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Status of hematopoietic stem cell transplantation in the WHO Eastern Mediterranean Region (EMRO)

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A B S T R A C T

Several centers are now performing allogeneic hematopoietic stem cell transplantation (HSCT) in the World Health Organization Eastern Mediterranean Region (EMRO) but the availability is still limited due to high cost and the need for multi-disciplinary team and an advanced laboratory support. Special issues including compatible donor availability, potential for alternate donor programs, differences in pattern of disease, pre-HSCT general status particularly for patients with BM failure, high sero-positivity for CMV, Hepatitis B and C infection and specific observations about GVHD with its relation to genetically homogeneous community are discussed. A total of 17 HSCT programs (performing five or more HSCTs annually) exist in nine countries of the EM region. Only six programs are currently reporting to EBMT or IBMTR. A total of 7617 HSCTs including 5701 allogeneic HSCTs have been performed. Due to low HSCT team density (1.5583 teams/10 million inhabitants versus 14.4333 in Europe) and very low HSCT team distribution (0.2729 teams/10,000 sq km area versus <1 to 6 teams in Europe) only 70.8% of total population has access to such a program in EM region. GNI/capita had no clear association with low HSCT activity; however improvement in infrastructure and establishment of EM regional HSCT registry need prioritization.

Hematopoietic stem cell transplantation (HSCT) is a life-saving treatment for many diseases. However, due to the relatively high cost, need for multi-disciplinary team and advanced laboratory support limited centers in the EMRO region are providing HSCT. European Bone Marrow Transplantation Group (EBMT) and the Center for International Bone Marrow Transplantation Research (CIBMTR)

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provide high quality data about HSCT activity. However, both registries contain more data from centers located in Western Europe and North America. Although the number of centers performing allogeneic HSCT in EMRO region as defined by the World Health Organization (WHO) [1] has increased, but, until recently, no data were available about the transplant activities in this region or the issues related to HSCT in the listed countries. During the last year, a cooperative effort has been carried out through program representatives in the EMRO region with the goal of simple identification of issues related to HSCT in the EMRO area and to conduct the first survey for this region. At the time of writing, with the help of the EBMT, CIBMTR and in collaboration with the World Bone Marrow Transplantation Group (WBMT), we have achieved success in formulating an eastern Mediterranean bone marrow transplant group (EMBMT).

Through our survey, conducted to find information about HSCT activity in EMRO region, included all programs in the WHO-designated EMRO region with consistent annual performance of equal or greater than five (5) cases per year for at least three (3) years, we identified some special issues pertaining to HSCT in the EMRO region [5]. Our region has a total of 21 countries with a total population of more than 540 million. These 21 countries include one country with low income category, five with lower middle income category, eight with upper middle income category and seven with high income category countries according to WHO income groups based on GNI per capita. Out of 21 only nine countries (Saudi Arabia, Egypt, Iran, Jordan, Lebanon, Morocco, Oman, Pakistan and Tunisia) encompassing 70.8% of the total EMRO region population have at least one active HSCT programs available for their population. The total numbers of the programs that exist as of present are 17. Unfortunately, only six out of this 17 do report data to EBMT and/or CIBMTR. Overall in EMRO region the rate of transplantation has increased over the last 5 years but the ratio of transplantation to the total population of the individual country has remained low. Table 1 lists the number of patients who received allogeneic or autologous HSCT in the nine countries and some of the main issues related to HSCT in each country [2–9].

The specific issues related to allogeneic HSCT in Eastern Mediterranean Region can be divided into donor availabil-

Table 1
Number of HSCT recipients in various countries (data from major centers*) in the EMRO region and some of the main issues related to allogeneic HSCT in each country.

Countries (HSCT data up to)	Allo-HSCT	Auto-HSCT	Total	Some of the reported special issues
Saudi Arabia (up to December 2006)	2135	654	2789	Heavily pre-transfused aplastic anemia patients High CMV – sero-positivity High prevalence of HBV and HCV Poor tolerance to 4th dose (day 11) Methotrexate Lack of national or regional registry for alternate donor program Genetic tools for better risk profiling for GVHD needed
Iran [5] (up to October 2007)	1381	598	1979	β-Thalassemia is common
Egypt [4] (up to June 2007)	1,090	272+	1362	Low motivation of donors Lack of matched unrelated donors High prevalence of HBV and HCV. Schistosomiasis endemicity High prevalence of β-thalassemia (carrier state 9–11%) and such patients are heavily pre-transfused and poorly chelated
Pakistan [2] (up to December 2006)	350	50	400	Only three small centers for a population of 165 million 100% CMV positive donors and patients. Patients with aplastic anemia and β-thalassemia are the most common recipients Sub-optimal transfusion services Endemicity of malaria, hepatitis B and C and tuberculosis High rate of fungal infections
Tunisia [3] (up to June 2007)	299	Data N/A	299+	Majority of transplants are done for non-malignant disorders (mostly aplastic anemia) and Fanconi's anemia
Jordan [6] (up to March 2007)	237	83	320	Most common malignant indications are leukemia and MDS 90% Thalassemia patients on waiting list with 3 years average waiting time High rate of invasive fungal infection along with high cost of new anti-fungals
Oman [7] (up to August 2006)	125	4	129	High rate of consanguinity (first cousins 24.1%). 42% transplant patients have inherited disorders including β-Thalassemia Primary immunodeficiency increasingly being recognized as an important HSCT indication
Lebanon [8] (up to March 2007)	84	228	312	High number of thalassemia patients High rate of consanguinity in mountainous regions
Morocco [9] (up to May 2007)	0	27	27	Limited number of beds available for HSCT High prevalence of sickle cell disease Efforts to start allogeneic HSCT program are ongoing
Total	**5701**	**1916**	**7617**	

N/A: Not available.
* Programs with annual accrual of ⩾5 HSCT cases per year for at least 3 years.

ity, genetic issues, issues related to specific diseases, pattern of infections and logistics. Each is discussed below in detail:

1. Donor availability

Due to large size of families in the EMRO region and high population growth, the likelihood of finding a full matched sibling donor is far higher than the likelihood of finding a donor for European and North American patients. (e.g. in Saudi Arabia 63.5% [10] and 70% in some areas in Pakistan [2]). Additionally, the overall outcome of class one antigen mismatch sibling allogeneic transplantation yields similar result to fully matched sibling transplantation which is likely to reflect ethnically and genetically the homogenous make up of the population. A lower occurrence of acute and chronic graft-versus-host disease (GVHD) has also been observed [11–14], as reported earlier in other ethnic populations [15]. Cord blood transplantation remains the preferred alternate donor transplantation modality in the centers that offer alternate donor HSCT. This is due to relatively lower likelihood of finding a match through western registries and the logistic difficulties in timely performance of HSCT from matched unrelated donor typically available in Western Europe and North America.

2. Genetic issues

A local pharmacogenomic study from Saudi Arabia has shown a unique profile of variations in metabolism genes in Arab population [16]. PCR analysis revealed that the frequencies of alleles and/or genotypes for CYP1A1 2A, GSTT1 null, GSTT1 and GSTM1 double null, and GSTP1 A1578G in Arabs were significantly higher than those reported in Caucasians. Other alleles in Arabs, including CYP1A1 T3801C and GSTP1 A1578G were present in frequencies similar to Africans [16]. Knowledge of the prevalence of polymorphism in certain genes such as cytokines genes related to the risk of development of GVHD as well as genes coding for enzymes responsible for drug metabolism is badly needed in certain communities with high likelihood of consanguinity and in the EMRO region at large. Inactivating mutations have been found in genes coding for enzymes belonging to the cytochrome P-450 system, and also in genes coding for other enzymes. Several pharmacogenomic research projects are being pursued in the Eastern Mediterranean countries in relation to this matter.

3. Disease specific issues

(i) Severe aplastic anemia: Higher proportion of patients with severe aplastic anemia in EMRO region is heavily pretransfused when referred for allogeneic HSCT. Accordingly, a strong lymphoablative component has to be always included in the conditioning chemotherapy to avoid graft rejection. Fludarabine is being increasingly utilized as a lymphoablative component, traditionally with cyclophosphamide for conditioning of aplastic anemia patients. The major reasons for this are the prohibitive cost of antithymocytic globulin and lower likelihood of side effects with Fludarabine particularly in older patients. Large numbers of aplastic anemia patients are referred to the transplant centers with a variety of infections including viral, bacterial and fungal infections. However, new generation antifungal drugs are neither universally available nor affordable for all centers in the area. A small but a definite subset of patients presents with elevated liver enzymes on admission, some with positive hepatitis serology. However, a small but definite subset of patients has "sero-negative hepatitis aplasia syndrome" similar to what has been described in previous reports [17,18]. These patients with negative hepatitis serology tend to respond to treatment with immunosuppression therapy only.

(ii) Congenital bone marrow failure syndromes and hemoglobinopathies: Due to highly prevalent marital consanguinity in the EMRO countries, the prevalence of hemoglobinopathies including thalassemia and sickle cell anemia is high [4,7,8]. Patients with hemoglobinopathies and bone marrow failure syndromes are typically heavily pre-transfused; hence are iron overloaded and frequently with a positive serology for hepatitis B and/or C virus. Collectively these factors lead to increased hepatic veno-occlusive disease (VOD). Despite all of the limitations, non-neoplastic indications for allogeneic HSCT remain one of the main reasons for HSCT in certain Eastern Mediterranean transplantation centers. This is particularly common in countries where there is significant case attrition for acute leukemias because of the sub-optimal set-up conditions for chemotherapy induction in the referring centers [2,3].

(iii) Chronic myeloid leukemia: For centers where tyrosine kinase inhibitors (TKI) are available, allogeneic HSCT is no longer offered as a first-line treatment option for chronic myeloid leukemia (CML) patients in first chronic phase [19]. However, in countries where TKI therapy is not available because of its prohibitive costs, or in situations where the physician is unable to count on the continuation of the medication supply, the physician faces the dilemma of choosing the best management strategy "available to the patient" and not the best treatment strategy in absolute terms. Accordingly, allogeneic HSCT for CML in first chronic phase remains more cost effective as once in life time procedure and one of the main indications for transplantation in some centers. In few countries, generics of TKI at a very affordable cost are widely available. However, for majority of the EMRO countries, the medication has to be purchased at the standard price with no significant price adjustment based on the per capita income of each country. The issue of lower incidence of chronic GVHD is an issue of great relevance in relation to the risk of relapse in CML. Accordingly, many centers are practicing early reduction and discontinuation of post-HSCT immunosuppression for patients with no history of acute GVHD in attempt to induce a limited de novo chronic GVHD to promote the development of GVL.

(iv) Acute myeloid leukemia: An important requirement for offering allogeneic HSCT for patients with acute leukemias is the capability, both financially and logistically, of achieving complete remission through induction chemotherapy. At some centers in the EMRO region this becomes

one of the competing factors for the limited slots of allogeneic HSCT and eventually benign conditions, such as aplastic anemia and thalassemia, disproportionately become leading indication for allogeneic HSCT [2,3]. Another interesting regional observation is the relatively poor outcome of AML with *t*(8;21) which is generally considered favorable. Unpublished data from King Faisal Specialist Hospital and Research Centre in Riyadh suggested the event-free survival of this leukemia with standard induction and high dose cytarabine chemotherapy consolidation is 16%. The observed lower outcome may be related to different breakpoints or expression of other biologic and/or molecular markers that are known to be associated with poor prognosis [20].

(v) Lymphoid malignancies: A relatively higher percentage of intermediate and high grade lymphoma is observed in EMRO and accordingly, a relatively high proportion of eligible patients of the latter two entities are being transplanted compared to Western Europe and North America.

4. Issues related to infections

(i) Cytomegalovirus (CMV) infection: High sero-positivity for CMV was reported in many countries in the EMRO region reflecting high rate of previous exposure to this virus. The reported sero-positivity was 100% among the recipients and 96% among donors in Saudi Arabia [21] and 100% in donors and recipients in Pakistan [2]. There are several strategies for the prevention of CMV disease in high sero-prevalence set-up that apply to the EMRO region. On one hand, adequate pre-emptive therapy is to be applied with early detection of CMV infection and on the other hand, the pre-emptive therapy is not to be continued for extended period beyond establishment of CMV antigen negativity to prevent interference with development of CMV specific immune reconstitution [21,22].

(ii) Hepatitis B virus infection: The endemicity of hepatitis B virus (HBV) in the EMRO region is well established [23–25]. According to a report Egypt, Jordan, Oman, Palestine, Yemen and Saudi Arabia have high endemicity [25]. In a retrospective analysis performed in Saudi Arabia [26] among 128 patients with evaluable data, 42% had evidence of prior infection and recovery from HBV before transplant (hepatitis B core antibody positive, B surface antigen negative). After Allo-HSCT six patients (14%) reactivated with clinical flare as documented by sero-conversion and/or positive HBV DNA in the serum with biochemical hepatitis at 5.5, 18, 18, 19, 21 and 23 months after transplant. Five of 15 patients with chronic graft-versus-host disease (cGVHD) reactivated with clinical flare in contrast to 1/27 without cGVHD (RR: 9.0, $P < 0.02$). HBV re-activation with clinical flare occurred during immunosuppressive therapy tapering or withdrawal in all patients [26]. HBV re-activation may also be an additional risk factor in causation of VOD and other related complications. Another problem is encountered when the only matched donor is hepatitis B surface antigen positive and HSCT needs to be carried out for an urgent indication. The availability of Lamivudine and other effective therapies for hepatitis B virus, had remarkably improved the outcome of allogeneic HSCT with HBV positive recipient and/or donor during the last decade.

(iii) Hepatitis C virus infection: Hepatitis C virus (HCV) remains a major disease burden in the EMRO region. A high prevalence rate of HCV has been reported in Egypt in the recent past (up to 28% in some groups) [27]. Lower rates have been reported among blood donors from various regions of Saudi Arabia (0.4–4.3%) [28,29] and in Yemeni patients (2.1%) [30]. HCV genotype 1b is less responsive to alpha-interferon therapy compared to genotypes 2 and 3. Genotype 4 is the most common genotype in the EMRO region [29,31–34] which unfortunately is least likely to respond to the standard interferon therapy. A recent multicenter national study from Saudi Arabia, on patients with HCV showed that 59.6% had genotype 4, 25.1% had genotype 1, 8.3% had genotype 2 and 6.4% had genotype 3 [34]. However, distribution of HCV genotypes is not uniform in the EMRO region, e.g. Iran has a major prevalence of HCV genotype 1 (55.8% cases) [35]. Traditionally, HCV is known to have less contribution to early post transplant morbidity and mortality. Difficult situations sometimes exist where the only matched donor is hepatitis C antibody positive and allogeneic HSCT is urgently needed such as in cases of acute leukemia or aplastic anemia.

(iv) Mycobacterium tuberculosis: Although mycobacterium tuberculosis is relatively an endemic disease in certain areas of EMRO region, the likelihood of re-activation after HSCT is less frequent than what would be expected in an endemic area [36]. As a significant proportion of the population, especially older individuals, has a positive PPD status either from previous exposure or BCG vaccination in childhood, the appropriateness of the universal routine prophylaxis with Isoniazid (INH) for PPD positive HSCT recipient who has a low likelihood of re-activation can be questioned. Accordingly, many centers in EMRO believe that prophylaxis with INH in PPD positive patients should not be given routinely for patients who are completely asymptomatic with negative chest X-ray, which otherwise would expose the majority of patients to potential hepatotoxic medication that has many potential drug interactions with other medications used during HSCT. This practice may not be in line with the published Centers for Disease Control and Prevention (CDC) guidelines [37] but is substantiated with our observations in the EMRO region [2].

(v) Other infections: High prevalence of schistosomiasis in Egypt [38] and endemicity of malaria in certain areas of Pakistan [39] is well documented. Relevantly, poor malaria screening of asymptomatic blood donors led to some incidences of transfusion transmitted malaria in HSCT recipients during early transplant period in Pakistan [2]. In Egypt the relative risk to develop VOD after Allo-HSCT was calculated to be 16.8-fold higher in patients with previous history of schistosomiasis [38].

5. Logistic issues important to EM region

Some EBMT reports have included data from few non-European countries (Iran, Saudi Arabia, and Tunisia) that fall in the EMRO region and report their HSCT activity to

EBMT registry. Hence, data published by the EBMT group may also be informative for patient counseling and decisions making by health care professionals and planners/administrators in the EMRO region [41]. The EBMT has analyzed factors associated with differences in HSCT activity between the participating teams from more than 240 countries over a time span of 15 years. Results have revealed that gross national income (GNI) per capita, numbers of transplant teams per 10 million inhabitants (team density) or per 10,000 km (team distribution), team size and team experience all had impact on transplant activity [42]. The recent EBMT report based on the activity survey 2006 [43] showed that transplant rates predictably increased over time with nearly linear trends, in association with GNI per capita and distinctly by World Bank income category [43].

Our survey about HSCT activity in EMRO region is based on cumulative experience of 17 teams in nine countries of the EMRO region over the last two decades. Of the 17 teams, 16 (94%) did both allogeneic and autologous HSCT and one (6%) restricted its activity to autologous HSCT only. Team density in the EMRO region is very low

Table 2
HSCT activity and the related economic/logistic indices in the EMRO region.

Countries	Population in millions [1]	Area × 10,000 sq km	GNI per capita US$ (WHO income Category)[b]	Total HSCT performed in major centers	Teams performing HSCT*	HSCT team density	HSCT team distribution
Saudi Arabia	24.175	214.969	14,740 (High)	2789	3	1.240951	0.013956
Iran [5]	70.270	164.8	8,050 (U. Middle)	1979	2	0.284616	0.012136
Egypt [4]	74.166	100.145	4,440 (U. Middle)	1362+	3	0.404498	0.029957
Pakistan [2]	160.943	80.394	2,350 (L. Middle)	400	3	0.186401	0.037316
Tunisia [3]	10.215	16.361	7900 (U. Middle)	299 +	1	0.978953	0.061121
Jordan [6]	5.729	9.23	5280 (U. Middle)	320	1	1.745505	0.108342
Oman [7]	2.546	21.246	14,680 (High)	129	1	3.927730	0.047068
Lebanon [8]	4.055	1.04	5740 (U. Middle)	312	2	4.932182	1.923077
Morocco[9]	30.853	4.4655	4360 (U. Middle)	27	1	0.324118	0.223939
Afghanistan	26.088	64.75	⩾1000[c] (L. Middle)	N/A	N/A	N/A	N/A
Bahrain	0.739	0.0665	15,110 (High)	N/A	N/A	N/A	N/A
Djibouti	0.819	2.3	2540 (L. Middle)	N/A	N/A	N/A	N/A
Iraq	28.506	43.7072	⩾3600[c] (U. Middle)	N/A	N/A	N/A	N/A
Kuwait	2.779	1.782	23,080 (High)	N/A	N/A	N/A	N/A
Libya	6.039	175.9540	⩾12,300[c] (High)	N/A	N/A	N/A	N/A
Qatar	0.821	1.1437	⩾80,900[c] (High)	N/A	N/A	N/A	N/A
Somalia	8.445	63.7657	⩾600[c] (Low)	N/A	N/A	N/A	N/A
Sudan	37.707	250.581	2160 (L. Middle)	N/A	N/A	N/A	N/A
Syria	19.408	18.405	3930 (U. Middle)	N/A	N/A	N/A	N/A
United Arab Emirates	4.248	8.36	22,630 (High)	N/A	N/A	N/A	N/A
Yemen	21.732	52.797	920 (L. Middle)	N/A	N/A	N/A	N/A
Total/(mean)	540.283	1296.2626	11,252.85 (U. Middle)	7,617[a]	17	(1.5583)[a]	(0.2729)[a]

N/A, Not available; U. Middle, Upper Middle; L. Middle, Lower Middle.

* Programs with annual accrual of ⩾5 HSCT cases per year for at least 3 years.

[a] Total/(mean) values from the reported nine countries having active HSCT programs

[b] Most of EM countries have a health care system that is economically supported by the state and acceptance at HSCT centers, where available, is through referral system.

[c] The quoted numbers are based on GDP per capita (2007 estimates) from https://www.cia.gov/library/publications/the-world-factbook/index.html because GNI per capita values for these five countries are not available on WHO EMRO site. As GNI comprises GDP plus net receipts of primary income (compensation of employees and property income) from non-resident sources, the GNI values are expected to be more than GDP.

(1.5583) as compared to 13.4333 in Europe) [44] and HSCT team distribution in the countries where significant HSCT exists is also very low (0.2729) in comparison to European countries where it ranges from <1 to 6 teams per 10,000 sq km area [43,45].

EBMT and CIBMTR earlier reported that number of transplants differ significantly between different countries [40]. It also holds true for the EMRO region. HSCT teams in Saudi Arabia, Iran and Egypt have crossed the figure of 1000 transplants. As shown in Table 2 Most of the reported countries in the EMRO region are in the upper middle income category (according to the GNI per capita based WHO income categories) except Saudi Arabia and Oman being in the high income group and Pakistan being in the lower middle income category. The HSCT team densities in most of the EMRO region are low except one relatively small country (Lebanon) with a density of 4.932182. These numbers are very low compared with European data. Table 2 shows HSCT activity and the related economic/logistic indices in the EMRO region. It is evident that more than the GNI per capita (which is not easily changeable factor), team densities and team distribution need special attention of the health care planners. Patients must have access to a transplant team in order to receive a transplant. EBMT survey figures illustrate that probably one team per 1–2 million inhabitants and one team per 10,000 km^2 are reasonable targets [43]. These findings and EBMT data indicate that although transplant teams do their best to meet the needs, they still fail to do so. They are limited by resources and lack of infrastructure, as documented by the association between transplant activity, team density and team distribution [43,44].

Most of the EMRO region countries have health care systems, economically supported by the state as is the case in the Europe. If HSCT is performed in a private centre, e.g. one in Pakistan, procedure cost is paid by the patient in full or in part and the remaining is paid by the charity resources. Most countries lack health care insurance systems covering the cost of HSCT procedure, making HSCT a financial ordeal for the patient and family. Many patients are referred to United States or Europe for HSCT from the EMRO region especially from the countries with WHO high income category.

The countries in EMRO region lacking significant HSCT activity suffer from limited economic resources and or lack of expertise and logistic support. In addition, more curable and more prevalent health problems may be competing for the limited resources in lower income category countries. Still it will be prudent to help such countries in establishing their own HSCT centres through collaboration, training and outreach programs such as those offered by EBMT to develop medical and nursing work force.

It is clear that the need for HSCT will continue to increase in the near future. Health care providers in the EMRO region should initiate conscientious efforts to put the infrastructure in place. Parenthetically it is important to find the correct balance between a restricted numbers of HSCT teams (so that they have sufficient expertise and quality service) and an adequate number in order to guarantee access for all patients, independently of travel distances. These data clearly illustrate the need for more research to understand the mechanism of HSCT activity and into the mechanisms of technology dissemination in the EMRO region. To improve the HSCT activity related performance standards acquisition of FACT and JACIE accreditation by the centres in EMRO region will obviously be helpful.

Newly formulated EMRO regional EMBMT will be a source of increasing awareness about HSCT, exchanging experiences, promoting recent technologies, providing training for new centers, and serving as a reference for standardization of procedures. There is severe shortage of trained personnel in the field of HSCT at all levels in EMRO region. Formation and identification of a regional HSCT training center for nurses, physicians, coordinators, researchers, data base instructors, etc. will be highly instrumental in accomplishing this goal. Others areas that need improvement include wider availability of options for fertility preservation, alternate donor sources for the minority of patients who do not have matched sibling donors and the need for national and regional registries of donors to make larger pool of genetically similar donors available. Leading teams in the EMRO region are now working to establish their own national cord blood and unrelated donor programs. These should offer a great potential for suitable alternative donors in an area where childbearing potential is high and many HLA antigens are expected to cluster, will minimize the incidence of not finding a matched donor. Finally regional HSCT registry (EMBMT) will be a step forward in promoting allogeneic HSCT in the EMRO region, identifying other regional problems, and may also be helpful in benchmarking HSCT outcomes.

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