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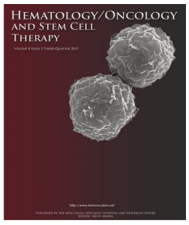

REVIEW ARTICLE

Strategic priorities for hematopoietic stem cell transplantation in the EMRO region

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Abstract
The World Health Organization-designated Eastern Mediterranean region (EMRO) consists of 22 countries in North Africa and Western Asia with a collective population of over 679 million. The area comprises some of the wealthiest countries per capita income and some of the poorest. The population structure is also unique and contrasts with western countries, with a much younger population. The region sits in the heart of the thalassemia belt. Many countries have a significant prevalence of sickle cell disease, and cancer is on the rise in the region. Therefore, the strategic priorities for the growth and development of hematopoietic stem cell transplantation (HSCT) differ from country to country based on resources, healthcare challenges, and prevalent infrastructure. Thirty-one reporting teams to the Eastern Mediterranean Blood and Marrow Transplantation Group have active HSCT programs in 12 countries; allogeneic transplants outnumber autologous transplants, and the proportion of allotransplants for non-malignant conditions is higher in the EMRO region than in Western Europe and North America. The vast majority (99%) of allotransplants are from matched related donors. Matched unrelated donors and other alternate donor transplants are underutilized. The chance of finding a matched related donor for allografts is higher, with a significant chance of finding matched donors among non-sibling related donors. Reasons for relatively lower rates of transplants compared with other countries are multifactorial. Capacity building, development of newer centers, innovative funding, and better utilization of information technology are required to make transplantation as an accessible modality to more patients. Cost-effectiveness and cost-containment, regulation, and ensuring quality will all be priorities in planning HSCT development in the region.

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Introduction

In nearly six decades since E. D. Thomas first performed bone marrow transplants in patients with leukemia, hematopoietic stem cell transplantation (HSCT) has gone from being an experimental therapy, considered by early critics to be dangerous and futile, to a potentially life-saving therapy that is a standard of care for many diseases. Between 1957 and 2019, over 1.5 million transplants were recorded, and thousands of lives have been saved [1,2]. The transplant activity is currently increasing at an unprecedented pace, with more than 90,000 transplants carried out annually worldwide; however, most of these are carried out in developed countries [2]. With each decade, the efficacy

and safety of the procedure is improving, and new transplant centers are established [3]. More than 1,500 centers exist across the five continents; however, the pace of transplant adoption and the center density according to the population is disproportionately larger in North America and Europe than in other parts of the world [4,5]. The World Health Organization divides the world into several regions with regional offices (namely the Americas, Africa, South-East Asia, Europe, Eastern Mediterranean, and Western Pacific). The Eastern Mediterranean regional office (EMRO) represents 22 countries in North Africa and Western Asia with diverse resources and per capita income. Thirty-one teams in 12 EMRO countries have reported stem cell transplant; however, the transplant activity is still lower than that in countries in the northern hemisphere with a similar population, and populations in almost half of the EMRO countries do not have access to transplant programs. The Eastern Mediterranean Blood and Marrow Transplantation (EMBMT) Group was established in 2007 as a collaborative platform to promote transplantation in the region and allow collaboration between centers in the region [6,7]. Here we discuss some of the strategic priorities that countries may want to address to increase the access and availability of transplants for the EMRO population.

Regional background

The EMRO comprises countries that economically fall into four categories: the high income, upper-middle income, lower-middle income, and low income. In this regard, the region is characterized by starkly contrasting levels of wealth of even neighboring nations. Qatar, Kuwait, and Saudi Arabia have gross domestic products (GDPs) per capita of $61,650, $30,000, and $20,178, respectively. In contrast, they are juxtaposed with some of the poorest countries such as Somalia (per capita GDP $348), Yemen (per capita GDP $620), and Djibouti (per capita GDP $3,074) [8]. The vast majority of the population in the EMRO (70%) live in lower-income or lower-middle-income countries. Given the economic disparity in the region, priorities and recommendations can hardly be generalized across the region. Many of these countries do not have access to the most basic healthcare provisions. The population of the region is also quite distinct from the Western world. In the Middle East and North African countries, 30% of the population is under 14 years of age compared with the European Union (16%) or North America (19%) [9]. In addition, the region is characterized by changing population demographics. As the growth rate is expected to decrease, families become smaller and many societies become more urbanized. This will be expected to impact HSCT in many ways, including the chance of finding a sibling donor.

Healthcare setting

The healthcare issues are also unique to the region related to those diseases for which an HSCT may be carried out, or may complicate a transplant. Cancer is one of the top causes of death in the EMRO region, while the top five causes of disability-adjusted life years are ischemic heart disease, lower respiratory tract infections, preterm birth complications, diarrheal diseases, and congenital anomalies [10]. Most, if not all, of the EMRO region falls within the thalassemia belt. For patients with beta-thalassemia in the region, only 17% of patients who need transfusions receive them. More than 7,000 deaths occur per year due to lack of transfusions, and over 28,000 patients have inadequate or no chelation, leading to over 1,400 deaths per year due to iron overload [11]. While epidemiologic data do not exist for the prevalence of aplastic anemia in the Middle East, comparative data indicate a higher prevalence of aplastic anemia in Asia than in Europe and North America by approximately 2—3 folds [12]. Transplantation data, which may be used as a surrogate indicator of prevalence, suggest that as an indication, aplastic anemia may be more prevalent: 20% of allografts in the EMRO region were for aplastic anemia compared with 5% in the European Society for Blood and Marrow Transplantation (EBMT) registry, and a proportion of these would have been transplanted in the EMRO countries reporting to the EBMT [13,14]. Again patients with non-malignant diseases are more likely to present late, often with infections and significant iron overload. This has implications on the risk of morbidity and mortality of the transplant procedure [7]. Several infection-related issues are pertinent for transplant programs in the region. Cytomegalovirus seropositivity is reported to be as high as 100% among recipients in Saudi Arabia and donors and recipients in Pakistan [7]. There is high seropositivity for hepatitis B in Egypt, Jordan, Oman, Palestine, Yemen, and Saudi Arabia. Hepatitis C is highly endemic in Egypt, which also has a high prevalence of schistosomiasis [5].

Donor-related issues

The family size is larger in the EMRO countries than in Europe and the United States, which increases the chances of finding matched sibling donors [15]. The likelihood of finding a sibling donor has been reported to be as high as 63% in Saudi Arabia and 70% in Pakistan versus 13—51% in the United States [16]. In addition, consanguinity is not uncommon in the EMRO region. While consanguinity rates are low in Europe, countries of the EMRO region may have consanguinity rates as high as 67% in some countries [17]. This allows a further pool of donors in patients who may not have a matched sibling donor or where matched unrelated donor (MUD) registries are unavailable. One study from Iran reported 109 non-sibling matches found in 523 searches (20%) [18]. A similar experience has been reported from Jordan [19]. This is an important pool that is unique not only in being more easily accessible and thus reducing time to transplant, but these donors are also likely to be more motivated to donate to a relative. This also warrants exploring an alternative donor search algorithm for countries with high levels of consanguinity, large families, and no volunteer donor registries.

Transplant activity

The EMBMT Group has reported transplant activity since the inception of transplantation in the region in 1984. Data have

been collected up to 2012, with a total of 15,388 transplants carried out [4,7,13,20–22]. Of these, and in contrast to data reported by EBMT and Center for International Blood and Marrow Transplant Research where autografts outnumber allografts, 10,578 (68%) were allografts. Nearly all allografts in the EMRO region and Africa are from family donors versus 57% in the Americas and 48% in Europe [1]. Negligible MUD transplants are carried out due to the unavailability of functioning MUD registries in most countries. In addition, and as stated above, there is a much higher chance of finding a matched related donor. Only 10% of allogeneic transplants are for non-malignant disorders in the Americas and Europe versus 34.5% in the EMRO region and Africa. The survey carried out by the EMBMT for 2011–2012 gathered reports from 21 centers in nine countries, though more countries have since started programs (Qatar, Kuwait, Bahrain, etc.). The median number of transplants during 2011–2012 was 47 transplants per center per year (range, 4–373) [13], but the transplant rates per 10 million population remain very low compared with the rates in Europe as reported to the EBMT [14,23]. It varied in 2011 from 0.3 per year in Pakistan to 25 per year in Lebanon, with a median of 9.2 per 10 million per year [13]. As of the 2012 survey, the most common indication for allogeneic transplants was acute leukemia in first remission and beyond (45%), followed by bone marrow failure syndromes (20%), thalassemia (10%), and primary immune deficiency (7.8%). Furthermore 63% of allografts were myeloablative; bone marrow was a source of hematopoietic cells in 28%, peripheral blood in 68%, and umbilical cord transplants made up 6%. The most common indications for an auto transplant were similar to western practices, namely plasma cell dyscrasias (37.7%), Hodgkin lymphoma (21%), non-Hodgkin lymphoma (22.4%), and neuroblastomas (13.5%) [13]. As reported by Gratwohl et al., transplant rates in the region were 47.7 (range, 2.8–95.3) in the Eastern Mediterranean and Africa compared with 268.9 (range, 5.7–792.1) in Europe. Multiple factors, macroeconomic (gross national income [GNI] per capita, team density, and team distribution) and microeconomic (team sizes, team experience, and innovator status), contribute to variation in transplant rates. Greater healthcare expenditure and a higher human development index, more donors, bigger cord blood banks are all factors that affect transplant rates [1,13]. An important consideration is whether transplant rates are increasing sufficiently. The total number of transplants was 392, 973, and 1,413 for 2000, 2005, and 2010, respectively, constituting a 260% increase over the last decade. The HSCT rate of transplants per 10 million population was 10.6, 23.9, and 33.6, respectively, constituting a 210% increase in rates over 10 years. HSCT rates were increasing at a rate greater than the increase in population in these countries. This is important for transplant planning of resources and staffing levels [21].

Identifying priorities and strategic planning

Cancer is one of the major causes of morbidity and mortality around the world. Statistical predictions expect much of the cancer burden (incidence, morbidity, and mortality) in the developing world [24,25]. This disproportionate distribution of cancer burden is multifactorial (poor access to advanced diagnostic and therapeutic modalities, near absence of research and epidemiologic data, paucity of cancer control and prevention strategies, etc.) [26,27]. This disparity may even get wider, as the young population in the developing countries will accelerate the population growth and, as such, the demand for medical care [28]. These facts highlight the importance of adopting policies to close the gap and facilitate transplants in the ''increasing-demand'' countries. The first step toward this goal is to understand the challenges faced in these countries and implement strategies to address the priorities. Authorities involved in the transplant program's establishment/development will have to extensively plan and study the various aspects/processes to ensure the functionality of their strategy. Miscalculations and incomplete understanding of the various aspects of the process can have a tremendous impact, especially in developing countries. Advantages, costs, alternatives, technical, financial, and geopolitical issues have to be considered. Even with extensive planning, unforeseen circumstances will occur and the strategy and priorities have to be adjusted over time.

Having too many goals can be detrimental to strategic planning and dilute attention from what matters. Establishing and maintaining transplant programs needs significant economic and human resources investment. As such, the rates of HSCT use are highly associated with higher GNI per capita, governmental healthcare expenditures, and human development index [29]. For these reasons, HSCT is more common in affluent countries; nevertheless, interest to develop HSCT programs in resource-limited countries is steadily increasing. Of the high-income countries in the EMRO region (Saudi Arabia, Kuwait, Qatar, UAE, Bahrain, Oman), transplant programs are reported in five countries. Saudi Arabia has an established program since 1984, but per capita rates suggest an unmet demand [30]. High-income countries continue to send patients overseas, and not only does this constitute a significant healthcare expenditure but it also means that patients get treated without their extended family support, and national services fail to develop. Given the variation in the socioeconomic landscape and healthcare settings of different countries in the region, strategic priorities vary from country to country.

Priorities for countries with no established HSCT programs

Most countries in the EM region lacking significant HSCT activity suffer from limited economic resources. However, some of the affluent countries in the region do not have local transplant programs, and their patients are typically referred to the United States or Western Europe for HSCT. From a public health perspective, these affluent countries may not invest in transplant programs as many of their inhabitants lack the financial cover for complex procedures. A change in the insurance coverage or a decision to invest in medical tourism will easily swing the balance in favor of establishing local HSCT programs. For the EM countries with limited resources, economic justification is the foremost hurdle as more prevalent and curable health conditions compete for the limited resources. Once these critical decision-making issues are resolved, and the planning phase

Table 1 Stages of Development of HSCT Program.

	Stage I	Stage II	Stage III
Types of transplant performed	■Autologous ■HLA-matched sibling donors	Stage I + ■All MSD transplants including MMSD ■Autologous with cryopreserved products	Stage II + ■Haploidentical ■&/or MUD, MMUD ■&/or UCB ■&/or T-cell depleted
Number of HSCT	5 Auto-HSCT/year 3—5 Allo-HSCT/year	10 Auto-HSCT/year 5—10 Allo-HSCT/year	>10 Auto-HSCT/year >10 Allo-HSCT/year

allo-HSCT = allogeneic hematopoietic stem cell transplant; auto-HSCT = autologous hematopoietic stem cell transplant; HLA = human leukocyte antigen; MMSD = mismatched sibling donor; MMUD = mismatched unrelated donor; MSD = matched sibling donor; MUD = matched unrelated donor; UCB: umbilical cord blood.

starts, these countries with no established HSCT programs will have a nearly similar pathway to develop such programs. The transplant procedure is complex; a complicated infrastructure and multiple disciplines are involved. Usually, the programs are developed using an organized stepwise approach starting with autologous and a small number of allogeneic transplants. Table 1 summarizes the Worldwide Network for Blood and Marrow Transplantation definition and recommendations of development stages of transplant programs [31,32]. Healthcare providers and planners should initiate rigorous actions to put the infrastructure in place. Critical components of a functioning transplantation program include but are not limited to: (a) human resource capacity building (nurses, physicians, pharmacist, laboratory technicians, etc.), (b) apheresis and cell processing, (c) transfusion medicine and blood banking, (d) pharmaceutical division, (e) sanitation and environmental services, (f) infection control, (g) radiology, (h) diagnostic and HLA laboratory, (i) quality control, and (j) uninterrupted power supply system. All these have to be planned in the context of changing geopolitical and socioeconomic conditions of the EM countries. We strongly recommend implementing a collaborative partnership with a regional or international well-established transplant center to build these capacities through staff exchange, outreach programs, logistic support, monitoring visits, shared activities, and standards of practice. Of note, most of the EM region countries have healthcare systems supported economically by the state and since maintaining these programs is expensive, we recommend allocating the budget appropriately depending on the country's constraints and economic status and to explore and benefit from the available global health initiatives. Having a financial backup and addressing future challenges that may arise are critical. Table 2 summarizes the author's opinion regarding the strategic priorities for HSCT in the EMRO region.

Priorities for countries with established HSCT programs

Several well-established HSCT programs exist in the EMRO countries. The HSCT practice is dynamic and continuous improvements are essential for programs to advance. Many barriers stand in the way of program development in the region and having good strategies may help circumvent some of these limitations. A set of common strategies may help both countries with high and middle-to-low economic resources. These include but are not limited to: (a) expanding the transplant bed capacity to provide access for patients in need, (b) skilled staff recruitment and retention, (c) integration and empowerment of specialized nurses and other support staff and have them participate and make decisions on daily rounds as an essential part of the healthcare team as these support teams have been historically undervalued, (d) create education and training curricula relevant to the local context, (e) public education and campaigns using modern tools and platforms to teach the public about various conditions that can be cured by transplantation as this may engage more volunteers and may help to disseminate the mission, and (f) establish local registries and databases to generate local data and to collaborate with the existing international registries. In addition to these common strategies, countries with limited resources may want to invest in: (a) haploidentical transplant as a default alternate donor transplant as this will provide a donor for virtually all patients in need with a lower total cost than other alternate sources (MUD or cord blood) [33], (b) tailoring the conditioning regimens based on locally generated data, (c) outsourcing some expensive tests to reference labs as this may save some funds to use in other areas, (d) explore alternate funding pathways as most of these programs run on a tight governmental budget (charity, support organizations, etc.), and (e) explore opportunities offered by global health initiatives. For countries with high income, programs probably operate on a more relaxed budget and strategies to invest in advanced options and high-tech in the transplant field are needed: (a) seek accreditation to improve quality and performance (Foundation for the Accreditation of Cellular Therapy [FACT] and Joint Accreditation Committee of the ISCT-EBMT [JACIE] accreditation), (b) reduce dependence on referrals to outside countries so that local expertise can be built, (c) advance research opportunities and collaboration to generate local data (pharmacogenomics effects in specific population [34], study regional differences in the outcomes depending on genetic background [e.g., unpublished data from King Faisal Specialist Hospital and Research Center showing a higher risk of relapse with translocation (8:21)-acute myeloid leukemia], genetic polymorphism, consanguinity effects on transplant outcomes, inherited diseases outcomes post-transplant, graft-versus-host disease [GvHD] in

Table 2 Author's Opinion Regarding the Strategic Priorities for HSCT in the EMRO Region.

	Countries with no established HSCT program	Countries with established HSCT program
Common strategies regardless of the economic resources	-Partnership with a regional or international well-established transplant center -Human resource capacity building -Apheresis and cell processing -Transfusion medicine and blood banking -Pharmaceutical division -Environmental services -Infection control -Radiology, intensive care, and other supportive disciplines -Diagnostic and HLA laboratory -Quality control and standard operating procedures -Use strategic planning tools to help with planning	-Expand transplant bed capacity -Establish outpatient HSCT service -Skilled staff recruitment and retention -Integration and empowerment of all supportive services in patient care -Create education and training curricula relevant to the local context -Public education campaigns -Establish local registries and databases to generate local data and to collaborate with the existing international registries
Countries with high income	-Outreach programs -Medical tourism -Staff exchange and training partnership -Advanced laboratory technologies -Information technology software and artificial intelligence	-Seek accreditation -Reduce dependence on referrals to outside countries -Advance research opportunities and collaboration to generate local data -Invest in advanced laboratory techniques -Build long-term survivorship programs -Invest in cellular and gene therapy techniques and therapeutics -Explore new concepts in conditioning -Fertility preservation services -Invest in information technology platforms
Countries with middle and low income	-Assess the economic impact -Infrastructure development -Focus on haploidentical transplant -Seek support from global health initiatives -Secure financial backup -Uninterrupted power supply system	-Establish haploidentical transplant as the default alternate donor transplant -Tailor conditioning regimens according to local data and diseases -Outsource expensive tests to reference labs -Encourage the use of generic drugs and biosimilars -Explore alternate funding pathways (charity, support organizations, volunteers etc.) -Explore opportunities offered by global health initiatives

EMRO = Eastern Mediterranean regional office; HLA = human leukocyte antigen; HSCT = hematopoietic stem cell transplant.

genetically homogenous communities, infectious disease issues related to transplantation in specific geographic areas etc.), (d) invest in advanced laboratory techniques (e.g., whole genome and next-genome sequencing, etc.), (e) build long-term survivorship programs as HSCT survivors are living longer and are expected to face late complications (second cancers, endocrinopathies, cardiac effects, etc.), (f) invest in evolving cellular and gene therapy techniques and therapeutics, (g) explore new concepts in conditioning and how to integrate the novel therapies or techniques in the existing transplant platforms (clonal antibodies conditioning, targeted drug delivery, chimeric antigen receptor T-cell therapy, etc.), (h) fertility preservation services as these are limited and poorly regulated in the EM region (cultural issues, scarcity of credible sperm banking facilities, state regulations, etc.), and (i) invest in information technology platforms which may help predicting outcomes after allo-HSCT and even in GvHD (artificial intelligence, machine learning, build in-house software and programs tailored to local needs, etc.). Table 2 summarizes the author's opinion regarding the strategic priorities for HSCT in the EMRO region.

Conclusion

Establishing or maintaining an HSCT program is not an easy task and requires many predictions and preparations in a constantly evolving world, especially in the setting of limited resources and competition from emerging alternatives. We herein present a brief overview of the transplant landscape in the EMRO region and provide a list of potential strategies to push the field forward in these countries. These strategies provide a starting point that can help healthcare planners to lay out their policies and approaches in the context of the local conditions as priorities and resources are different for each country. Transplant programs constitute a financial ordeal. However, with the increasing trend of worldwide transplant activity and the paucity of alternatives, countries with minimal resources need to establish or further develop their programs to accommodate the demands. Of note, the cost of transplants in developing countries is much less compared with that in developed countries [5,35—38]. However, it remains a significant economic burden. Therefore, the planning phase is critical and a comprehensive team should allocate ample time to lay out a master plan. Collaborative partnership with well-established national or international centers is essential to mitigate the risk and appropriately allocate the available resources.

Declaration of Competing Interest

All authors declare no conflicts of interest.

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