special research report

Hematopoietic stem cell transplantation in the Eastern Mediterranean Region (EMRO) 2011–2012: A comprehensive report on behalf of the Eastern Mediterranean Blood and Marrow Transplantation group (EMBMT)

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OBJECTIVE/BACKGROUND: The Eastern Mediterranean Blood and Marrow Transplantation (EMBMT) group has accumulated over 31 years of data and experience in hematopoietic stem cell transplantation (HSCT), particularly in hemoglobinopathies, severe aplastic anemia, inherited metabolic and immune disorders, in addition to a wide array of hematologic malignancies unique to this region. A regional update in current HSCT trends is highly warranted. We studied the trends of HSCT activities in World Health Organization-Eastern Mediterranean (EMRO) region, surveyed by the EMBMT, between 2011 and 2012.

METHODS: Retrospective analysis of the survey data mainly of cumulative number of transplants, types of transplants (autologous vs. allogeneic), types of conditioning such as myeloablative versus reduced intensity was conducted. Also, trends in leukemias, hemoglobinopathies, severe aplastic anemia, inherited bone marrow failure syndromes, amongst others were analyzed.

RESULTS: Twenty-one teams from nine EMRO countries reported their data (100% return rate) to the EMBMT for the years 2011–2012, with a total of 3,546 first HSCT (1,670 in 2011; 1,876 in 2012). Allogeneic HSCT (allo-HSCT) represented the majority (62%) in both years. The main indications for allo-HSCT were acute leukemias (988; 46%), bone marrow failure syndromes (421, 20%), hemoglobinopathies (242; 11%), and immune deficiencies (157; 7%). There was a progressive increase in the proportions of chronic myeloid leukemia cases transplanted beyond first chronic phase (37 [7%] of all chronic myeloid leukemia cases in 2011 vs. 39 [29%] in 2012). The main indications for autologous transplants were multiple myeloma/plasma cell disorders (510; 39%), Hodgkin lymphoma (311; 24%), non-Hodgkin lymphoma (259; 20%), and solid tumors (163; 12%).

Reduced intensity conditioning continued to show a progressive decrease over years (9.5% in 2011 vs. 7.9% in 2012), yet remained relatively low compared with contemporary practices in Europe published by EBMT. The vast majority (91%) of allo-HSCT source was from sibling donors with continued dominance of peripheral blood (64%) followed by bone marrow (33%).While umbilical cord blood transplants increased to 4% of allo-HSCT, matched unrelated donor remained underutilized and there was no haplo-identical transplant reported. Large centers with >50 HSCT/year, showed a continued increase in the total number of allo-HSCT over the past 2 years that may be related to capacity building issues and require further studies.

CONCLUSION: There is a discernable increase of HSCT rate in the EMRO region with a significant expansion in utilization of cord blood transplants and allogeneic peripheral blood-HSCT as a valuable source. However, further research of outcome data and the development of regional donor banks (cord blood and matched unrelated donors) may help to facilitate future planning to satisfy the escalating regional needs and augment collaboration within the EMBMT and globally.

KEYWORDS: Conditioning; EMRO; Hematopoietic stem cell transplantation; Stem cell source

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a well-established therapeutic procedure for many hematologic and nonhematologic disorders. The exponential increase in the number of transplants performed yearly reflects the expanding indications, as well as the growth of the population and the awareness of HSCT among physicians.

The Eastern Mediterranean Bone Marrow Transplant registry (EMBMT) is a nongovernmental, nonprofit organization that was conceived in 2007 to facilitate communication, exchange of knowledge, and experience across the registered countries and centers in the Eastern Mediterranean Region (EMRO), as defined by the World Health Organization.[1,2]

EMBMT has a mission to promote research and collaborative studies across the organization and to promote the best practices in all aspects of bone marrow (BM) transplant, including donor selection, stem cell source and collection, conditioning, supportive care, post-transplant follow-up, staff education, implementation of quality assurance programs, and standardization of the level of care.

The activity of EMBMT centers increases from year to year as more patients are referred for HSCT due to several factors including: broadening of the indications for transplantation, increasing diagnostic and therapeutic facilities, and increasing the availability of matched donors with the establishment of alternate donor programs. Improving the supportive care also allowed raising of the upper age limit for transplant.

The annual activity survey, describing the status of HSCT in EMBMT, is an important tool to observe trends and to monitor advances in HSCT practice in the EMRO region.

Organized reporting helps the registry, as well as different participating teams, to observe changes in the trends of HSCT and to evaluate factors associated with such changes. This report is based on the 2011–2012 survey data.

MATERIALS AND METHODS

Data collection

Each participating team was requested to fill in a form for uniform reporting of data from 2011 and 2012. Reported data include indication, conditioning regimen, stem cell source, and donor type. Details of reporting are already published in a previous EMBMT report.[3]

Each team is responsible for applying quality control measures to assure validity of the entered data. Data are mailed to the EMBMT office for final analysis. Collective and center-based data were further discussed with the relevant teams at the EMBMT business meeting in 2013, and then a draft of the final report was sent to each center before final publication.

The main reported data included cumulative number of transplants, transplant indications, donor type, stem cell source, and intensity of conditioning such as myeloablative versus reduced intensity conditioning (RIC) versus others.

Participating centers

A total of 21 centers from nine countries participated in the 2011 and 2012 report. Only data from centers performing more than five transplants per year for the previous 3 years were included in this report. Participating teams and countries are listed in Table 1.

Table 1. Transplant activities at different countries and centers in alphabetical order.

Country	2011				2012			
	Allo-SCT	Auto-SCT	UCBT	Total	Allo-SCT	Auto-SCT	UCBT	Total
Algeria	111	82	0	193	120	52	1	173
Egypt	144	72	2	218	165	137	0	302
Iran	298	139	6	443	320	175	4	499
Jordan	53	42	2	97	56	54	3	113
Lebanon	45	65	0	110	40	91	0	131
Oman	21	7	0	28	19	5	0	24
Pakistan	61	8	0	69	63	6	0	69
Saudi Arabia	240	130	34	404	272	151	41	464
Tunisia	54	54	0	108	48	53	0	101
	1027	599	44	1670	1103	724	49	1876

Note. Allo-SCT = allogeneic stem cell transplantation; Auto-SCT = autologous stem cell transplantation; UCBT = umbilical cord blood transplantation.

Definitions

Patient and transplant numbers

Wherever appropriate, "patient numbers" refer to the number of patients receiving a first transplant and "transplant numbers" refer to the total number of transplants performed including first and subsequent transplant.

Transplantation rates

Transplantation rates were defined as number of HSCTs per 10 million inhabitants. They were computed as previously defined for each year, disease indication, donor type, stem cell source, conditioning, and country. Population data have been obtained from the World Bank data base.[4]

Stem cell sources

Data were reported according to stem cell source into BM, peripheral blood (PB), or umbilical cord blood. Transplants with more than one source of stem cell like BM stem cell transplant followed by a PB derived stem cell boost were reported according to the source of stem cells first infused.

Conditioning intensity

Conditioning regimens were reported as conventional myeloablative or RIC as defined by EBMT.[5] Conditioning regimens reported as unknown or others include unclear or incompletely reported conditioning regimen.

RESULTS

General overview of 2011–2012 transplant activity in EMBMT encompass twenty-one teams in nine EMRO countries. All centers (100% return) responded. The contacted teams are listed in Table 1 in alphabetical order according to country and city, as well as transplant numbers for each center. Figure 1 shows the number of transplants for each country in 2011–2012.

Overall, in 2011–2012 there were 3,546 transplantations reported by the participating teams, of which 2,130 (62.1%) were allogeneic and 1,311 (37.9%) were autologous stem cell transplantations (auto-SCTs). As compared with 2011, the total number of transplants increased by 12.3% in 2012 (7% in allogeneic stem cell transplantation [allo-SCT] and 21% in auto-SCT).

Transplants are grouped into eight main disease categories, namely, leukemias (1,203 patients; 34.8%), lymphoproliferative disorders (1,156 patients; 33.4%), solid tumors (165 patients; 4.2%), BM failure (421 patients; 12.2%), hemoglobinopathies (242 patients; 7%), primary immune deficiency (162 patients; 4.7%), inherited metabolic disorders (41 patients; 1.2%), and others (6 patients; 0.1%).

The transplant number increased in 2012 for most indications and type of transplants. Between 2011 and 2012, the number of allo-SCTs increased from 1,027 to 1,103 transplants respectively, while the number of

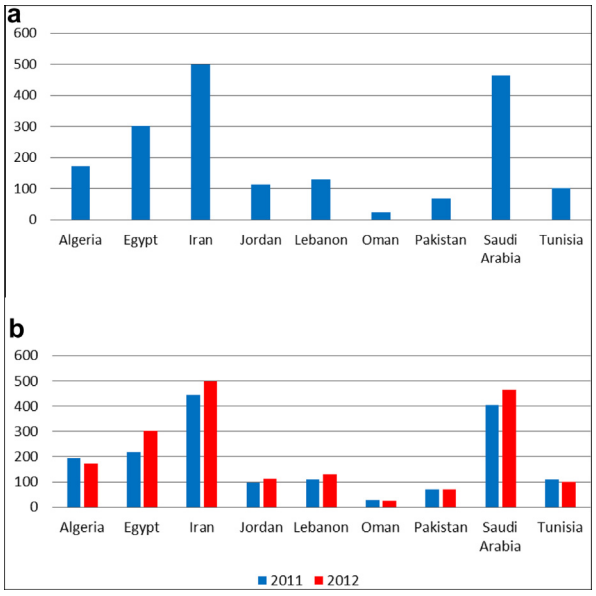

Figure 1. (A) Distribution of transplant numbers by country; (B) transplant number for each country in the Eastern Mediterranean Region in 2011–2012. *Note.* EMRO = Eastern Mediterranean Regional Office.

auto-SCT also increased from 599 to 724 transplants, respectively.

Figures 2 and 3 show the numbers of patients receiving auto-SCT and allo-SCT, respectively, by disease indication for the years 2011–2012.

Transplant rates

Transplant rates differed substantially between participating EMRO countries. The differences were related to all types of SCT.

The transplant rates were also variable among different teams; with some teams performing only autologous transplants and others doing only related donor transplants.

The median number of transplants during 2011–2012 was 47 transplants per center per year (range, 4–373).

Transplant rates per 10 million population remain very low when compared with the rates in EBMT data.[6,7]

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.

Figure 4 show the transplant rate per 10 million inhabitants for each country in the EMRO.

Patients with leukemias were mainly treated with allo-SCT (96.1%). Patients with lymphoproliferative disorders were treated predominantly with auto-SCT (93.4%). Patients with solid tumors were almost exclusively treated with autologous HSCT (99–100%). By contrast, patients with BM failure, hemoglobinopathies, immunodeficiency disorders, or inborn errors of metabolism, almost exclusively underwent allo-SCT (100%).

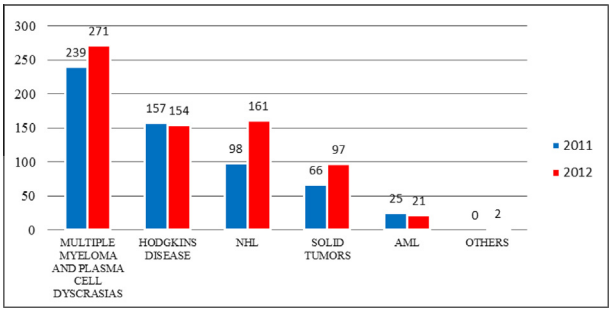

Figure 2. Distribution of different indications for autologous stem cell transplantation in 2011–2012. *Note.* AML = acute myeloid leukemia; Auto-SCT = autologous stem cell transplantation; NHL = non-Hodgkin lymphoma.

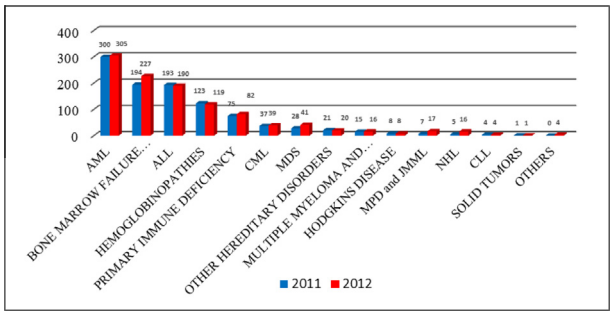

Figure 3. Distribution of different indications for allogeneic stem cell transplantation in 2011–2012. *Note.* ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; JMML = juvenile myelomonocytic leukemia; MPD = myeloproliferative disease; NHL = non-Hodgkin lymphoma.

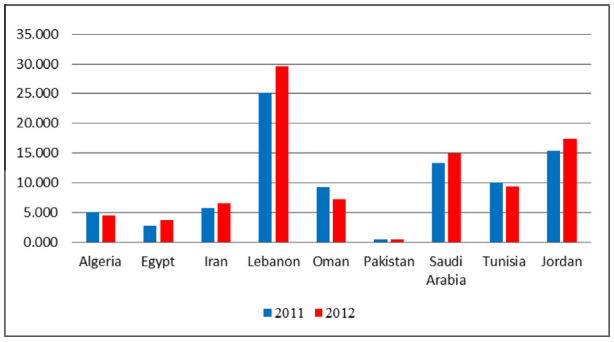

Figure 4. Transplant rate per 10 million inhabitants for each country in the Eastern Mediterranean Regional Office (EMRO) Region.

Donor type and stem cell source

As previously reported in the EMBMT area, the prevalence of matched family donors is relatively high.[8] This is in part due to relatively higher family size and consanguinity where a restricted pool of genes is being inherited.

Most of the donors for allo-SCT were human leukocyte antigen matched family members (936 [91%] patients in 2011 and 1,009 [91%] patients in 2012). Alternate donor transplants were performed in only 45 patients and 59 patients (4% and 5% in 2011 and 2012, respectively).

Most alternate donor transplants were done for patients with acute leukemia (33% and 47%, respectively) and primary immune deficiency syndromes (16.5% and 19%, respectively). However, 16% and 7% of alternate donor transplants were offered to patients with BM failure in 2011 and 2012, respectively. Figure 5 shows the different donor types in 2011 and 2012.

The increase in alternate donor transplant was mainly for patients with acute leukemia beyond first complete remission at time of transplant and primary immune deficiency. Umbilical cord blood is still the main source of stem cells when alternate donor is concerned, representing 89% and 82% of alternate donor transplant in 2011 and 2012, respectively. Most umbilical cord blood transplantations (UCBTs) were done from unrelated donors. Only four (9%) and three (5%) patients of all UCBTs were from related donors in 2011 and 2012, respectively. The other UCBTs were from unrelated donors.

Matched unrelated donor transplants increased from 3 transplants during 2011 to 13 transplants in 2012 (333.3%).

Figure 6 represents the number and indications of alternate donor transplant in 2011–2012.

All auto-SCTs done in 2011 were from PB stem cells. In 2012, only one out of 724 auto-SCTs was from BM derived stem cells.

In allo-SCT, PB was the dominant source of stem cells in 2011 (59%); there was a trend towards increased utilization of PB stem cells in 2012 (68%) and a decrease in BM as a source of stem cells.

Figures 7 and 8 represent the stem cell source in 2011 and 2012.

The choice of stem cell source differed much by indication for all types of allogeneic HSCT. PB remained the preferred source of stem cells for most cases of allogeneic transplants. In 2011, BM was the

main source of stem cell for allo-SCT for marrow failure syndromes including severe aplastic anemia; (107 of 194 patients [55%]). However, in 2012 there was a trend toward utilizing PB as the main source of allo-SCT for the same indication, with 124 of 227 transplants (55%) being of PB source.

Although the number of alternate donor transplants had increased, the percentage of the total transplant number remained at 4%.

Indications for allogeneic stem cell transplant in 2011–2012

On review of the allo-SCTs performed between 2011 and 2012, overall, there was no major change in the performance of transplants for most of the indications. In general, the changes in trends for allo-SCT were much less obvious than in auto-SCT.

Acute leukemia including myeloid and lymphoid leukemia in first complete remission was the most

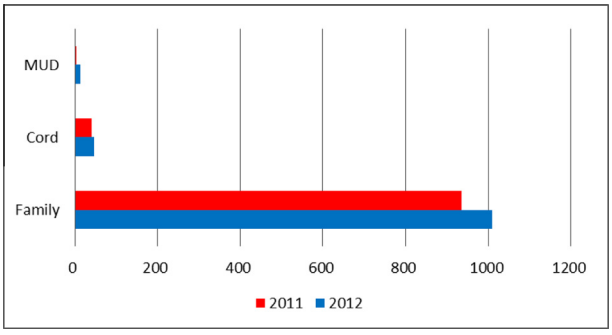

Figure 5. Different donor types in 2011 and 2012. *Note.* MUD = matched unrelated donor.

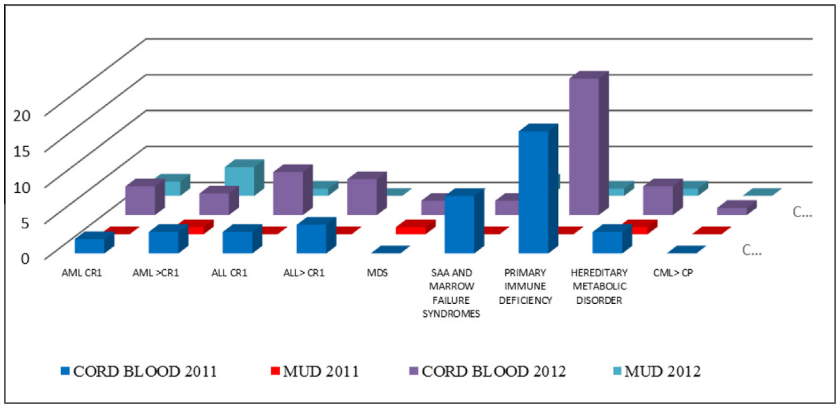

Figure 6. Stem cell source and indications of alternate donor transplant in 2011–2012. *Note.* ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CML = chronic myeloid leukemia; MUD = matched unrelated donor; SAA = severe aplastic anemia; SCT = stem cell transplantation.

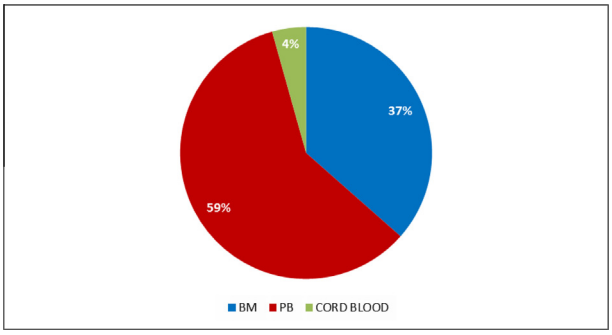

Figure 7. Stem cell source for allogeneic hematopoietic stem cell transplantation in 2011. *Note.* Allo-SCT = allogeneic hematopoietic stem cell transplantation; BM = bone marrow; PB = peripheral blood.

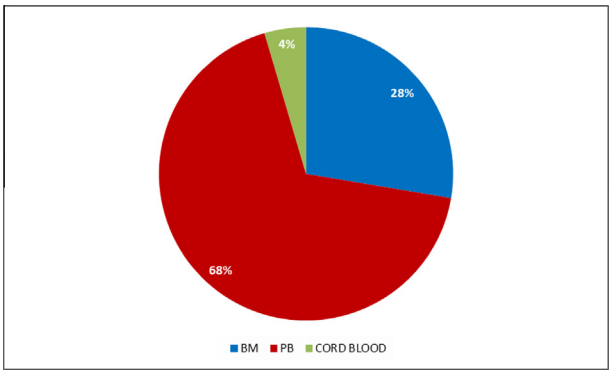

Figure 8. Stem cell source for allogeneic hematopoietic stem cell transplantation in 2012. *Note.* Allo-SCT = allogeneic hematopoietic stem cell transplantation; BM = bone marrow; PB = peripheral blood.

frequent indication for allo-SCT in 2011–2012 (33.2% and 30.6%, respectively). Acute leukemia beyond first complete remission was a less frequent indication for allo-SCT in 2011–2012 (14.9% and 14.3%, respectively).

Other common indications for allo-SCT in 2011–2012 include: marrow failure syndromes (18.9% and 20.6%, respectively), hemoglobinopathies, particularly thalassemias, (12% and 10.8%, respectively), and primary immunodeficiency syndromes (7.3% and 7.4%, respectively).

Less common indications that contributed to <5% of all allo-SCTs in 2011–2012 include chronic myeloid leukemia either in chronic phase (2.6% and 1.9%, respectively), or at more advanced stage (0.9% and 1.6%, respectively), myelodysplastic syndrome (2.7% and 3.7%, respectively), myeloproliferative disorder including juvenile myelomonocytic leukemia (0.68% and 1.5%, respectively), lymphoproliferative disorders including myeloma, non-Hodgkin lymphoma (NHL), and Hodgkin lymphoma (3.1% and 4%, respectively), and hereditary metabolic disorders (2.05% and 1.8%, respectively).

Figure 3 represent the distribution of various indications of allo-SCT patients in the EMBMT data base.

Indications for auto-SCT in 2011–2012

Like the previous years, auto-SCT was less frequently performed than allo-SCT. There was a 21% increase in number of auto-SCTs in 2012 compared with 2011. The most frequent indications for auto-SCT in 2011 and 2012 were plasma cell dyscrasias (40% and 37.7%, respectively), Hodgkin's disease (26.4% and 21.4%, respectively), NHL (16.5% and 22.4%, respectively), and solid tumors, mainly neuroblastoma (11.1% and 13.5%, respectively).

The most significant increase in transplant activity was an increase in auto-SCT for NHL (64.2%), for solid tumors, mainly neuroblastoma (46%), and for multiple myeloma (13.4%). Figure 2 represent the distribution of auto-SCT patients in the EMBMT data base.

Conditioning

Conventional myeloablative conditioning was the most utilized throughout 2011–2012 (63.9% and 63.3%, respectively). RIC was used in 9.5% of all allo-SCTs in 2011. There was a trend towards less utilization of RIC in 2012 both in number (98 vs. 87) and in percentage (9.5% vs. 7.9%). Only 9 out of the 21 participating centers reported using RIC allo-SCT.

In RIC-SCT, the stem cell source was PB (74% and 61%), BM (12% and 21%), and cord blood (11% and 6.7%) in 2011 and 2012, respectively.

In 2012, the reported number of unknown conditioning/others decreased to 18 versus 28 in 2011 (1.5% vs. 3.5%) reflecting improvement in the accuracy of reporting and completion of details of conditioning regimens.

DISCUSSION

The need for SCT will continue to grow, as will the need for improvements in all the transplant related activities from donor selection, availability of alternate donors, conditioning regimen, and supportive care.

The challenges imposed by population growth as well as the advances in transplantation practice in general are stimulating EMBMT centers to create uniform policies to optimize resource utilization to face such challenges.

The EMBMT activity survey has been conducted regularly since EMBMT was established in 2007. The 2011–2012 survey had reported 3,546 patients with a trend to an additional increase by 12.3% in 2012.

Although the annual increase in transplant rate is double that observed in EBMT data (6%),[6] yet the transplant rate per 10 million inhabitants' remains significantly lower. We have previously reported that the transplant activity in the region between 1990 and 2010 is increasing at a rate greater than the population increase; furthermore, the transplant activity in the region is rising at a rate greater than that reported for the EBMT.[9] In the nine EMBMT countries with a collective population of 420 million in 2011 that increased to 427 million in 2012,[2] 1,670 and 1,876 SCTs were performed respectively corresponding to 39.7 per 10 million and 43.9 per 10 million population.

Transplantation rates per 10 million inhabitants for auto-SCT were 14.1 and 16.8 in 2011–2012 respectively, remaining significantly lower than that reported in EBMT region with a median of auto-SCT of 151 transplants per 10 million inhabitants. The same holds true for allo-SCT with a rate of 24.3 and 25.7 per 10 million inhabitants for the same period compared with a median of 109 in the EBMT region.[7]

The increase in transplant rates were variable among different indications; transplants for some indications continued to increase while others did not (see Table 2).

The most notable growth of transplant rate was in auto-SCT for NHL and myeloma reflecting the success of the newer therapeutic agents in rendering more patients eligible for transplant.

Of interest is the continued sharp decrease of transplant number for chronic myeloid leukemia patients from the main indication for allo-SCT two decades ago to 2.2% in 2011–2012, where tyrosine kinase inhibitor successfully eliminated the need for SCT for most chronic myeloid leukemia patients.

Human leukocyte antigen matched family donors remain the dominant modality of allo-HSCT. Large family sizes and high rates of population growth significantly contribute to the high availability of related family donors in the EMBMT region.[8]

Unrelated donor transplant rates remain significantly lower than in the western world and almost restricted to UCBT. Very few matched unrelated donor transplants were performed in 2011–2012. Lack of alternate donor programs, national donor registries, and regional donor registries in the EMBMT region limits the utilization of this stem cell source.

The number of patients undergoing cord transplantation has increased as a consequence of increasing experience of this technique and availability of evidence based data supporting its use. The number of cord blood banks in the EMRO region remains small. The establishment of more cord blood banks will help in improving the availability of this alternate transplantation modality for patients with no matched related donors.

Table 2. Transplant rates per 10 million of different EMRO countries.

Country	2011			2012		
	Population size	No. of transplant	% per 10 million	Population size	No. of transplant	% per 10 million
Algeria	37,762,962	193	5.111	38,481,705	173	4.470
Egypt	79,392,466	218	2.721	80,721,874	302	3.741
Iran	75,424,285	443	5.794	76,424,443	449	6.477
Lebanon	4,382,790	110	25.098	4,424,888	131	29.605
Oman	3,024,774	28	9.257	3,314,001	24	7.242
Pakistan	176,166,353	69	0.392	179,160,111	69	0.385
Saudi Arabia	27,761,728	404	13.328	28,287,855	464	14.953
Tunisia	10,673,800	108	10.118	10,777,500	101	9.371
Jordan	6,181,000	97	15.370	6,318,000	113	17.411

The practice of haploidentical transplant is still in its infancy in the EMRO region with no reported cases during both 2011 and 2012.

There is a trend towards more use of PB as a stem cell source even for patients with SAA and non-neoplastic hematologic disorders in spite of the concerns of higher risk for chronic graft-versus-host disease associated with PB as a stem cell source.[10,11]

PB was the stem cell source for 34.3% of allo-SCTs for SAA in 2011 compared with 56.6% in 2012.

In many developing countries, the use of PB in aplastic anemia as well as non-neoplastic hematologic disorders is favored in order to promote fast engraftment and independence from platelet and red cell transfusions, as well as infections and is likely to balance the morbidity risk of increase graft-versus-host disease, especially in the context of a late diagnosis.

In total, PB was the main stem cell source in all types of allo-SCT (72.6% and 81.7% in 2011 and 2012, respectively). As noted above, rapid engraftment and immune reconstitution observed with PB transplants as well the large proportion of hematologic malignancies among the transplant indications make it the preferred stem cell source.

Although there is improved reporting of cases by participating centers as reflected by less number of conditioning regimens marked as "others" or "unknown", there was a trend towards less utilization of RIC transplants in 2012. As we do not have the data of indications of RIC-SCT at different centers, we cannot explain the decrease in both number and percentage of RIC transplants in 2012.

It would be of interest to report on the outcome data, measuring the effect of transplant rates at different centers on the outcome, but unfortunately these data are currently not included in the annual survey. Again, some other important data are missing from the survey including data on additional cellular therapies like donor lymphocyte infusion and mesenchymal-SCTs. Further modification of the survey to capture more outcome data in the coming years will make the report more informative and will help transplant authorities in planning and adopting more optimum policies to satisfy the growing need for SCTs in the region of EMRO.

CONFLICTS OF INTEREST

None declared.

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