Bone Marrow Transplantation (2009) 43, 1–12

www.nature.com/bmt

SPECIAL REPORT

Special issues related to hematopoietic SCT in the Eastern Mediterranean region and the first regional activity report

MD Aljurf[1,2], SZ Zaidi[3], H El Solh[1,2], F Hussain[1,2], A Ghavamzadeh[4], HK Mahmoud[5], T Shamsi[6], T Ben Othman[7], MM Sarhan[8,9], D Dennison[10], A Ibrahim[11], S Benchekroun[12], N Chaudhri[1,2], B Labar[13], M Horowitz[14], D Niederwieser[15] and A Gratwohl[16]

[1]*Adult HSCT, King Faisal Cancer Center, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia;* [2]*Pediatric HSCT, King Faisal Cancer Center, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia;* [3]*Prince Sultan Hematology Oncology Center, King Fahad Medical City, Riyadh, Saudi Arabia;* [4]*Hematology-Oncology and SCT Research Center, University of Medical Sciences, Tehran, Iran;* [5]*BMT Unit, National Cancer Institute, Cairo University, Cairo, Egypt;* [6]*Bismillah Taqee Institute of Health Sciences and Blood Diseases Center, Karachi, Pakistan;* [7]*Centre National de Greffe de Moelle Osseuse de Tunis, Tunis, Tunisia;* [8]*Centre National de Transfusion Sanguine de Tunis, Tunis, Tunisia;* [9]*Bone Marrow and Stem Cell Transplantation Program, King Hussein Cancer Center, Amman, Jordan;* [10]*Sultan Qaboos University Hospital, Muscat, Oman;* [11]*Makassed General Hopspital, Beirut, Lebanon;* [12]*Service d'Hématologie et Oncologie Pédiatrique, Children's Hospital, Casablanca, Morocco;* [13]*Division of Hematology, University Hospital Center, Zagreb, Croatia;* [14]*Center for International Blood and Marrow Transplant Research, Miwaukee, WI, USA;* [15]*University Hospital, Leipzig, Germany and* [16]*University Hospital of Basel, Basel, Switzerland*

Although several centers are now performing allogeneic hematopoietic SCT (HSCT) in the Eastern Mediterranean (EM) region, the availability is still limited. Special issues including compatible donor availability and potential for alternative donor programs are discussed. In comparison to Europe and North America, differences in patterns of diseases and pre-HSCT general status, particularly for patients with BM failure, are described. Other differences including high sero-positivity for CMV, hepatitis B and C infection, and specific observations about GVHD and its relation to genetically homogeneous communities are also discussed. We report that a total of 17 HSCT programs (performing five or more HSCTs annually) exist in 9 countries of the EM region. Only six programs are currently reporting to European Group for Blood and Marrow Transplantation or Center for International Blood and Marrow Transplantation Research. A total of 7617 HSCTs have been performed by these programs including 5701 allogeneic HSCTs. The area has low-HSCT team density (1.56 teams per 10 million inhabitants vs 14.43 in Europe) and very low-HSCT team distribution (0.27 teams per 10 000 sq km area vs <1–6 teams in Europe). Gross national income per capita had no clear association with low-HSCT activity. Much improvement in infrastructure and formation of an EM regional HSCT registry are needed.

Correspondence: Dr MD Aljurf, King Faisal Cancer Center (MBC 64), King Faisal Specialist Hospital and Research Centre, PO Box 3354, Riyadh 11211, Kingdom of Saudi Arabia.
E-mail: maljurf@kfshrc.edu.sa
Received 15 July 2008; revised 30 September 2008; accepted 4 October 2008; published online 1 December 2008

Bone Marrow Transplantation (2009) **43,** 1–12; doi:10.1038/bmt.2008.389; published online 1 December 2008
Keywords: HSCT programs; Eastern Mediterranean; regional activity; donor availability; genetic issues; pattern of infections

Introduction

Hematopoietic SCT (HSCT) is a life-saving treatment for many diseases. However, because of the relatively high cost and the need for a multi-disciplinary team and advanced laboratory support, limited numbers of centers in the developing world are providing this modality of treatment.

High-quality data about HSCT activity are widely available through the European Group for Blood and Marrow Transplantation (EBMT) and the Center for International Blood and Marrow Transplantation Research (CIBMTR). However, both registries contain more data from centers located in Western Europe and North America.

Although the number of centers performing allogeneic HSCT in the Eastern Mediterranean (EM) region as defined by the World Health Organization (WHO)[1] (Figure 1) has increased, there are no data available currently about the transplant activities in this region or the issues related to HSCT in the listed countries.

During the last year, a collective effort has been carried out through program representatives in the EM region with the goal of simple identification of issues related to HSCT in the EM area and to conduct the first survey ever done for this region.

This is a part of an ongoing collective effort by the programs in the region to ultimately establish an EM

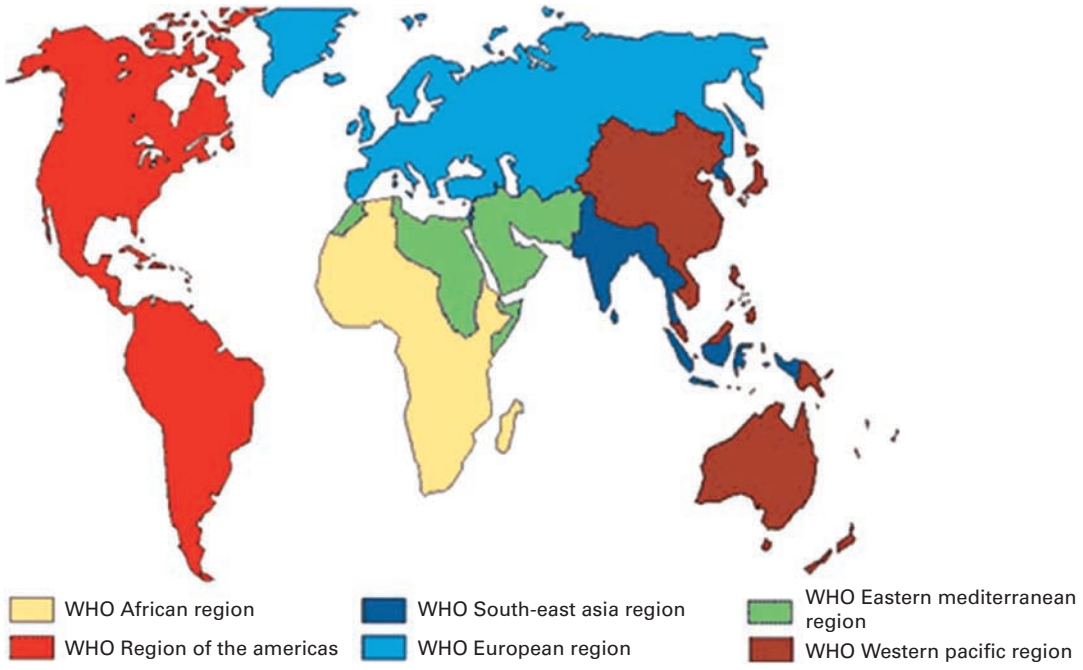

Figure 1 World Health Organization (WHO)—regions of the world. Taken from WHO website: http://www.who.int/about/regions/en/index.html.

HSCT organization with the help of the EBMT, the CIBMTR and in collaboration with the World Bone Marrow Transplantation Group.

Methods

All programs in the WHO-designated EM region with consistent annual performance of $\geqslant 5$ cases per year for at least 3 consecutive years were identified and included. Programs from each country were asked to submit a standardized report to include the following information:

1. Total population and Gross National Income (GNI) (For uniformity the population and GNI per capita for the reported countries were obtained from WHO Eastern Mediterranean Regional Office (EMRO) website (http://www.who.int/about/regions/emro/en/index.html) (last accessed on 12 September 2008) and divided according to the 'World Bank income categories', that is, high income ($11 116 or higher), upper middle income ($3596–$11 115), lower middle income ($906–$3595) and low income ($905 or less), as displayed at the website of the World Bank: (http://web.worldbank.org/WBSITE/EXTERNAL/DATASTATISTICS). Because GNI per capita values for five countries were not available on the WHO EMRO website, the quoted numbers in the table are based on gross domestic product per capita (2007 estimates) from https://www.cia.gov/library/publications/the-world-factbook/index.html. As GNI comprises GDP plus net receipts of primary income (compensation of employees and property income) from nonresident sources, the GNI values are expected to be more than GDP.
2. Geographic area of coverage for patient referral in each country. (The areas of the reported countries were obtained from the website https://www.cia.gov/library/publications/the-world-factbook/index.html.)
3. Number of transplant centers and types of transplantation performed by each center.
4. Approximate total number of transplants performed per year.
5. Predominant type of transplant performed, including sibling donor availability vs alternative donor
6. Distribution of disease entities and prevalent diseases being transplanted.
7. Special observations regarding transplantation, such as the low prevalence of GVHD in genetically homogenous communities.
8. Infectious disease issues related to transplantation in specific geographic areas.
9. Approximate actual cost of transplantation, cost to the patient and type of coverage for HSCT.
10. Obstacles in the performance of transplantation (for example, prohibitive cost, donor availability).
11. Any additional unique observational issues related to transplantation in specific geographic areas.
12. Participation in international registries.
13. Areas of active research.

As far as possible, the EBMT Group Activity Survey was used as a template for analysis of the activity data, and supplementary data were obtained from EBMT and CIBMTR as necessary.

HSCT 'team density' was calculated as the number of HSCT teams per 10 million inhabitants in each country. HSCT 'team distribution' was calculated as the number of transplant teams per 10 000 sq km area in each country.

Results

The EM region has a total of 21 countries with a total population of more than 540 million. These 21 countries include 1 country with low-income category, 5 with lower middle-income category, 8 with upper middle-income category and 7 with high-income category countries according to WHO income groups based on GNI per capita. Only 9 of the 21 countries (70.8% of the total EM region population) have at least one active HSCT programs available for their population (Table 1). The total number of programs existing at present is 17. Unfortunately only 6 of this 17 report data to EBMT and/or CIBMTR.

Table 2 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,[2–8] which will be discussed in detail below along with the economic–logistic indices related to the HSCT activity, team density and team distribution in this region. Overall, it is easy to comprehend that although the rate of transplantation has generally increased over the last 5 years, the ratio of transplantation to the total population of the individual country has remained low.

The specific issues related to allogeneic HSCT in the EM region can be divided into donor availability, genetic issues, issues related to specific diseases, pattern of infections and logistics. Each is discussed below in detail.

Donor availability

The EM region consists of communities of large families with high-population growth, which certainly increases the likelihood of finding a fully HLA-matched sibling donor. For example, the reported likelihood of finding a fully matched sibling donor in Saudi Arabia is 63.5%,[9] whereas the number can be as high as 70% in some areas in Pakistan.[2] This is far higher than the likelihood of finding a sibling donor for European and North American patients. Additionally, the overall outcome of class I antigen mismatch sibling allogeneic transplantation yields a similar result as for full-matched sibling transplantation, which is likely to reflect ethnically and genetically the homogenous make-up of the population. This leaves a smaller percentage of patients requiring an alternative donor source for their transplantation. A lower occurrence of acute and chronic GVHD (cGVHD) has also been observed.[10–13] This has also been supported by similar observations made in larger studies comparing the risk of GVHD in different ethnic populations.[14] The lower occurrence of cGVHD may have an obvious impact on diseases that are susceptible to GVL effects such as CML and diseases with a low-proliferation rate. Cord blood transplantation remains the preferred alternative donor transplantation modality in the centers that offer alternative donor HSCT. This is because of the relatively lower likelihood of finding a match through Western unrelated donor registries and the logistic difficulties in timely performance of HSCT from matched unrelated donors, typically available in Western Europe and North America.

Table 1 Eastern Mediterranean region countries[1]—populations and status of HSCT programs.

Country	*Population*[1]	*Active HSCT program available*[a]
Afghanistan	26 088 000	
Bahrain	739 000	
Djibouti	819 000	
Egypt	74 166 000	Yes
Iran	70 270 000	Yes
Iraq	28 506 000	
Jordan	5 729 000	Yes
Kuwait	2 779 000	
Lebanon	4 055 000	Yes
Libya	6 039 000	
Morocco	30 853 000	Yes
Oman	2 546 000	Yes
Pakistan	160 943 000	Yes
Qatar	821 000	
Saudi Arabia	24 175 000	Yes
Somalia	8 445 000	
Sudan	37 707 000	
Syria	19 408 000	
Tunisia	10 215 000	Yes
United Arab Emirates	4 248 000	
Yemen	21 732 000	

Abbreviation: HSCT = hematopoietic SCT.
[a]Program with consistent annual accrual of $\geqslant 5$ HSCT cases per year for at least 3 consecutive years.

Polymorphism of genes

Knowledge of the prevalence of polymorphism in certain genes, such as cytokine 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 EM 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. A local pharmacogenomic study from Saudi Arabia has shown a unique profile of variations in metabolism genes in Arab population.[15] 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.[15] Other alleles in Arabs, including CYP1A1 T3801C and GSTP1 A1578G were present in frequencies similar to Africans.[15] Several pharmacogenomic research projects are being pursued in the EM countries in relation to this matter.

Disease-specific issues

Severe aplastic anemia. A higher proportion of patients with severe aplastic anemia in the EM were heavily pretransfused when referred for allogeneic HSCT. Accordingly, a strong lymphoablative component always has to be included in the conditioning chemotherapy to avoid graft rejection. Fludarabine is being increasingly utilized as a lymphoablative component, traditionally with CY for conditioning of aplastic anemia patients. The major reason for the emerging utilization of fludarabine as the lymphoablative component is the prohibitive cost of anti-thymocyte globulin in addition to the lower likelihood of side effects with fludarabine, particularly in older patients. Large

Table 2 List of the number of patients who received HSCT in various countries (data from major centers[a]) in the EM 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 pretransfused 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)	1090	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. Suboptimal transfusion services. Endemicity of malaria, hepatitis B and C, and tuberculosis. High rate of fungal infections.
Tunisia[3] (up to June 2007)	299	Data NA	299+	Majority of transplants are done for nonmalignant 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 antifungals.
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	

Abbreviations: EM = Eastern Mediterranean; HBV = hepatitis B virus; HCV = hepatitis C virus; HSCT = hematopoietic SCT; NA = Not available.
[a]Programs with annual accrual of $\geqslant 5$ HSCT cases per year for at least 3 consecutive years.

numbers of aplastic anemia patients are referred to the transplant centers with a variety of infections including viral, bacterial and fungal infections. Recently, availability of new generation anti-fungal therapies has led to a dramatic improvement in the outcome of patients with fungal infections. Sometimes, short-term use of these combined drugs to treat proven fungal infection facilitates the timely performance of transplantation procedures. However, these new generation anti-fungal 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 that described in earlier reports.[16,17] These patients with negative hepatitis serology tend to respond to treatment with immunosuppression therapy only.

Congenital BM failure syndromes and hemoglobinopathies. Marital consanguinity is highly prevalent in the EM countries, and consequently there is a high prevalence of hemoglobinopathies including thalassemia and sickle cell anemia.[4,6,7] Patients with hemoglobinopathies and BM failure syndromes are typically heavily pretransfused before they are transferred to the transplant centers, and consequently these patients are iron overloaded and frequently have positive serology for hepatitis B and/or C virus. Collectively, all these factors are a set-up for organ dysfunction and transplantation complications, most notably hepatic veno-occlusive disease. Despite all these limitations, non-neoplastic indications for allogeneic HSCT remain one of the main reasons for HSCT in certain EM transplantation centers. This is particularly common in countries where there is significant case attrition for acute leukemias because of the suboptimal set-up conditions for chemotherapy induction in the referring centers.[2,3]

Chronic myeloid leukemia. With the availability of tyrosine kinase inhibitor therapy, allogeneic HSCT is no longer offered as a first-line treatment option for CML patients in first chronic phase, as is now also accepted

practice in other centers worldwide.[18] This is true for centers where tyrosine kinase inhibitor therapy is available. However, in countries where tyrosine kinase inhibitor therapy is not available because of its prohibitive costs, or in situations where the physician is unable to rely on 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 a lifetime procedure and one of the main indications for transplantation in some centers. This is also related to the fact that CML patients do not need an urgent transplantation and are frequently in optimal physical condition to undergo such a procedure. This is in contrast to acute leukemias, where timely transplantation is needed and where the patient is in less optimal shape to survive the procedure. In a few countries, generics of tyrosine kinase inhibitor are widely available at a very affordable cost. However, for majority of 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 cGVHD 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* cGVHD to promote the development of GVL.

AML. An important requirement for offering allogeneic HSCT for patients with acute leukemias is the capability, both financially and logistically, of achieving CR through induction chemotherapies. At some centers in the EM region this becomes one of the competing factors for the limited slots for allogeneic HSCT and eventually benign conditions, such as aplastic anemia and thalassemia (not requiring daunting cost and support for induction chemotherapy), 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 Center in Riyadh suggested the EFS of this leukemia with standard induction and high-dose cytarabine chemotherapy consolidation is 16%. The relatively more aggressive behavior of AML with t(8; 21) has been reported in South-East Asia.[19] The observed lower outcome of management of this leukemia in non-whites in North American data also suggested that the behavior of this disease is not consistently favorable, possibly related to different breakpoints or expression of other biologic and/or molecular markers that are known to be associated with poor prognosis.[20,21]

Lymphoid malignancies. It is well established that the incidence of indolent lymphoid malignancies decreases as one moves east across the globe. A relatively higher percentage of intermediate- and high-grade lymphoma is observed in the EM and, accordingly, a relatively high proportion of eligible patients with the latter two entities are being transplanted compared with Western Europe and North America.[22]

Issues related to Infections

CMV infection. High levels of sero-positivity for CMV was reported in many countries in the EM 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,[23] and 100% in donors and recipients in Pakistan.[2] These data are also consistent with reports from India.[24] 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 can be based on early detection of CMV infection and on the other hand the pre-emptive therapy need not to be continued for any extended period beyond establishment of CMV antigen negativity to prevent interference with the development of CMV-specific immune reconstitution.[23,25]

Hepatitis B virus infection. The endemicity of hepatitis B virus (HBV) in the EM region is well established.[26–28] According to a report[28] in the EM region, Bahrain, Iran and Kuwait are areas of low endemicity; Iraq and the United Arab Emirates have intermediate endemicity; and Egypt, Jordan, Oman, Palestine, Yemen and Saudi Arabia have high endemicity.[28]

Viral replication is expected to take place during chemotherapy and immunosuppression with the risk of fulminant hepatitis at the time of tapering of the immunosuppressive therapy. In a retrospective analysis performed in Saudi Arabia[29] with the aim of identifying risk factors and clinical characteristics associated with HBV reactivation and clinical flare after allogeneic HSCT 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). Six (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 post transplant. In total, 5/15 patients with cGVHD reactivated with clinical flare in contrast to 1/27 without cGVHD (relative risk: 9.0, $P<0.02$). HBV reactivation with clinical flare occurred during immunosuppressive therapy tapering or withdrawal in all patients.[29]

HBV reactivation may also be an additional risk factor in causation of veno-occlusive disease 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. It is to be noted that the availability of lamivudine and other effective therapies for HBV had remarkably improved the outcome of allogeneic HSCT with HBV-positive recipient and/or donor during the last decade.

Hepatitis C virus infection. Hepatitis C virus (HCV) remains a major disease burden in the EM region. Prevalence rates across the world have changed with increased awareness about transfusion-related hepatitis C

and more and more evidence supporting intravenous illicit drug use as the leading risk factor for the spread of virus.[30] A high-prevalence rate of HCV has been reported in Egypt in the recent past (up to 28% in some groups).[31] Lower rates have been reported among blood donors from various regions of Saudi Arabia (0.4–4.3%)[32,33] and in Yemeni patients (2.1%).[34]

HCV has six genotypes with numerous subtypes. Depending on the HCV genotype, length of the treatment can differ. Genotype 1b is less responsive to α-interferon therapy when compared with genotypes 2 and 3. Genotype 4 is the most common genotype in the EM region,[30,33,35–38] which unfortunately is least likely to respond to the standard interferon therapy, though recent studies using pegylated interferon showed better results. A recent multi-center 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.[38] However, distribution of HCV genotypes is not uniform in the EM region, for example, Iran has a major prevalence of HCV genotype 1 (55.8% cases).[39]

Traditionally, HCV is known to have less contribution to early post transplant morbidity and mortality, but obviously is likely to cause complications later in life such as liver cirrhosis. 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.

Mycobacterium tuberculosis. Although mycobacterium tuberculosis is relatively an endemic disease in certain areas of EM, the likelihood of reactivation after HSCT is less frequent than what would be expected in an endemic area. Additionally, the likelihood of reactivation after HSCT is less than the reported rate of activation after transplantation for solid organs in the same set-up.[40] As a significant proportion of the population, especially older individuals, has a positive purified protein derivative (PPD) status either from previous exposure or BCG vaccination in childhood, the appropriateness of the universal routine prophylaxis with isoniazid (isonicotinyl hydrazine (INH)) for PPD-positive HSCT recipient who has a low likelihood of re-activation will be questioned. Accordingly, many centers in the EM 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 guidelines[41] regarding infection prophylaxis in HSCT, but is substantiated by our observations in the EM region.[2]

Other Infections. High prevalence of schistosomiasis in Egypt[42] and endemicity of malaria in certain areas of Pakistan[43] are well documented. Relevantly, poor malaria screening of asymptomatic blood donors led to some incidences of transfusion-transmitted malaria in HSCT recipients during the early transplant period in Pakistan.[2] In Egypt, the relative risk of developing veno-occlusive disease after allogeneic HSCT was calculated to be 16.8-fold higher in patients with previous history of schistosomiasis.[42]

Logistic issues important to the EM region

Reports from the EBMT and CIBMTR have illustrated earlier that the number of transplants differ significantly between countries.[44] This is true for all regions, but no detailed information is available about the EM region.

By tradition, some EBMT reports include data from a few non-European countries that fall in the EM region (Iran, Saudi Arabia and Tunisia) and report their HSCT activity to EBMT registry. Their data are in part included in some of the analyses. Hence, data published by the EBMT group may also be informative for patients' counseling and decisions made by health care professionals, planners and administrators in the EM region. However, more detailed information specific to this region is desirable.[45]

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 GNI per capita, numbers of transplant teams per 10 million inhabitants or per 10 000 km, team size and team experience all had an impact on transplant activity.[46] Moreover, it was realized that some other factors might have been involved in the decisions to perform or not to perform HSCT.

The recent EBMT report based on the activity survey for 2006[47] shows that transplant rates predictably increased over time with nearly linear trends, in clear association with GNI per capita and distinctly by the World Bank income category within a narrow window of variation for both autologous HSCT and allogeneic HSCT when breast cancer (autologous) and CML (allogeneic) were excluded.[47] Team density and team distribution were also associated with transplant rates.[47] Table 3 summarizes the various factors that affect HSCT activity in European countries as reported by the EBMT group.[47,48] These included economic factors such as GNI per capita or health care expenditures per capita, team density and team distribution. There were also clear differences in transplant rates for certain disease indications, which might relate to a different prevalence of the disease, for example hemoglobinopathies.[47,48]

Table 3 Factors associated with differences in transplant rates between European countries[40,41]

Economic factors
Gross national income per capita
Health care expenditures per capita
Health care system
Logistic factors
Team density
Team distribution
Local factors
Disease prevalence
Infrastructure
Ongoing studies
Unknowns

Our preliminary findings reported here are based on cumulative experience of 17 teams in 9 countries of the EM region over the last two decades. Of the 17 teams, 16 (94%) performed both allogeneic and autologous HSCT and 1 (6%) restricted its activity to autologous HSCT only.

Team density in the EM region is very low (1.56 compared with 13.43 in Europe)[48] and HSCT team distribution in the countries where significant HSCT exists is also very low (0.27) in comparison to European countries where it ranges from <1 to 6 teams per 10 000 sq km area.[47,49]

Figure 2 shows that the total HSCT performed to date in the reported countries of the EM region is quite variable. HSCT teams in Saudi Arabia, Iran and Egypt have exceeded 1000 transplants. Figure 3 displays GNI per capita-based WHO income categories in the EM region. Most of the reported countries are in the upper middle-income category, except Saudi Arabia and Oman, which are in the high-income group and Pakistan in the lower middle-income category. Figure 4 reflects low-HSCT team densities in most of the EM region, except one relatively small country (Lebanon) with a density of 4.93. These numbers are very low compared with European data. Table 4 shows HSCT activity and the related economic–logistic indices in the EM 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 from health care planners. Patients must have access to a transplant team to receive a transplant. EBMT survey figures illustrate that probably one team per 1–2

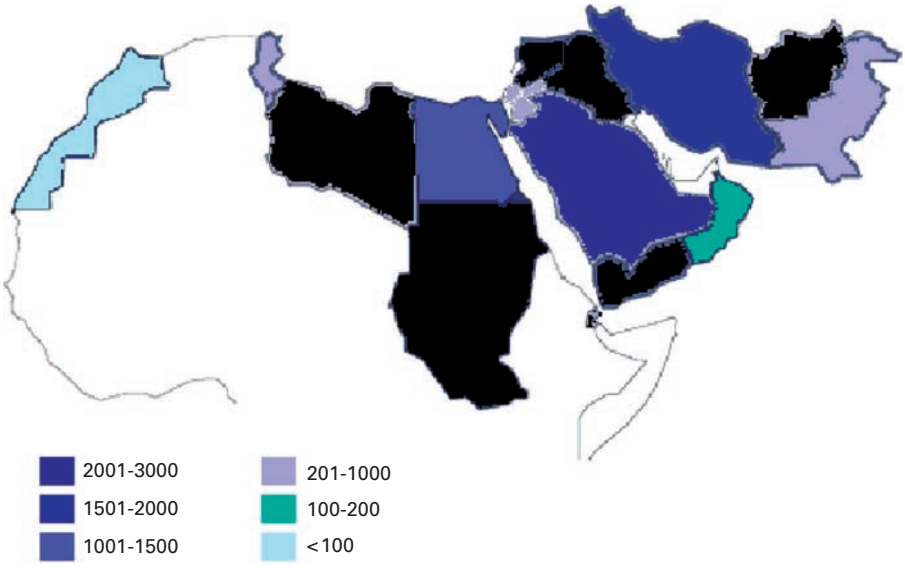

Figure 2 Total HSCT performed in nine countries of the EM region with significant HSCT programs. EM = Eastern Mediterranean; HSCT = hematopoietic SCT.

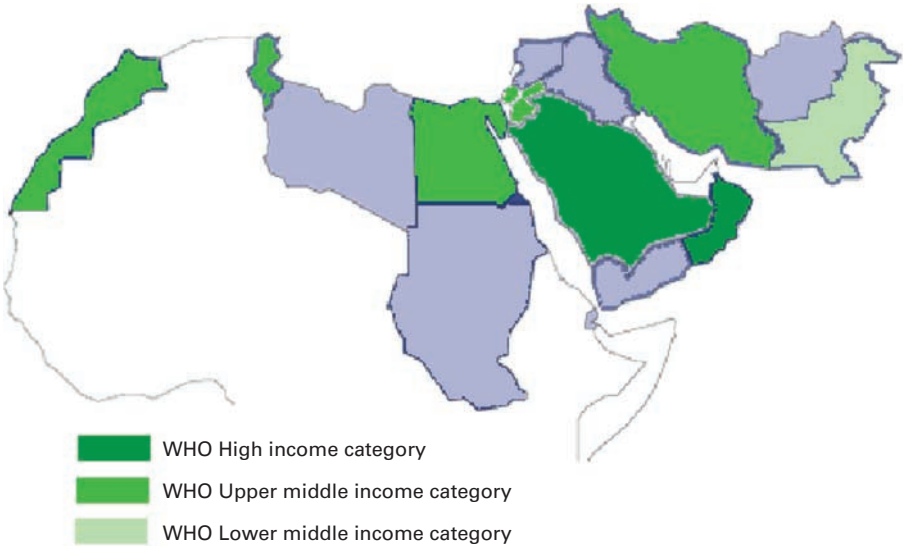

Figure 3 GNI per capita-based WHO income categories of the nine countries of the EM region with significant HSCT programs. WHO = World Health Organization; EM = Eastern Mediterranean; HSCT = hematopoietic SCT; GNI = Gross National Income.

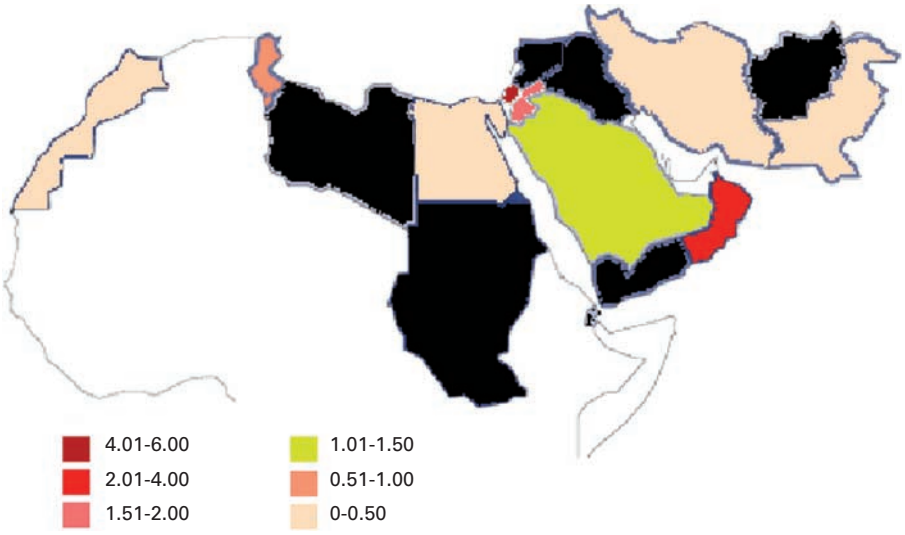

Figure 4 HSCT team densities in nine countries of the EM region with significant HSCT programs. EM = Eastern Mediterranean; HSCT = hematopoietic SCT.

million inhabitants and one team per 10 000 km^2 are reasonable targets.[47] Currently, a good but uncertain number of patients from the EM region, especially from countries with WHO high-income category, are referred to the United States or Western Europe for HSCT. However the authors have no estimates of such referrals. Such cases are mostly sponsored by the state, charity support or family resources.

For comparison, the EBMT data based on a 15-year observation period within the EBMT activity survey show that transplant rates in Europe are highly predictable, show a clear association with GNI per capita and are distinct in their evolution by the World Bank income category.[47] These data indicate that although transplant teams do their best to meet the needs, they still fail to do so. They are limited by resources, as illustrated by the clear association of transplant rates with GNI per capita and the World Bank income category.[47] EBMT data and our initial findings indicate that HSCT activity is also limited by the infrastructure, as documented by the association between transplant activity, team density and team distribution.[48]

The countries in the EM 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. A significant number of patients are referred from the EM region, especially from countries with WHO high-income category, to the United States or Western Europe for HSCT. However, as noted above, the authors have no estimates of such referrals. Obviously, the programs offering HSCT facilities in the region are unable to meet the needs of the patients from their respective countries. Hence the desirable referral between countries of the EM region is not yet fully developed, although such a referral system may help those EM countries, who particularly have no internal access to HSCT. Practically, it will be more prudent to help such countries in establishing their own HSCT centers through collaboration, training and outreach programs, such as those offered by EBMT to develop the medical and nursing workforce.

This report is based on initial data from the EM region, which is obviously limited. Recent EBMT analysis on predictability of HSCT rates[47] also had some limitations. Firstly, there is no uniform database on the incidence or prevalence of the individual disease categories in the participating countries. Secondly, data were limited to Europe and it is difficult to extrapolate the conclusions to other continents. Nevertheless, it is likely that similar factors, such as GNI per capita and team density also affect transplant rates in the EM region. It is also likely that considerations on cost-effectiveness will affect decisions between HSCT and lifelong expensive therapies in countries of the EM region (CML being a typical example).[50,51]

Most of the EM region countries have health care systems, supported economically by the state, as is the case in the Europe. If HSCT is performed in a private center, the procedure cost is paid by the patient in full, or in part with the remainder being paid by 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.

It is clear that the need for HSCT will continue to increase in the near future. Improvement in supportive care and antimicrobial therapy, increasing donor pools worldwide, increasing availability of cord blood products and novel conditioning regimens should provide access to HSCT for patients not considered earlier as candidates for these procedure.[1] Health care providers in the EM region will face this complex problem and they should initiate rigorous actions to put the infrastructure in place.

It is important to find the correct balance between a restricted number of HSCT teams (that they have sufficient expertise and quality of service) and an adequate number in order to guarantee access for all patients, independently of travel distances. Above all, there is no indication of an abundance of transplant beds. There is a need to provide infrastructure for more HSCT centers. The anxiety of

Table 4 HSCT activity and the related economic/logistic indices in the EM region

Countries	*Population in millions*[1]	*Area × 10 000 sq km*	*GNI per capita US$ (WHO income category)*[a]	*Total HSCT performed in major centers*	*Teams performing HSCT*[b]	*HSCT team density*	*HSCT team distribution*
Saudi Arabia	24.175	214.969	14 740 (High)	2789	3	1.24	0.01
Iran[5]	70.270	164.8	8050 (U. Middle)	1979	2	0.28	0.01
Egypt[4]	74.166	100.145	4440 (U. Middle)	1362+	3	0.40	0.03
Pakistan[2]	160.943	80.394	2350 (L. Middle)	400	3	0.19	0.04
Tunisia[3]	10.215	16.361	7900 (U. Middle)	299+	1	0.98	0.06
Jordan[6]	5.729	9.23	5280 (U. Middle)	320	1	1.75	0.11
Oman[7]	2.546	21.246	14 680 (High)	129	1	3.93	0.05
Lebanon[8]	4.055	1.04	5740 (U. Middle)	312	2	4.94	1.92
Morocco[9]	30.853	4.4655	4360 (U. Middle)	27	1	0.32	0.22
Afghanistan	26.088	64.75	$\geqslant$1000[c] (L. Middle)	NA	NA	NA	NA
Bahrain	0.739	0.0665	15 110 (High)	NA	NA	NA	NA
Djibouti	0.819	2.3	2540 (L. Middle)	NA	NA	NA	NA
Iraq	28.506	43.7072	$\geqslant$3600[c] (U. Middle)	NA	NA	NA	NA
Kuwait	2.779	1.782	23 080 (High)	NA	NA	NA	NA
Libya	6.039	175.9540	$\geqslant$12 300[c] (High)	NA	NA	NA	NA
Qatar	0.821	1.1437	$\geqslant$80 900[c] (High)	NA	NA	NA	NA
Somalia	8.445	63.7657	$\geqslant$600[c] (Low)	NA	NA	NA	NA
Sudan	37.707	250.581	2160 (L. Middle)	NA	NA	NA	NA
Syria	19.408	18.405	3930 (U. Middle)	NA	NA	NA	NA
United Arab Emirates	4.248	8.36	22 630 (High)	NA	NA	NA	NA
Yemen	21.732	52.797	920 (L. Middle)	NA	NA	NA	NA
Total/(Mean)	540.283	1296.2626	11252.85 (U. Middle)	7617[d]	17[d]	(1.56)[d]	(0.27)[d]

Abbreviations: EM = Eastern Mediterranean; GDP = gross domestic product; GNI = gross national income; HSCT = hematopoietic SCT; L. Middle = lower middle; NA = not available; U. Middle = upper middle.

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

[b]Programs with annual accrual of $\geqslant$5 HSCT cases per year for at least 3 consecutive years.

[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 nonresident sources, the GNI values are expected to be more than GDP.

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

health care agencies fearing over-abundance of HSCT centers (owing to the example of CML) now seems unnecessary and they can be reassured that trends, with the advent of novel therapies which affect the demand for HSCT, are recognized in a timely fashion. With up-to-date instruments, such as the EBMT activity survey, changes in therapy can easily be recognized at an early stage and appropriate measures can be taken to curtail the feared unnecessary growth of HSCT centers.

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 EM region. If possible, such studies should be performed on a wider collaborative basis. This appears essential to enable health care agencies to provide adequate infrastructure for this high-cost procedure, especially in the EM region and other developing countries.

To improve HSCT activity-related performance standards, acquisition of Foundation for the Accreditation of Cellular Therapy (FACT) and Joint Accreditation Committee of the ISCT-EBMT (JACIE) accreditation by the centers in the EM region will obviously be helpful. However, potential logistic hurdles in accreditation related to transplant volumes, access to collection and processing facilities, and geographical factors might present challenges. Moreover, such requirements for accreditation may result in rationalization of health resources into centers capable of achieving accreditation where resources are limited. On the other hand, mandatory application of accreditation requirements, at least in the beginning, may challenge the efforts to establish new centers with already limited enthusiasm and resources.

Severe shortage of trained personnel in the field of HSCT at all levels mandates the need for an EM HSCT League to promote recent technologies and improve experience related to HSCT in the region. Formation and identification of a regional HSCT training center for nurses, physicians, coordinators, researchers, data base instructors and so on will be highly instrumental in accomplishing this goal. This will be a source of exchanging experiences, providing training for new centers and also serves as a reference for standardization of procedures. Other strategies may include initiating an EM 'Nursing Board' to manage the problems related to paramedical manpower, updating HSCT procedures and increasing awareness about HSCT among the staff and the patients.

Other issues

Options for fertility preservation in the EM region are limited and are not optimally discussed with the patient and family due to other priorities competing for the resources and cultural issues related to scarcity of credible sperm banking facilities. Such facilities need to be built and strictly regulated, as concept of surrogate sperm donor is socially not acceptable in most of the EM region.

Others areas that need improvement, as mentioned earlier in the paper, include wider availability of alternative donor sources for the minority of patients who do not have matched sibling donors, and the necessity of national and regional registries of donors to make a larger pool of genetically similar donors available. Initiation of Regional Cord Blood Banks, which 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.

Leading teams in the EM region are now working to establish their own national cord blood and unrelated donor programs.

Finally, a regional HSCT registry will be a step forward in promoting allogeneic HSCT in the EM region, identifying other regional problems and may also be helpful in benchmarking HSCT outcomes. A study from the United Kingdom and Ireland recently compared their data with the EBMT and showed the potential for using national registries to benchmark transplant outcome using EBMT registry as reference.[52]

Acknowledgements

We thank and acknowledge all participating physicians and centers in the Eastern Mediterranean region, who forwarded their data to the corresponding author from their country.

References

1 Countries in the WHO Eastern Mediterranean Region shown on http://www.who.int/about/regions/emro/en/index.html (last accessed on 12th September 2008).
2 Shamsi T, Hashmi K, Irfan M, Ahmed P, Farzana T, Satti T *et al*. The stem cell transplant program in pakistan—the first decade. *Bone Marrow Transplant* 2008; **42**: S114–S117.
3 Othman TB, Torjemane L, Abdelkefi A, Lakhal A, Ladeb S, Hamed LB *et al*. Allogeneic stem cell transplantation in Tunisia. *Bone Marrow Transplant* 2008; **42**: S139–S141.
4 Mahmoud HK, El-Haddad AM, Fahmy OA, El-Emary M, Nassar A, Abdel-Mooti M *et al*. Hematopoietic stem cell transplantation in Egypt. *Bone Marrow Transplant* 2008; **42**: S76–S80.
5 Abdel-Rahman F, Hussein AA, Rihani R, Hlalah OA, El Taani H, Sharma S *et al*. Bone marrow and stem cell transplantation at King Hussein Cancer Center (KHCC) Amman—Jordan. *Bone Marrow Transplant* 2008; **42**: S89–S91.
6 Dennison D, Al Kindi S, Pathare A, Daar S, Nusrat N, Rehman J *et al*. Hematopoietic stem cell transplantation in Oman. *Bone Marrow Transplant* 2008; **42**: S109–S113.
7 Bazarbachi A, Hatoum HA, Mugharbel A, Otrock ZK, Yassine N, Muwakkit S *et al*. Hematopoietic stem cell transplantation in Lebanon: first comprehensive report. *Bone Marrow Transplant* 2008; **42**: S96–S102.
8 Benchekroun S, Harif M, Madani A, Quessar A, Zafad S, Rachid R. Present and future of hematology and stem cell transplantation in Morocco. *Bone Marrow Transplant* 2008; **42**: S106–S108.
9 Sheth KV, Elkhalifa M, Kelly T, Sahovic E. What are the chances of finding related HLA match donors for allogeneic BMT recipients in Saudi Arabia? *Blood* 1996; **88**(Suppl 1): 265b (Abstract 3787).
10 Gyger M, Sahovic E, Al Mohareb F, Chaudhri N, Al Zahrani H, Al Sharif F *et al*. A prospective randomized trial of marrow versus mobilized peripheral blood in HLA-matched related allogeneic transplants using a three-day short course methotrexate and cyclosporin as prophylaxis for acute graft versus host disease. *Bone Marrow Transplant* 2002; **29**(Suppl 2): 677 (abstract 84).

11 Al Beihany A, Sahovic E, Chaudhri N, Almohareb F, Alsharif F, Alzahrani H *et al*. Leukemia relapse after allogeneic bone marrow transplantation—how does chronic GVHD influence the pattern and onset of relapse? *Bone Marrow Transplant* 2005; **35** (Suppl. 2): S135 (Abstract 536).
12 Stem Cell Trialists' Collaborative Group. Individual patient data met-analysis of allogeneic peripheral blood stem cell transplant vs bone marrow transplant in the management of hematological malignancies: indirect assessment of the effect of day 11 methotrexate administration. *Bone Marrow Transplant* 2006; **38**: 539–546.
13 Stem Cell Trialists' Collaborative Group. Allogeneic peripheral blood stem-cell compared with bone marrow transplantation in the management of hematologic malignancies: an individual patient care data meta-analysis of nine randomized trials. *J Clin Oncol* 2005; **23**: 5074–5087.
14 Oh H, Loberiza Jr FR, Zhang MJ, Ringdén O, Akiyama H, Asai T *et al*. Comparison of graft-versus-host disease and survival after HLA-identical sibling bone marrow transplantation in ethnic population. *Blood* 2005; **105**: 1408–1416.
15 Bu R, Gutierrez MI, Al-Rasheed M, Belgaumi A, Bhatia K. Variable drug metabolism genes in Arab population. *Pharmacogenomics J* 2004; **4**: 260–266.
16 Brown KE, Tisdale J, Barrett AJ, Dunbar CE, Young NS. Hepatitis-associated aplastic anemia. *N Engl J Med* 1997; **336**: 1059–1064.
17 Hibbs JR, Frickhofen N, Rosenfeld SJ, Feinstone SM, Kojima S, Bacigalupo A *et al*. Aplastic anemia and viral hepatitis non-A, non-B, non-C? *JAMA* 1992; **267**: 2051––2054.
18 Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM *et al*. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med* 2001; **344**: 1031–1037.
19 Lee KW, Choi IS, Roh EY, Kim DY, Yun T, Lee DS *et al*. Adult patients with t(8;21) acute myeloid leukemia had no superior treatment outcome to those without t(8;21): a single institution's experience. *Ann Hematol* 2004; **83**: 218–224.
20 Marcucci G, Maharry K, Radmacher MD, Mrózek K, Vukosavljevic T, Paschka P *et al*. Prognostic factors and outcome of core binding factor acute myeloid leukemia patients with t(8;21) differ from those of patients with inv(16): a Cancer and Leukemia Group B study. *J Clin Oncol* 2005; **23**: 5705–5717.
21 Nucifora G, Rowley JD. AMLl and the 8;21 and 3;21 Translocations in Acute and Chronic Myeloid Leukemia. *Blood* 1995; **86**: 1–14.
22 Muller AMS, Ihorst G, Mertelsmann R, Engelhardt M. Epidemiology of non-Hodgkin's lymphoma (NHL): trends, geographic distribution, and etiology. *Ann Hematol* 2005; **84**: 1–12.
23 Sahovic E, Al-Suliman A, Aslam M, Seth P, Akhtar J, Aljurf M *et al*. Successful prevention of CMV disease after allogeneic BMT in 100 consecutive CMV seropositive recipients. *Blood* 1999; **94**: 372b (Abstract 4888).
24 Chandy M, Srivastava A, Dennison D, Mathews V, George B. Allogeneic bone marrow transplantation in the developing world: experience from a center in India. *Bone Marrow Transplant* 2001; **27**: 785–790.
25 Boeckh M, Bowden RA, Gooley T, Myerson D, Corey L. Successful modification of a pp65 antigenemia-based early treatment strategy for prevention of cytomegalovirus disease in allogeneic marrow transplant recipients. *Blood* 1999; **93**: 1781.
26 Al-Faleh FZ. Hepatitis B infection in Saudi Arabia. *Ann Saudi Med* 1988; **8**: 474–480.
27 Arya SC, Ashraf SJ, Parande CM, el-Sayed M, Sahay R, Ageel AR *et al*. Hepatitis B virus in Gizan. Saudi Arabia. *J Med Virol* 1985; **17**: 267–274.
28 Andre F. Hepatitis B epidemiology in Asia, the Middle East and Africa. *Vaccine* 2000; **18** (Suppl 1): S20–S22.
29 Seth P, Alrajhi AA, Kagevi I, Chaudhary MA, Colcol E, Sahovic EA *et al*. Hepatitis B virus reactivation with clinical flare in allogeneic stem cell transplants with chronic graft-versus-host disease. *Bone Marrow Transplant* 2002; **30**: 189–194.
30 Theodore SY, Jamal MM. Epidemiology of hepatitis C virus (HCV) infection. *Int J Med Sci* 2006; **3**: 41–46.
31 Saeed AA, Al-Admawi AM, Al-Rasheed A, Fairclough D, Bacchus R, Ring C *et al*. Hepatitis C virus in Egyptian blood donors in Riyadh. *Lancet* 1991; **33**: 359–360.
32 El-Hazmi MM. Prevalence of HBV, HCV, HIV-1, 2 and HTLV-I/II infections among blood donors in a teaching hospital in the Central region of Saudi Arabia. *Saudi Med J* 2004; **25**: 26–33.
33 Mahaba H, el-Tayeb Ael-K, Elbaz H. The prevalence of antibodies to hepatitis C virus in Hail region, Saudi Arabia. *J Egypt Public Health Assoc* 1999; **74**: 69–80.
34 El Guneid AM, Gunaid AA, O'Neill AM, Zureikat NI, Coleman JC, Murray-Lyon IM. Prevalence of hepatitis B, C and D virus markers in Yemeni patients with chronic liver disease. *J Med Virol* 1993; **40**: 330–333.
35 Al-Ahdal MN, Rezeig MA, Kessie G. Genotyping of hepatitis C virus isolates from Saudi patients by analysis of sequences from pcr-amplified core region of the virus genome. *Ann Saudi Med* 1997; **17**: 601–604.
36 Osoba AO. Hepatitis C virus genotypes in Saudi Arabia. *Saudi Med J* 2002; **23**: 7–12.
37 Bdour S. Hepatitis C virus infection in Jordanian haemodialyis units, serological diagnosis and genotyping. *J Med Microbiol* 2002; **51**: 700–704.
38 Shobokshi OA, Serebour FE, Skakni L, Al Safy YH, Ahdal MN. Hepatitis C genotypes and subtypes in Saudi Arabia. *J Med Virol* 1999; **58**: 44–48.
39 Kabir A, Alavian S, Keyvani H. Distribution of hepatitis C virus genotypes in patients infected by different sources and its correlation with clinical and virological parameters: a preliminary study. *Comp Hepatol* 2006; **5**: 4; doi:10.1186/1476-5926-5-4.
40 Aljurf M, Gyger M, Alrajhi A, Sahovic E, Chaudhri N, Musa M *et al*. Mycobacterium tuberculosis infection in allogeneic bone marrow transplantation patients. *Bone Marrow Transplant* 1999; **24**: 551–554.
41 Centers for Disease Control and Prevention; Infectious Diseases Society of America; American Society of Blood and Marrow Transplantation. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients; recommendations of the CDC, the Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation. *Biol Blood Marrow Transplant* 2000; **6**: 659–734.
42 Mahmoud HK. Schistosomiasis as a predisposing factor to veno-occlusive disease of the liver following allogeneic bone marrow transplantation. *Bone Marrow Transplant* 1996; **17**: 401–403.
43 Roll Back Malaria Monitoring and Evaluation in Pakistan–WHO report http://www.rbm.who.int/wmr2005/profiles/paquistan.pdf.
44 Gratwohl A, Baldomero H, Horisberger B, Schmid C, Passweg J, Urbano-Ispizua A. Accreditation Committee of the European Group for Blood and Marrow Transplantation (EBMT). Current trends in haematopoietic stem cell transplantation in Europe. *Blood* 2002; **100**: 2374–2386.
45 Gratwohl A, Baldomero H, Frauendorfer K, Urbano-Ispizua A, Joint Accreditation Committee, International Society for Cellular Therapy; European Group for Blood and Marrow Transplantation. EBMT activity survey 2004 and changes in

disease indication over the past 15 years. *Bone Marrow Transplant* 2006; **37**: 1069–1085.
46 Gratwohl A, Baldomero H, Frauendorfer K, Niederwieser D. Why are there regional differences in stem cell transplantation activity? An EBMT analysis. *Bone Marrow Transplant* 2008; **42**: S7–S10.
47 Gratwohl A, Baldomero H, Schwendener A, Gratwohl M, Apperley J, Niederwieser D *et al*. Predictability of hematopoietic stem cell transplantation rates. *Haematologica* 2007; **92**: 1679–1686.
48 Gratwohl A, Baldomero H, Passweg J, Frassoni F, Niederwieser D, Schmitz N *et al*., for the Accreditation Committee of the European Group for Blood and Marrow Transplantation (EBMT) in cooperation with the Working Parties Acute (ALWP) and Chronic Leukemias (CLWP) and the Lymphoma Working Party Hematopoietic stem cell transplantation for hematological malignancies in Europe. Hematopoietic stem cell transplantation for hematological malignancies in Europe. *Leukemia* 2003; **17**: 941–959.
49 Gratwohl A, Passweg J, Baldomero H, Horisberger B, Urbano-Ispizua A, for the Accreditation Committee of the European Group for Blood and Marrow Transplantation (EBMT). Economics, health care systems and utilization of hematopoietic stem cell transplants in Europe. *Br J Haemtol* 2002; **117**: 451–468.
50 Gratwohl A, Baldomero H, Schwendener A, Gratwohl M, Urbano-Ispizua A, Frauendorfer K. Haematopoietic stem cell transplants for chronic myeloid leukemia in Europe. Impact of cost considerations. *Leukemia* 2007; **21**: 383–386.
51 Gajewski JL. Do affluent societies have the only options for the best therapy. *Leukemia* 2007; **3**: 387–388.
52 Russell NH, Szydlo R, McCann S, Potter MN, Craddock C, Towlson K *et al*. British Society for Blood and Marrow Transplantation. The use of a national transplant registry to benchmark transplant outcome for patients undergoing autologous and allogeneic stem cell transplantation in the United Kingdom and Ireland. *Br J Haematol* 2004; **124**: 499–503.