart K, Wendelin K, Pilz B, Wilhelm M, Thalheimer M, et al. Therapeutic platelet transfusion versus routine prophylactic transfusion in patients with haematological malignancies: an open-label, multicentre, randomised study. Lancet 2012;380(9850):1309—16.

[25] Schiffer CA, Bohlke K, Delaney M, Hume H, Magdalinski AJ, McCullough JJ, et al. Platelet transfusion for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2017;28(JCO201776173):4. https://doi.org/10.1200/JCO.2017.76.1734.

[26] Estcourt LJ, Birchall J, Allard S, Bassey SJ, Hersey P, Kerr JP, et al. Guidelines for the use of platelet transfusions. Br J Haematol 2017;176(3):365—94.

[27] Slichter SJ, Kaufman RM, Assmann SF, McCullough J, Triulzi DJ, Strauss RG, et al. Dose of prophylactic platelet transfusions and prevention of hemorrhage. N Engl J Med 2010;362:600—13.

[28] Hechler G, Weide R, Heymanns J, Köppler H, Havemann K. Storage of noncryopreserved periphered blood stem cells for transplantation. Ann Hematol 1996;72(5):303—6.

[29] Lopez-Otero A, Ruiz-Delgado GJ, Ruiz-Arguelles GJ. A simplified method for stem cell autografting in multiple myeloma: a single institution experience. Bone Marrow Transplant 2009;44 (11):715—9.

[30] Ramzi M, Zakerinia M, Nourani H, Dehghani M, Vojdani R, Haghighinejad H. Non-cryopreserved hematopoietic stem cell transplantation in multiple myeloma, a single center experience. Clin Transplant 2012;26(1):117—22.

[31] Carey PJ, Proctor SJ, Taylor P, Hamilton PJ. Autologous bone marrow transplantation for high-grade lymphoid malignancy using melphalan/irradiation conditioning without marrow purging or cryopreservation. The Northern Regional Bone Marrow Transplant Group. Blood 1991;77(7):1593—8.

[32] Gomez-Almaguer D. The simplification of the SCT procedures in developing countries has resulted in cost-lowering and availability to more patients. Int J Hematol 2002;76(Suppl 1):380—2.
[33] Wannesson L, Panzarella T, Mikhael J, Keating A. Feasibility and safety of autotransplants with noncryopreserved marrow or peripheral blood stem cells: a systematic review. Ann Oncol 2007 Apr;18(4):623—32.
[34] Bekadja MA, Brahimi M, Osmani S, Arabi A, Bouhass R, Yafour N, et al. A simplified method for autologous stem cell transplantation in multiple myeloma. Hematol Oncol Stem Cell Ther 2012;5(1):49—53.
[35] Kardduss-Urueta A, Gale RP, Gutierrez-Aguirre CH, Herrera-Rojas MA, Murrieta-Álvarez I, Perez-Fontalvo R, et al. Freezing the graft is not necessary for autotransplants for plasma cell myeloma and lymphomas. Bone Marrow Transplant 2018;53 (4):457—60.
[36] Naithani R, Dayal N, Pathak S, Rai R. Hematopoietic stem cell transplantation using non-cryopreserved peripheral blood stem cells graft is effective in multiple myeloma and lymphoma. Bone Marrow Transplant 2018;53(9):1198—200.
[37] Pavletic ZS, Bishop MR, Tarantolo SR, Martin-Algarra S, Bierman PJ, Vose JM, et al. Hematopoietic recovery after allogeneic blood stem cell transplantation compared to bone marrow transplantation in patients with hematologic malignancies. J Clin Oncol 1997;15:1608—13.
[38] Faucher C, Fortanier C, Viens P, Le Corroller AG, Chabannon C, Camerlo J, et al. Clinical and economic comparison of lenograstim-primed blood cells (BC) and bone marrow (BM) allogeneic transplantation. Bone Marrow Transplant 1998;21 (Suppl. 3):S92—8.
[39] Körbling M, Przepiorka D, Huh YO, Engel H, van Besien K, Giralt S, et al. Allogeneic blood stem cell transplantation for refractory leukemia and lymphoma: potential advantage of blood over marrow allografts. Blood 1995;85:1659—65.
[40] Bennett C, Waters T, Stinson T, Almagor O, Pavletic Z, Tarantolo S, et al. Valuing clinical strategies early in development: a cost analysis of allogeneic peripheral blood stem cell transplantation. Bone Marrow Transplant 1999;24(5):555—60.
[41] Kline RM, Meiman S, Tarantino MD, Herzig RH, Bertolone Jr SJ. A detailed analysis of charges for hematopoietic stem cell transplantation at a children's hospital. Bone Marrow Transplant 1998;21(2):195—203.
[42] Storek J, Gooley T, Siadak M, Bensinger WI, Maloney DG, Chauncey TR, et al. Allogeneic peripheral blood stem cell transplantation may be associated with a high risk of chronic graft versus host disease. Blood 1997;90:4705—9.
[43] Kumar R, Kimura F, Ahn KW, Hu ZH, Kuwatsuka Y, Klein JP, et al. Comparing outcomes with bone marrow or peripheral blood stem cells as graft source for matched sibling transplants in severe aplastic anemia across different economic regions. Biol Blood Marrow Transplant 2016;22(5):932—40.
[44] Vicent MG, Madero L, Chamorro L, Madero R, Diaz MA. Comparative cost analysis of autologous peripheral blood progenitor cell and bone marrow transplantation in pediatric patients with malignancies. Haematologica 2001;86 (10):1087—94.
[45] Vellenga E, van Agthoven M, Croockewit AJ, Verdonck LF, Wijermans PJ, van Oers MH, et al. Autologous peripheral blood stem cell transplantation in patients with relapsed lymphoma results in accelerated haematopoietic reconstitution, improved quality of life and cost reduction compared with bone marrow transplantation: the Hovon 22 study. Br J Haematol 2001;114(2):319—26.
[46] Woronoff-Lemsi MC, Arveux P, Limat S, Deconinck E, Morel P, Cahn JY. Cost comparative study of autologous peripheral blood progenitor cells (PBPC) and bone marrow (ABM) transplantations for non-Hodgkin's lymphoma patients. Bone Marrow Transplant 1997;20(11):975—82.
[47] Kucharski AJ, Ghalie R, Greenstein S, Matuszewski K. The clinical effectiveness and financial impact of utilizing peripheral blood progenitor cells as rescue therapy following autologous bone marrow transplant. Int J Tech Assess Health Care 1996;12:172—9.
[48] Majhail NS, Mothukuri JM, Brunstein CG, Weisdorf DJ. Costs of hematopoietic cell transplantation: comparison of umbilical cord blood and matched related donor transplantation and the impact of posttransplant complications. Biol Blood Marrow Transplant 2009;15(5):564—73.
[49] Kanate A, Szabo A, Raj R, Bower K, Grulke R, Shah N, et al. Comparison of graft-acquisition and early direct charges of haploidentical related donor transplantation versus umbilical cord blood transplantation. Biol Blood Marrow Transplant 2019.
[50] Roth JA, Bensink ME, O'Donnell PV, Fuchs EJ, Eapen M, Ramsey SD. Design of a cost-effectiveness analysis alongside a randomized trial of transplantation using umbilical cord blood versus HLA-haploidentical related bone marrow in advanced hematologic cancer. J Comp Eff Res 2014;3(2):135—44.
[51] Pechlivanoglou P, De Vries R, Daenen SM, Postma MJ. Cost benefit and cost effectiveness of antifungal prophylaxis in immunocompromised patients treated for haematological malignancies: reviewing the available evidence. Pharmacoeconomics 2011;29(9):737—51.
[52] Stewart BL, Storer B, Storek J, Deeg HJ, Storb R, Hansen JA, et al. Duration of immunosuppressive treatment for chronic graft-versus host disease. Blood 2004;104(12):3501—6.
[53] Yalniz FF, Murad MH, Lee SJ, Pavletic SZ, Khera N, Shah ND, et al. Steroid refractory chronic graft-versus-host disease: cost-effectiveness analysis. Biol Blood Marrow Transplant 2018;24(9):1920—7.
[54] Kneale M, Bartholomew JS, Davies E, Denning DW. Global access to antifungal therapy and its variable cost. J Antimicrob Chemother 2016;71(12):3599—606.
[55] European Medicines Agency. Guideline on similar biological medicinal products. May 2013. Available from: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/ 2013/05/ WC500142978. Pdf.
[56] Abraham I, Tharmarajah S, MacDonald K. Clinical safety of biosimilar recombinant human granulocyte colony stimulating factors. Expert Opin Drug Saf 2013;12:235—46.
[57] Dylst P, Vulto A, Godman B, Simoens S. Generic medicines solutions for a sustainable drug market?. Appl Health Econ Health Policy 2013;11:437—43.
[58] Gascon P. Presently available biosimilars in hematologyoncology: G-CSF. Target Oncol 2012;7(Suppl 1):29—34.
[59] Shaw BE, Confer DL, Hwang WY, Pamphilon DH, Pulsipher MA. Concerns about the use of biosimilar granulocyte colony-stimulating factors for the mobilization of stem cells in normal donors: position of the World Marrow Donor Association. Haematologica 2011;96:942—7.
[60] Lefrère F, Brignier AC, Elie C, Ribeil JA, Bernimoulin M, Aoun C, et al. First experience of autologous peripheral blood stem cell mobilization with biosimilar granulocyte colony-stimulating factor. Adv Ther 2011;79:92—8.
[61] Publicover A, Richardson DS, Davies A, Hill KS, Hurlock C, Hutchins D, et al. Use of a biosimilar granulocyte colony-stimulating factor for peripheral blood stem cell mobilization: an analysis of mobilization and engraftment. Br J Haematol 2013;162:107—11.
[62] Cesaro S, Tridello G, Prete A, Dallorso S, Cannata E, Massaccesi E, et al. Biosimilar granulocyte-colony-stimulating factor for mobilization of autologous peripheral blood stem cells in pediatric hematology-oncology patients. Transfusion 2015;55 (2):246—52.

[63] Roger SD. Biosimilars: current status and future directions. Expert Opin Biol Ther 2010;10(7):1011—8.
[64] Svahn BM, Remberger M, Myrbäck KE, Holmberg K, Eriksson B, Hentschke P, et al. Home care during the pancytopenic phase after allogeneic hematopoietic stem cell transplantation is advantageous compared with hospital care. Blood 2002;100 (13):4317—24.
[65] Human United Nation Development Program: Human Development Reports. UNDP. 2018 [Accessed on December 19, 2018]. Available from: http://hdr.undp.org/en/2018-update. Development Index.
[66] Giebel S, Labopin M, Ehninger G, Beelen D, Blaise D, Ganser A, Bacigalupo A, et al. Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Association of Human Development Index with rates and outcomes of hematopoietic stem cell transplantation for patients with acute leukemia. Blood 2010;116(1):122—8.
[67] McWhirter WR, Smith H, McWhirter KM. Social class as a prognostic variable in acute lymphoblastic leukaemia. Med J Aust 1983;2(7):319—21.
[68] Coebergh JWW, van der Does-van den Berg A, Hop WCJ, van Weerden F, Rammeloo JA, van Steensel HA, van Wering ER, Kamps WA. Small influence of parental educational level on the survival of children with leukaemia in the Netherlands between 1973 and 1979. Eur J Cancer 1996;32(2):286—9. https://doi.org/10.1016/0959-8049(95)00577-3.
[69] Pollock BH, DeBaun MR, Camitta BM, Shuster JJ, Ravindranath Y, Pullen DJ, et al. Racial differences in the survival of childhood B-precursor acute lymphoblastic leukemia: a Pediatric Oncology Group study. J Clin Oncol 2000;18(4):813—23.
[70] Bhatia S, Sather HN, Heerema NA, Trigg ME, Gaynon PS, Robison LL. Racial and ethnic differences in survival of children with acute lymphoblastic leukemia. Blood 2002;100 (6):1957—64.
[71] Dai W, Brisimi TS. AdamsWG, Mela T, Saligrama V, Paschalidis IC, Prediction of hospitalization due to heart diseases by supervised learning methods. Int J Med Inf 2015;84(3):189—97.
[72] Bates DW, Saria S, Ohno-Machado L, Shah A, Escobar G. Big data in health care: using analytics to identify and manage high-risk and high-cost patients. Health Aff 2014;33 (7):1123—31.
[73] Warner JL, Zhang P, Liu J, Alterovitz G. Classification of hospital acquired complications using temporal clinical information from a large electronic health record. J Biomed Inform 2016;59:209—17.
[74] Mortazavi A, Khamseh AA, Azimi P. Designing of an intelligent self-adaptive model for supply chain ordering management system. Eng Appl Artif Intell 2015;37:207—20.
[75] Vemulapalli Vijetha, Qu Jiaqi, Garren Jeonifer M, Rodrigues Leonardo O, Kiebish Michael A, Sarangarajan Rangaprasad, Narain Niven R, Akmaev Viatcheslav R. Non-obvious correlations to disease management unraveled by Bayesian artificial intelligence analyses of CMS data. Artif Intell Med 2016;74:1—8. https://doi.org/10.1016/j.artmed.2016.11.001.
[76] Srinivas S, Ravindran AR. Optimizing outpatient appointment system using machine learning algorithms and scheduling rules: A prescriptive analytics framework. Expert Syst Appl 2018;102:245—61.
[77] Wang J, Yang X, Cai H, Tan W, Jin C, Li L. Discrimination of breast cancer with microcalcifications on mammography by deep learning. Sci Rep 2016;6:27327.