special report

Hematopoietic Stem Cell Transplantation in the Eastern Mediterranean Region (EMRO) 2008-2009: Report on behalf of the Eastern Mediterranean Bone Marrow Transplantation (EMBMT) Group

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BACKGROUND: The Eastern Mediterranean Bone Marrow Transplantation (EMBMT) Group has accumulated over 25 years of data and experience in hematopoietic stem cell transplantation (HSCT), most particularly in hemoglobinopathies, severe aplastic anemia (SAA), and inherited metabolic and immune disorders, in addition to hematologic malignancies peculiar to the region and where recent updates in trends in activities are warranted.
OBJECTIVES: To study trends in HSCT activities in the World Health Organization-Eastern Mediterranean (EM) region surveyed by EMBMT between 2008 and 2009. STUDY DESIGN: Retrospective analysis of the survey data, mainly of the cumulative number of transplants, types of transplants (autologous vs. allogeneic), types of conditioning as myeloablative (MAC) vs. reduced intensity conditioning (RIC) and trends in leukemias, hemoglobinopathies, SAA, inherited bone marrow failure syndromes amongst others.
RESULTS AND DISCUSSION: Fourteen teams from ten Eastern Mediterranean Region Organization (EMRO) countries reported their data (100% return rate) to the EMBMT for the years 2008-2009 with a total of 2608 first HSCT (1286 in 2008; 1322 in 2009). Allogeneic HSCT represented the majority (63%) in both years. The main indications for allogeneic HSCT were acute leukemias (732; 44%), bone marrow failure syndromes (331, 20%), hemoglobinopathies (255; 15%) and immune deficiencies (90; 5%). There was a progressive increase in the proportions of chronic myeloid leukemia (CML) cases transplanted beyond the first chronic phase (3; 7% of all CML cases in 2008 vs 13; 29% in 2009). The main indications for autologous transplants were plasma cell disorders (345; 36%) Hodgkin disease (256; 27%), non-Hodgkin lymphoma (207; 22%) and solid tumors (83; 9%). RIC continued to show a progressive increase over the years (7% in 2007, 11% in 2008 and 13% in 2009), yet remained relatively low compared to contemporary practices in Europe published by EBMT. The vast majority (95%) of allo-HSCT sources were from sibling donors with a continued dominance of peripheral blood (PB) (1076; 63%), while cord blood transplant (CBT) increased to 83 (5% of allo-HSCT), matched unrelated donor (MUD) remained underutilized (1; 0%) and there were no haploidentical transplants reported. Large centers with >50 HSCT/year showed a plateau of the total number of allo-HSCT over the last 5 years that may be related

to capacity issues and needs further study.
CONCLUSIONS AND RECOMMENDATIONS: There is an overall increased rate of HSCT in the EMRO region with a significant increase in utilization of CBT and allogeneic PB-HSCT as a valuable source. However, further research on outcome data and development of regional donor banks (CB and MUD) may help facilitate future planning to satisfy the regional needs and increase collaboration within the group and globally.

Hematopoietic stem cell transplantation (HSCT) has become an important and well established curative procedure for many congenital and acquired disorders of the hematopoietic system. Annual reports from various HSCT groups and registries like European Bone Marrow Transplant (EBMT), International Bone Marrow Transplant Registry (IBMTR), World Bone Marrow Transplant (WBMT) and Asia-Pacific Bone Marrow Transplant (APBMT) groups have become important instruments to describe the status of hematopoietic SCT in different regions, to observe trends and to monitor the technology used.[1-7]

EMBMT is a relatively new group that was established in 2007 after a number of meetings between transplant teams from the WHO EMRO region,[8] with the aim of sharing experience, initiation of collaborative trials and the establishment of common strategies for transplantation, taking into consideration the specific issues and peculiarities relevant to the region.[9]

Although many of the included teams also report to and exchange experience with other international registries, like EBMT and IBMTR, their data may get diluted and probably particular features of transplant activities may be overlooked. This would make the EMBMT report an important source that details important issues related to the HSCT activities and the specific challenges in the region. This report should serve as a basis for decision making on how to provide the necessary infrastructure, set up the best referral system and initiate support services like alternate donor or cord blood banking, and algorithm of management based on the best available options and optimal utilization of services without denying the patient the need for new modalities in transplant procedures.[9-14]

In previous reports[15-22] from the region, it was clear that the chance of finding a matched sibling donor is probably one of the highest in the world,[23] making sibling donors the overwhelmingly best available option for the majority of patients. The relatively younger age of patients and donors is also of importance. On the other hand, many challenges are frequently faced, like the relatively high rate of cytomegalovirus (CMV) positivity, hepatitis C virus (HCV), hepatitis B- virus (HBV), and tuberculosis (TB) infections.[9]

In some countries, the choice between transplantation and other modalities like tyrosine kinase inhibitors (TKI) for chronic myeloid leukemia (CML) or antithyocyte globulin (ATG) for severe aplastic anemia (SAA) is tipped in favor of transplantation as the best "available" cost-effective option.[15-16]

The first detailed EMBMT report[24] showed an impressive increase over many years in the number of centers and number of HSCT in the region. The majority of allo-HSCT had been done for proportionately younger patients and the most common indications were acute leukemia, bone marrow failure syndromes, thalassemia, and inherited immune deficiencies. For autologous HSCT (auto-HSCT), the most common indications were myeloma and lymphomas in adults and solid tumors, especially neuroblastoma in children. The report also stressed the marked variability in the rate and trends in utilization of HSCT amongst EMRO countries and between the EMBMT centers and globally. In the current report, recent trends and activities in 2008 and 2009 will be discussed with a special focus on a comparison to contemporary trends from EBMT.[13] Additional details of numerical performance of allo-HSCT at large centers across the last five years will also be discussed.

STUDY DESIGN AND METHODS

The goal was to study the trends of transplant activities in the EMRO region as reported to the EMBMT group in the years 2008-2009 and compare these to previous trends in the region and to contemporary trends by EBMT.[13]

Organization, teams, data collection and validation

This study was conducted by the EMBMT center with waived informed consent of patients. No individual data was uncovered by any of the investigators or the authors. Data was used only for collective analysis of trends at the center, national or regional level. This was a retrospective survey among all transplant teams (n=14) that are members of EMBMT and known to the investigators. One team can be working at more than one center and a center may be served by two teams. For

transplant by indication, only the first transplant was reported to avoid re-reporting. After data entry and computation, a review of the final draft by the referring team was done before the final analysis and graph plotting. Centers with less than 5 transplants/year for the last 3 years were not included. Moreover, transplants done to patients who cross borders outside the relevant country were not reported. Further details of reporting are already published in a previous EMBMT report.[24]

Data was validated through a written survey form submitted by each transplant center followed by verbal communication between the central offices of the EMBMT and the reporting teams. Collective and center-based data were further discussed with the relevant teams on EMBMT business meeting in 2010, and then a draft of the final report was sent to each center before final publication.

The main outcome measures included cumulative number of transplants, types of transplants (autologous vs. allogeneic), types of conditioning such as myeloablative conditioning (MAC) vs. reduced intensity conditioning (RIC) vs. others, and study of the trends in indications with a special focus on hemoglobinopathies, severe aplastic anemia (SAA), inherited bone marrow failure syndromes and leukemias, among others.

Definitions

Team size is defined according to previous reports[1,25] as the number of first HSCT for patients transplanted in the relevant year.

Team density is defined as the number of transplant teams per 10 million inhabitants and is computed for each country and for the whole region.

Transplant number and sources: The current report is focused on the number of patients transplanted for the first time. Additional transplants were further reported under each disease category, whether they were a second transplant in a pre-planned double transplant, e.g., autologous followed by RIC allogeneic transplant or a tandem (double autologous) transplant.

Transplant rate is the number of transplants performed within the borders of that country per 10 million inhabitants as previously defined.[25] Transplant rate refers to the number of transplants in a given country compared to its own population. No adjustments were made for those who crossed borders to receive transplants outside their country. Population data were obtained from the US census office (http://www.census.gov).[26]

Re-transplant is defined as unplanned HSCT for relapse or rejection.

Stem cells source: information on stem cell source was reported as bone marrow (BM), cord blood (CB) and peripheral blood (PB). Any transplants with a combination of stem cell source that included CB were reported as CBT; BM and PB combinations were reported as PB.

Conditioning: MAC and RIC were reported by each team following the recently published definitions.[14] For those with incomplete details or who did not appear to the reporting team to fit into a clear category were reported as unknown or others, respectively.

Statistical analysis

Descriptive data analysis was performed with a focus on 2008 and 2009. EBMT practice guidelines were used for disease indications. The transplant rate was calculated according to the number of transplants by disease indication in relation to the mean population census (http://www.census.gov)[26] for the corresponding period 2008-2009. The above descriptive definitions and calculations in transplant rate, team size and team density were also applied.

RESULTS

Survey outcome and participating teams

A total of 14 reporting teams from 10 countries reported their data (100% return rate) for the years 2008-2009. These countries in alphabetical order were: Algeria, Egypt, Iran, Jordan, Lebanon, Saudi Arabia, Morocco, Oman, Pakistan, and Tunisia. Teams from Algeria reported their data for the first time to EMBMT (**Table 1**)**.** The corresponding addresses are listed also in alphabetical order in Appendix 1. Six countries also report to EBMT and include Algeria, Iran, Jordan, Lebanon, Saudi Arabia and Tunisia. All teams performed both allogeneic and autologous transplantations with marked variation in the rate of each of these modalities (**Figure 1**).

There was a significant improvement in reporting details of transplants compared to 2007 (**Table 2**). For example, the details of conditioning were reported as unknown/others in 41.8% in 2007, compared to 4.4% in 2008 and 5.6% in 2009. Meanwhile, the allogeneic stem cell source was reported as unknown in 7.9% in 2007 and became 0% in both 2008 and 2009.

The total number and the proportions of all indications of transplants per each country are collectively illustrated in **Table 1** and **Figure 1** and varied greatly between countries (13 to 389 in 2008, 15 to 366 in 2009). The mean rate of HSCTs for the whole region for the period of observation was 29.2 and it was <25 for 3 countries, 25-50 for 2 countries, 51-100 for 2 coun-

Table 1. Number of HSCTs in EMRO per each EMBMT country in 2008-2009.

Country	2008		2009		Total 2008-9	%
	Allo	Auto	Allo	Auto		
Algeria*	95	38	100	76	309	11.8
Egypt	103	25	110	12	250	9.5
Jordan*	49	41	38	48	176	6.7
Iran*	247	142	249	117	755	28.9
Saudi Arabia*	173	78	179	75	505	19.3
Lebanon*	16	60	25	53	154	5.9
Morocco	0	20	2	20	42	1.6
Oman	9	4	15	0	38	1.4
Pakistan	73	9	69	15	166	6.3
Tunisia*	51	53	52	67	223	8.5
Total	816	470	839	483		
Overall	**1286**		**1322**		**2608**	

HSCT: Hematopoietic stem cell transplants; Allo: Allogeneic HSCT; Auto: Autologous HSCT; *Also report to EBMT.

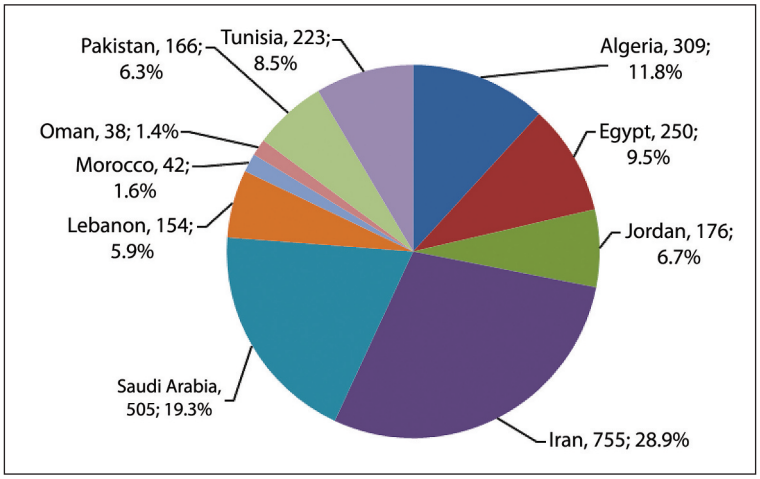

Figure 1. Number and proportions of total HSCTs per each EMBMT country in 2008-2009.

tries and 101-200 for the remaining 3 teams (**Table 3, Figure 2**).

Trends of transplantation compared to the previous report in 2007

Overall, there was a trend towards an increased total number of transplants (both allo- and auto-HSCT) across the years 2008-2009 compared to 2007, (**Table 2, Figure 3**). In 2008, the total number of transplants was 1286 (816 allogeneic, 470 autologous) with an increase of reporting by 17.2% compared to 2007 (total 1097).[24] This was attributed mainly to the addition of Algeria. However, even without Algeria, the group showed a marginal increase of 5.1%. In 2009, the total number reached 1322 (839 allogeneic; 483 autologous) with an increase of 2.8% compared to the previous year. Allo-HSCT remained the predominant type in the region (62% in 2007, 63% in both 2008 and 2009). As shown in **Table 2**, the trend of change was consistent with an increased rate across all indications except a trend towards a reduction in allogeneic transplants for CML and in auto-HSCT for acute leukemias.

Trends in allogeneic and autologous transplantation

All centers, except one, performed both Allo- and Auto-HSCT and the majority of the cord blood transplants were performed by 2 centers although 7 did at least one CBT in 2 years.

Also, RIC trend was towards an increase, yet modest, across 2007-2009 in both absolute number and in ratio. Although, the ratio of cord blood utilization remains nearly the same in 2008-2009 (~5%), it increased from 28 (4.4%) in 2007 to 42 (4.9%) in 2009. Other peculiar trends are also explained in the relevant sections of the study. The main indications for HSCT in 2008 and 2009 in comparison to the previous year are listed in **Table 2** and their distribution is illustrated in **Figures 4-7**.

Allogeneic transplantation

A total of 1700 stem cell sources were used for 1655 transplant indications in 2008 (816 cases) and 2009 (839 cases). There was a non-significant increase (2.8%) in the number of transplants in 2009 compared to 2008. However, as shown in **Table 2** and **Figure 3**, 2008 witnessed an increase by 19.3% when compared to 2007 (total 684), largely due to the addition of a new team, in addition to an increase in the rate of transplants (5.4%).

Indications of allogeneic transplantation by disease

There was a marked variation in the indications among centers. More than half of allo-HSCT were done for clonal hematologic disorders (465; 57% in 2008; 466 55.5% in 2009), mainly acute leukemia (372; 45.6% in 2008 and 360; 42.9% in 2009) with more cases (223; 27% in 2008, 217; 26% in 2009) of AML than for ALL (149; 18% in 2008 and 143; 17% in 2009). There was a trend for transplanting AML cases in CR1 (78% of cases across both years) which did not differ from 2007 (77%) (**Figure 8**). The same trend was also observed in ALL but with a lesser degree (60% in CR1 in 2007, 53% in 2008 and 61% in 2009) (**Figure 9**).

CML cases (**Figure 10**) represented a small minor-

ity (41; 5% in 2008; 45; 5.4% in 2009) and remained nearly stable over the 2-year period. However, there was a significant increase in the number of patients transplanted beyond first chronic phase (3 cases in 2008 and 13 in 2009).

For MDS, there were more transplants (n=36; 4.3%) performed in 2009 than in 2008 (n=23; 2.8%) with a significant increase (57%) (**Table 2**). Only 7 (<1%) transplants had been performed for MPNs in 2008 and 6 (<1%) performed in 2009. Lymphomas (HD, NHL) and multiple myeloma represented a relatively small minority (22; 2.7% in 2008 and 19; 2.3% in 2009); nearly half of them were high grade/or aggressive lymphomas.

Bone marrow failure syndromes represented the second largest single indication after leukemias in both 2008 (165; 20.2%) and in 2009 (166; 19.8%) and included acquired SAA (131; 16.1% in 2008; 133; 15.9 % in 2009) and congenital bone marrow failure syndromes (31; 3.8 % in 2008 and 27; 3.2 % in 2009), amongst others (**Figure 4, 5**). Hemoglobinopathies (mostly B-thalassemia) were the third most common indication for allo-HSCT in both 2008 (124; 15.2%) and 2009 (131; 15.6%) (**Figure 4, 5**). These were largely contributed by Iran (63; 7.7 % in 2008; 73; 8.7 % in 2009) and Pakistan (29; 3.5 % in 2008 and 20; 2.4 % in 2009), although other centers also performed a significant number of such cases (Saudi Arabia 10 and 9 cases; Egypt 8 and 10 cases in 2008 and 2009, respectively).

Of particular mention is the group of recipients with primary immunodeficiency syndrome (39; 4.8% in 2008 and 51; 6.1% in 2009) and those with inherited metabolic disorders (11 in 2008 and 14 in 2009) like osteopetrosis and other metabolic disorders.

Autologous stem cell transplantation

967 autologous stem cell sources were utilized for a total of 953 disease indications in the survey period (470 in 2008 and 483 in 2009), compared to 413 disease indications reported in 2007, with a progressive increase in absolute number by 57 (13.8%) in 2008 and 13 (2.7%) in 2009 (**Table 2**). The increase in 2008 was largely due to increased reporting after the addition of two teams from Algeria (n=38), but the increase in 2009 was real.

Nearly all the indications were for clonal disorders (456; 98.5% in 2008 and 479; 99.2% in 2009). For the year 2008, the most common indications were plasma cell disorders—mostly myeloma—in 158 (33.6%), followed by HD 121 (25.7 %) and NHL 112 (23.8%). Solid tumors accounted for 41 (8.7%); the most common solid tumor being neuroblastoma (29; 6.1%), although others like germ cell tumors were also per-

Table 2. Overall HSCT activities in 2008-2009 compared to 2007 in EMRO region as reported to EM-BMT by indications, stem cell source, and type of conditioning.

Total	2007	2008	2009
Allo-HSCT vs. Auto-HSCT	**684 vs. 413**	**816 vs. 470**	**839 vs. 483**
Main Indications of Allo-HSCT	**684**	**816**	**839**
Acute leukemia	289 (42%)	372 (45.6%)	360 (42.9%)
Acute myeloid leukemia	172 (25%)	223 (27%)	217 (26%)
CR1 vs. >CR1	133 (19%) vs. 38 (6%)	175 (20%) vs. 48 (6%)	170 (20%) vs. 47 (6%)
Acute lymphoblastic leukemia	109 (17%)	149 (18%)	143 (17%)
CR1 vs. CR2	65 (9%) vs 54 (8%)	80 (10%) vs. 69 (8%)	87(10%) vs. 56(7%)
Chronic myeloid leukemia	60 (8.7%)	41 (5%)	45 (5.4%)
CP-1 vs. >CP-1	55(8%) vs. 5 (<1%)	38 (4.4%) vs. 3 (0.3%)	32 (3.8%) vs. 13 (1.5%)
Myelodysplastic syndrome	39 (9.4%)	23 (2.8%)	36 (4.3%)
Myeloproliferative disorders	2 (0.4%)	7 (<1%)	6 (<1%)
NHL	7 (1.7%)	10 (1%)	10 (1%)
BM failure (all)	106 (15.5%)	165 (20.2%)	166 (19.8%)
Hemoglobinopathies	102 (15%)	124 (15.2%)	131 (15.6%)
Immune deficiency	42 (10.2%)	39 (4.8%)	51 (6.1%)
Indications of Auto-HSCT	**413**	**470**	**483**
Plasma cell disorders (including myeloma)	110 (26.6%)	158 (33.6%)	187 (38.7%)
Hodgkin's disease	128 (31%)	121 (25.7%)	135 (27.9%)
Non-Hodgkin's lymphoma	103 (24.9%)	112 (23.8%)	95 (19.7%)
Solid tumors	27 (6.5%)	41 (8.7%)	42 (8.6%)
Neuroblastoma	16 (3.9%)	29 (6.1%)	26 (5.3%)
Acute myeloid leukemia	42 (10.2%)	28 (5.9%)	19 (3.9%)
Others	3 (1%)	10 (2.1%)	5 (1%)
Conditionings for Allo-HSCT*	**684**	**775**	**791**
Conventional	347 (50.7%)	658 (84.9%)	645 (81.5%)
Reduced intensity conditioning	51 (7.4%)	83 (10.7%)	101 (12.8%)
Unknown/other	286 (41.8%)	34 (4.4%)	45 (5.6%)
Stem Cell source for Allo-HSCT	**647**	**837**	**863**
Bone marrow-related	156 (24.8%)	232 (27.7%)	254 (29.4%)
Peripheral blood-related	408 (64.8%)	535 (63.9%)	541 (62.7%)
Cord blood	28 (4.4%)	41 (4.9%)	42 (4.9%)
Matched unrelated donor	1 (0.1%)	1 (0.1%)	0 (0%)
PB+BM/BM+CB	NA	27 (3.2%)	26 (3%)
Unknown	54 (7.9%)	0 (0%)	0 (0%)
Stem cell source for Auto-HSCT	**413**	**474**	**495**
Bone marrow-related	6 (1.5%)	21 (4.4%)	13 (2.6%)
Peripheral blood-related	407 (98.5%)	452 (95.6%)	481 (97.4%)
Unknown		1 (0%0	1 (0%)

Auto-HSCT: autologous HSCT; Allo-HSCT: allogeneic hematopoietic SCT; CR1: first complete remission; >CR-1: beyond CR1; CP-1: first chronic phase; >CP-1: beyond CP-1; Others: autoimmune disorders , germ cell tumors, inherited metabolic disorders

Table 3. Rate of transplants per each EMBMT country according to population.

Country	Total 2008-2009	Mean census 2008-2009 (Million)	Rate** n/10M PC
Algeria*	309	34.1	45.3
Egypt	250	78	16
Jordan	176	6.15	143
Iran*	755	75.5	50
Saudi Arabia*	505	25.2	100
Lebanon*	154	4.1	187
Morocco	42	31.2	6.7
Oman	38	2.9	65.5
Pakistan	166	179.5	4.6
Tunisia*	223	10.35	107
Total	**2608**	**447**	**n= 29.2**

n: mean number of transplant per 10 million *Also report to EBMT.
**According to the mean population census 2008-9 (http://www.census.gov)[26]

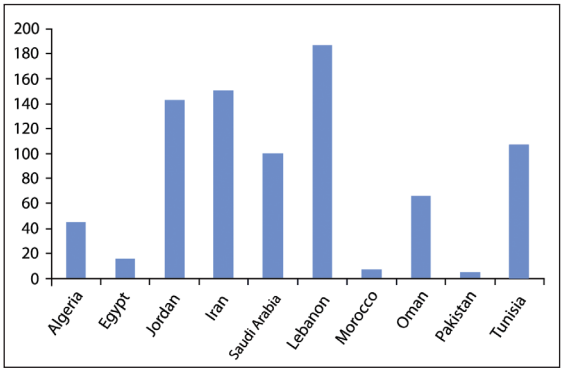

Figure 2. Transplant rate (per 10 million population) of EMBMT countries 2008-2009.

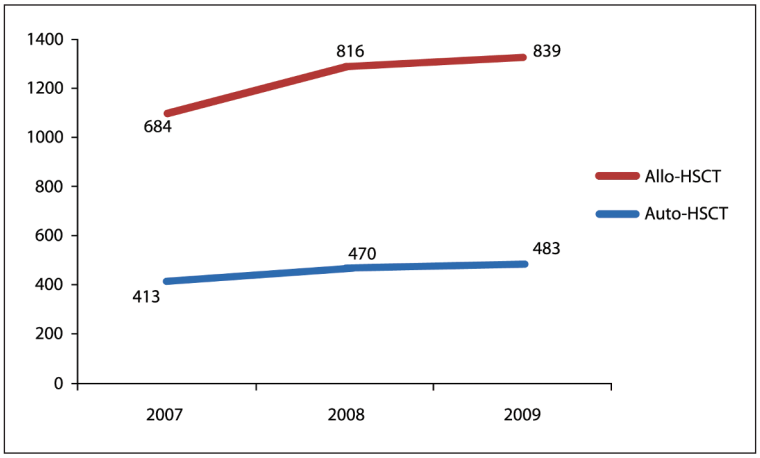

Figure 3. Trend in autologous and allogeneic HSCT in EMRO region as reported to EMBMT group in 2008-2009 compared to 2007.

formed (7; 1.4%). The main indications in 2009 were nearly the same: myeloma in 187 (38.7 %), HD in 135 (27.9 %), NHL in 95 (19.7%) and solid tumors at 42 (8.6%). A recognizable progressive increase was seen in the absolute number and percentage of myeloma transplanted over the last 3 years (110; 26.6% in 2007, 158; 33.6% in 2008 and 187; 38.7% in 2009).

Compared to myeloma, Hodgkin disease showed quite a similar, yet slightly lesser increase (11.6%) over the study period. The remarkable increase in reporting solid tumors was noticed mainly in 2008 with a 51.8% increase that was attributed to both the addition of Algeria and to an actual increase by the other countries. However, 2009 did not witness a significant increment (only 2.5%). About two-thirds of the transplants for solid tumors (71% in 2008 and 61% in 2009) were performed mainly for neuroblastoma and mainly for pediatric/adolescent patients. On the contrary, NHL cases decreased from 2008 (112; 23.8%) to 2009 (95; 19.6%), representing a relative decrease by 15.1%. Although the majority were of aggressive types like diffuse large cell lymphoma (DLBCL) and prolymphocytic leukemia (PLL), other forms were also performed.

There was also a progressive decline both in absolute number and percentage of acute myeloid leukemia (AML) during the observation period (28; 5.9% in 2008 and 19; 3.9% in 2009) while no center performed Auto-HSCT for acute lymphoblastic leukemia (ALL) (**Table 2, Figure 6, 7**). The decline in AML auto-transplanted has not been limited to the last 2 years but started even earlier (n=41; 12.4% in 2006, n=42; 10.2% in 2007). However, auto-HSCTs for AML were almost all done in CR1.

Literally, no single case of breast cancer or renal cell carcinoma was performed during the same period. There was a marked variation between countries in the utilization and overall rate of autotransplants (between 4-to-142 in 2008 and 0-to-117 in 2009), with a median of 53 in both 2008 and 2009.

By stem cell source

A total of 1700 allogeneic stem cell sources were used for a total of 1655 disease indications (837 in 2008 and 863 in 2009) (**Figure 11**). Bone marrow (BM) was the only source utilized in 232 (28%) in 2008 and in 254 (29%) in 2009. Although there was marked variability in the rate of utilization of stem cell sources among centers, peripheral blood stem cell (PBSC) alone was the predominant stem cell source (535; 64% in 2008 and 541; 63% in 2009) especially in acute leukemia beyond first complete remission, MDS and CML-AP/BC. The

only disease indications with more bone marrow source than peripheral stem cell donors are bone marrow failure syndromes (SAA) and congenital disorders.

Regarding donor types, the most common was related matched donors. Cord blood (CB) as the only source was used in 41 (5%) in 2008 and in 42 (5%) in 2009. Overall, cord blood sources were used mainly for pediatric patients. Combined CB+BM /PBSC+BM were used in 27 (3%) cases in 2008 and in 26 (3%) cases in 2009. A single case of matched unrelated donor and another single case of haplo-identical T cell-graft were used in the 2-year period. For cord blood transplantation, the most common indications were inherited immune deficiency and inborn errors of metabolism, mostly in pediatrics and the vast majority had been performed in Saudi Arabia and Jordan.

For the auto-HSCT, PB was the most common source utilized both in 2008 (452; 95%) and in 2009 9481; 97%). Overall, 95% of stem cell sources for AML patients were allogeneic and 5% were of autologous source, while all sources used for CML, MDS and ALL were allogeneic. There was a trend for more utilization of BM source in benign hematologic disorder and congenital diseases compared to malignant disorders.

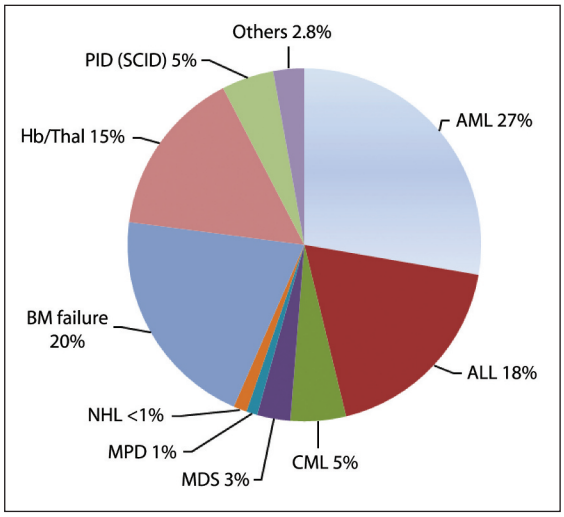

Figure 4. Absolute number and relative proportions of indications for Allo-HSCT in EMRO region as reported to EMBMT in 2008.
AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; CML: chronic myeloid leukemia; MDS: myelodysplastic syndrome; MPD: myeloproliferative disorders; Hb/Thal: hemoglobinopathies (thalassemia); NHL: non-Hodgkins lymphoma; BM failure: bone marrow failure syndromes; PID (SCID): primary immune deficiencies including severe combined immune deficiency diseases

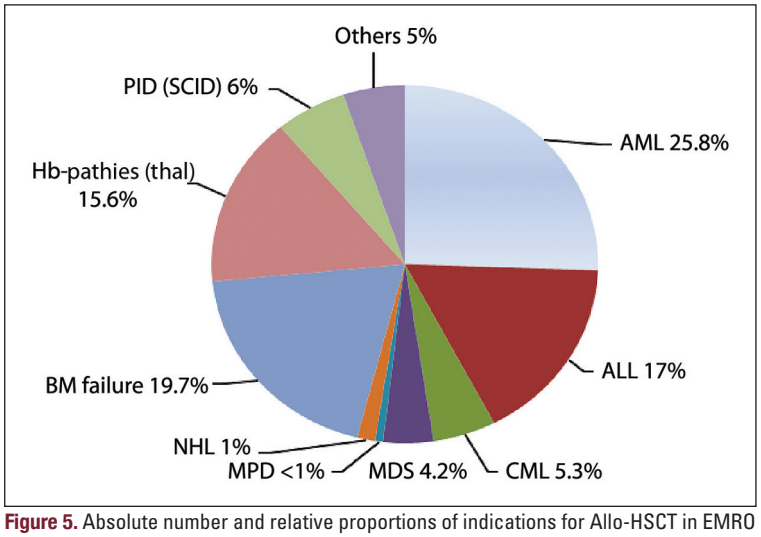

Figure 5. Absolute number and relative proportions of indications for Allo-HSCT in EMRO region as reported to EMBMT in 2009.
AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; CML: chronic myeloid leukemia; MDS: myelodysplastic syndrome; MPD: myeloproliferative disorders; Hb/ Thal: hemoglobinopathies (thalassemia); NHL: non-Hodgkins lymphoma; BM failure: bone marrow failure syndromes; PID (SCID): primary Immune deficiencies including severe combined immune deficiency diseases

Conditioning

For allogeneic HSCT, a total of 1566 conditioning regimens were reported in the 2-year period including 1303 (83%) conventional myeloablative and 184 (12%) reduced intensity by different protocols. There was a progressive increase in the absolute number and percentage of utilization of RIC in the region over the last few years most notably during the last 2 years (51; 7.4 % in 2007, 83; 10.7% in 2008 and 101; 12.7% in 2009) (**Table 2, Figure 12**). As indicated in Table 2, it is clear that there was an improvement in the accuracy of reporting and completing of details of conditioning as the reported number of unknown conditioning/others decreased to 4.4% and 5.6% only over the 2-year observation period .The minor difference between the total number of allo-HSCT indications and conditioning reported is likely due to some immune deficiency cases where conditioning may not be required. Because the information collected is generic, there were no further details of the disease distribution within each type of conditioning.

Novel Cellular Therapies

Donor lymphocyte infusion (DLI) is still underutilized in the region. In 2008, only 7 cases were reported (total number of sessions unknown) representing only 8.3% of reduced intensity conditioning and only 1% of all conditionings for allogeneic stem cell transplant. The corresponding number for the year 2009 was even lower at 3 cases (3% of RIC and <0.5% of all conditioning regimens delivered). Two cases of auto-HSCT for critical limb ischemia were performed (one with PB and one with BM-HSC) in 2009 at a single institution

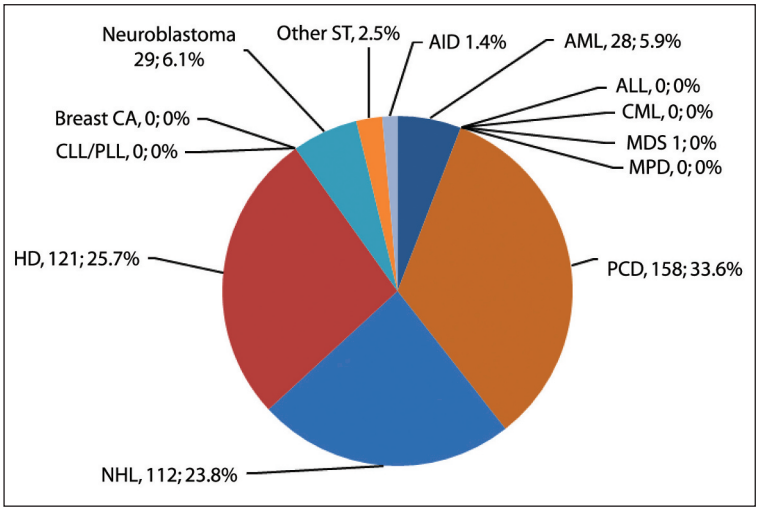

Figure 6. Absolute number and relative proportions of indications for Auto-HSCT in EMRO region as reported to EMBMT in 2008.
PCD: plasma cell disorders including multiple myeloma, NHL: Non-Hodgkin lymphoma; HD:Hodgkin's disease; CLL/PLL: chronic lymphocytic leukemia/prolymphocytic leukemia; Breast CA:breast cancer; GC:Germ Cell tumors; AID:autoimmune diseases; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; CML: chronic myeloid leukemia; MDS: myelodysplastic syndrome; MPD: myeloproliferative disorders; Other ST: other solid tumors.

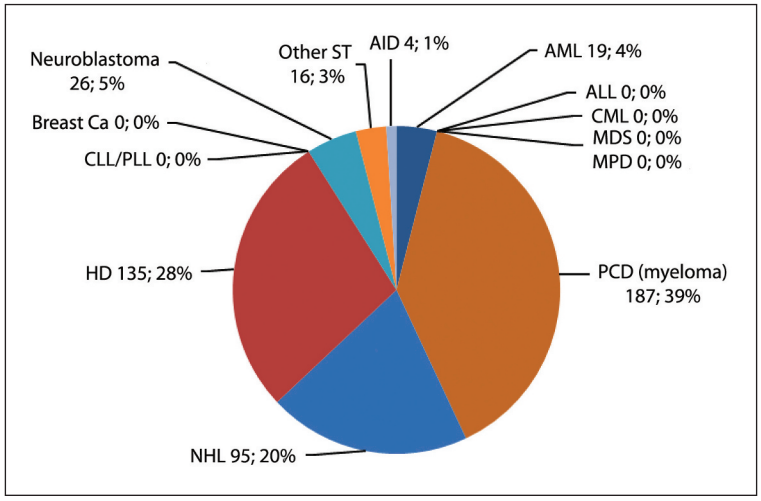

Figure 7. Absolute number and relative proportions of indications for Auto-HSCT in EMRO region as reported to EMBMT in 2009.
PCD: plasma cell disorders including multiple myeloma, NHL: non-Hodgkins lymphoma; HD: Hodgkin's disease; CLL/PLL: chronic lymphocytic leukemia/prolymphocytic leukemia; Breast Ca: breast cancer; GC: germ cell tumors; AID: autoimmune diseases; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; CML: chronic myeloid leukemia; MDS: myelodysplastic syndrome; MPD: myeloproliferative disorders

(KFSHRC), in a research protocol, but were not included in the statistical analysis as detailed information on the procedures was substantially limited.

DISCUSSION

The present data reflect the status of HSCT in the EMRO region as reported and reflected in the activities of EMBMT teams in 2 years, 2008-2009. Although it is just the second report, it confirms and highlights important developments and peculiar practices.[9,24]

Many of the EMRO countries are developing countries where stem cell transplant technology has started at single centers considered as "national" centers. It seems to be approved and supported by governmental and non-governmental bodies to help satisfy some of the sore needs of the region for such an economically intense procedure that depends on very intricate infrastructure and multidisciplinary activities.[15]

It is clear that the group is growing and new activities are added to the current report by the joining of Algeria. However, the team density in the region is still far less than the status in Europe (0.3 vs. 7.6) (**Table 4**) indicating a sore need for further increase in human resources to satisfy the region's increasing needs of such a high technology procedure. The trend of progressive increase in both allogeneic and autologous HSCT (**Figure 3**) is clearly noticed over the study period and confirms what was reported previously in the 2007 activities' report.[24] Nevertheless, the stand of allogeneic HSCT is still dominant (63.5% in 2009) (**Table 4**) which is opposite to the trend in Europe where Auto HSCT continued to outnumber allotransplants (59% vs. 41%).[13] Such dominance of Allo-HSCT in EMRO and dominance of Auto-HSCT in Europe could be attributed to the relatively older populations transplanted in Europe with higher proportions of lymphoid and plasma cell disorders requiring Auto-HSCT[13] in contradistinction to a relatively younger patients in EMRO with a larger need for allogeneic transplants.[9] Many other important differences also exist and may be explained by socioeconomic, prevalence of relevant diseases or even the demographic features of the target population of patients, but all mandate prospective collaboration and exchange of experience between study groups and registries.[28] Such a remarkable difference highlights the important variation in practices between world regions and illustrates the importance of key regional reports in the field for better assessment and decision making. Of particular interest is the observation that countries like Morocco, Tunisia and Lebanon are doing Auto- HSCT more than Allo-HSCT which parallels the practice in Europe.

Meanwhile, in Allo-HSCT, MUD is still markedly underutilized (n=1; 0%) (**Figure 11**), compared to the overwhelmingly increased rate in Europe (46% of allo-SCT in 2009)[13] which reflects many facts on the ground. First, disease distribution and indication with higher rates of indications for BM failure syn-

dromes and hemoglobinopathies in the EMRO region (35.4%) compared to the EBMT countries (8%).[13-18] In such conditions, sibling donors represent the best fit.[24] Second, the better availability of MRD (68%) in the EMRO region due to better ethnic homogeneity and consanguinity which perhaps leads to better clustering and retention of HLA antigens and also due to larger size of families.[23] Third, the cost and logistics of MUD transplant are resources-consuming that it would be very difficult for many centers to cope with the escalating needs while facing such very cost-intense procedure for a small minority.[29] Such difficulties would be considerably overcome by initiating loco-regional donor registries that would help find a suitable donor from the same ethnic group at lower costs.

For Allo-HSCT, myeloablative conditioning remained the predominant type preparation compared to RIC (12.8% in 2009) (**Figure 12**) and probably fits the optimal needs to achieve disease eradication, reducing rate of relapse and allowing good stable engraftment in a relatively young patient population.[9] In contrast, the EBMT survey[13] for the year 2009 demonstrated that RIC was utilized in 39% of all Allo-HSCT, and has been reported to be as high as 71% in some European countries.[28,29] Nonetheless, the trend of steady, yet slowly, increasing rate of RIC may probably suggest recent broadening of target population and indications and parallels the overall international trend of increased utilization.[27,30] The great variability in rate of utilization of RIC among centers could not be explained.

The lack of guidelines in use of DLI, limited availability of resources for further curative intents in case of relapse or the preference of a second transplant may be a plausible explanation for the markedly low rate of such a viable modality. It could also be, though partly, linked to the lower rate of RIC.[13]

Status of transplants in specific diseases

The main indications for allogeneic HSCT were acute leukemias, bone marrow failure syndromes and hemoglobinopathies, at 1318 (79.6% of Allo-HSCT). This represents a peculiar distribution reflecting not only the prevalence of such diseases in the region, but also the pressure of prioritization on the regional centers as most of the cases are relatively young compared to the west. The significantly large number of transplants for clonal hematologic diseases, mainly acute leukemia is matching with the rapidly increasing role of allogeneic HSCT for such disorders (**Figure 4, 5**). The majority of AML cases were transplanted in CR-1 compared to CR-2 and literally there were few, if any, transplanted in CR-3 which parallels the contemporary international

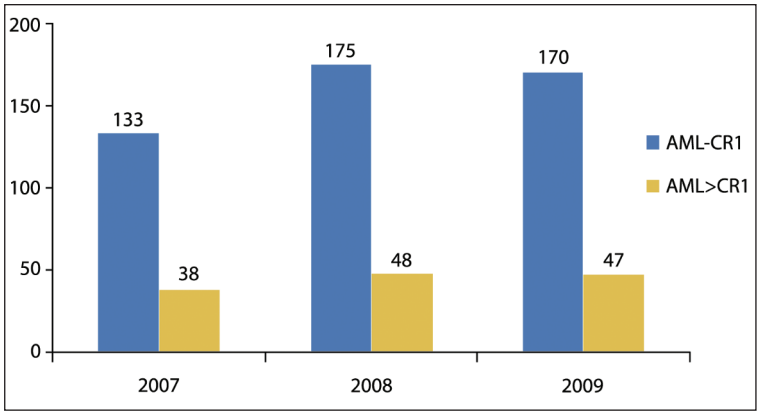

Figure 8. Trend of allogeneic-HSCT for acute myeloid leukemia in 2008-2009 compared to 2007 in EMRO region as reported to EMBMT.
AML: acute myeloid leukemia; CR1: first complete remission; >CR1: beyond first complete remission. Numbers posted are absolute numbers.

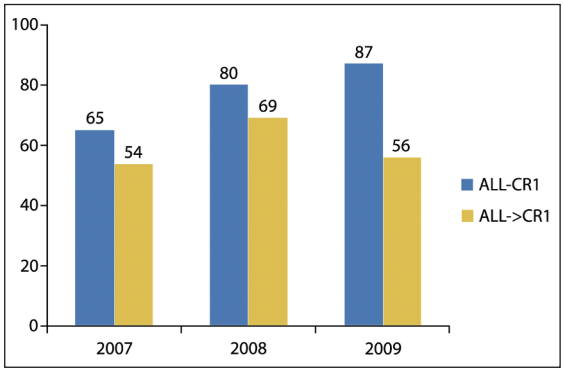

Figure 9. Trend of allogeneic-HSCT for acute lymphoblastic leukemia in 2008-2009 compared to 2007 in EMRO region as reported to EMBMT.
ALL: acute lymphoblastic leukemia, CR1: first complete remission; >CR1: beyond first complete remission. Numbers posted are absolute numbers.

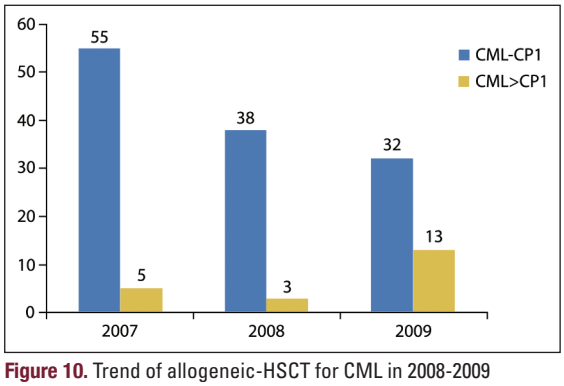

Figure 10. Trend of allogeneic-HSCT for CML in 2008-2009 compared to 2007 in EMRO region as reported to EMBMT.
CML: chronic myeloid leukemia; CP-1: first chronic phase; >CP-1: beyond first chronic phase. Numbers posted are absolute numbers.

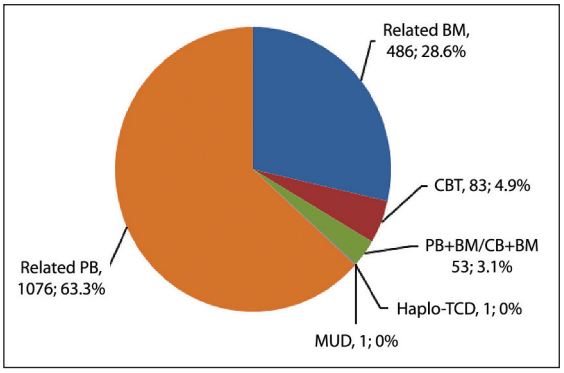

Figure 11. Proportions of Allo-HSCT sources in EMRO region as reported to EMBMT in 2008-2009.
Related PB: related peripheral blood HSCT; Related BM: related bone marrow HSCT; CBT: cord blood HSCT; PB+BM/CB+BM: peripheral blood plus bone marrow/ cord blood plus bone marrow; Haplo-TCD: haplo-identical -T cell depleted HSCT; MUD: matched unrelated donor HSCT.

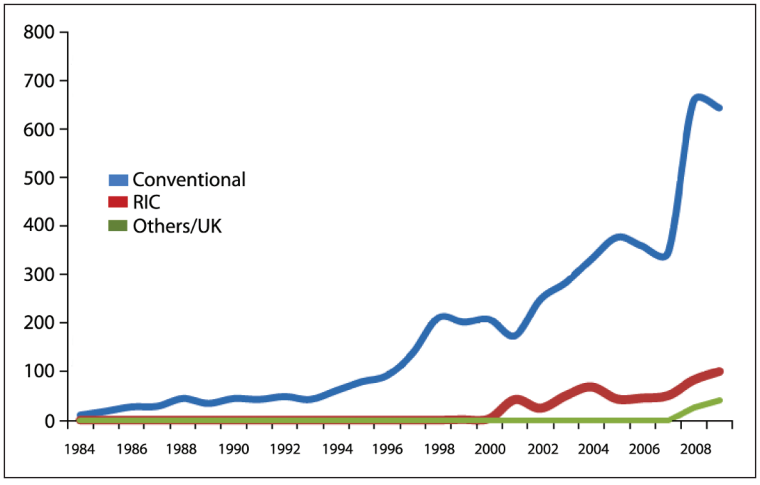

Figure 12. Trends in the use of reduced-intensity and conventional conditioning in EMRO region as reported to EM-BMT 1984-2009.
RIC: reduced conditioning regimens; UK: unknown. Numbers posted are absolute.

trends especially in the region's a relatively young population (**Figure 8**).[9,31-32] It may reflect not only tightened prioritization but also the incorporation of many prognostic and risk-stratification tools in upfront assessment of such a grave disease. Such a situation creates a sore need for further expansion with stronger support from both governmental and none governmental if such ultra-high risk cases were to be transplanted.

With the development of many comprehensive pediatric and adult programs for management of ALL patients in the region, it has become clear that many patients had been stratified upfront to receive Allo-HSCT in CR1 (10%) (**Figure 9**), which is matching in many ways the common practice as reflected in the EBMT and CIBMTR data.[33-35] This is further illustrated in the impressive lack of utilization of Auto-HSCT for ALL, which is probably based on the relatively recent results of large randomized studies showing no significant benefit of autologous SCT compared to chemotherapy in ALL patients with no donors.[35]

Two important phenomena are worth discussing in relation to CML. First, the noticeable progressive decline in the overall number and proportion of transplantation for CML patients over the last 5 years (n=103; 15% in 2006, n= 45; 5% in 2009) (**Figure 10**). Such trend was due to the positional success of TKI therapy in replacing transplantation as a first line of therapy.

This same era has witnessed also a trend of an increased ratio of transplants for accelerated and blastic crisis CML cases that reached to a peak in 2009 when nearly 30% of CML cases were advanced phase-CML compared to only 5-8% in the years 2005-2007. A recent survey by EBMT demonstrated that the number of Allo-HSCTs performed in CML patients beyond first chronic phase exceeds the number of Allo-HSCT performed in first CP.[36] Such a trend may be related to the ability of achieving a second chronic phase in some patients with the use of second generation TKI therapy without the need for intense chemotherapy induction.

The transplantation outcome in advanced phase CML patients is basically in line with earlier observations that the best long term survival results in blast crisis are achieved by allo SCT and that most long term survivors in blast crisis received an allo-HSCT, mostly in second CP.[37,38]

Benign hematologic disorders like aplastic anemia, congenital bone marrow failure syndromes and hemoglobinopathies represented the second largest group of indications in the region which contrasts very well with the temporal practice in Europe where all benign disorders represent only 8% of allotransplants,[13] compared to 35% in EMRO in 2009. For thalassemia, HSCT is probably more cost effective with worth risk-benefit ratio than chronic chelation and transfusion program in many countries in the region with very limited resources and heightened compliance issues.[15] It is mostly performed at centers where the prevalence of the disease represents a national problem, like in Egypt and Iran.[15,22] Risk stratification based on Pesaro criteria is applied by most centers to prioritize low and intermediate risk groups for transplantation.[15] In both Thalassemia and SAA, bone marrow is the preferred source of stem cells, explaining the relatively higher proportion of BM as a source of stem cells. Practices and data on inherited and acquired bone marrow failure syndromes represent one of the largest experiences that are previously published and illustrate a diverse distribution in the region.[16,39-41]

It is comforting to observe that Auto-HSCT is rising as the preferred modality in the management of multiple myelomas and lympho-proliferative disorders in spite of the relatively younger age of targeted patients and it appears to match the current world wide practices that are based on prospective studies.[42-46] This is closely similar to the EBMT[13] in myeloma (38.7% % of all auto-HSCTs in EMBMT and 43% in EBMT in 2009). However, Auto-HSCT is nearly the only modality of transplantation (97.7%) for lymphomas and myeloma in EMBMT while a significant minority (12%) underwent allo-HSCT in Europe for the same year (**Table 2, 4**).The recognizable progressive increase in the number and rate of Auto-HSCT for myeloma across the years 2007-2009 (110; 26.6%, 158; 33.6% and 187; 38.7%) is a natural product of improved performance of the teams, advancing technologies and probably also the ability to achieve meaningful remission status (VGPR or CR) with the advent of the new modalities of therapy.[42] Nonetheless, such a remarkably higher rate of Auto-HSCT would have not been attained without improved orientation about the important role of HSCT in improving outcome of such disease as outlined in recent practice guidelines.[43,44]

The trend of larger proportion of HD (27.9%) in the EMRO region compared to EBMT[13] (11%) with a completely opposite trend with NHL (19.6% vs. 32%) (**Table 2**), is largely due to the age-dependent prevalence of NHL and larger use of RIC and DLI in the West and the relatively younger population with more prevalent HD in the EMRO region. Amongst solid tumors, neuroblastoma remains the most common type treated by auto-HSCT by pediatric teams.[46] Such approach is based on important positional studies that have made auto-HSCT an important viable option for long term cure in high risk patients.[47]

Without both cost effective comparative analysis and outcome data analysis, it would be very misleading to depend only on crude data collection for decision making, especially in selecting transplantation compared to other dose- and cost- intense modalities available in the region. It would also be better to adjust for the patient mix and other clinico-biological features of transplanted patients when comparing between countries and global EMBMT data.

Numerical performance of allogeneic transplants by large centers

The current report also recognizes considerable variation amongst centers in the rate of transplants per year and per 10 million of the population, as well as in the distribution of indications. Operational factors may be

Table 4. Comparison between Trends in HSCT between EBMT and EMBMT in 2009.

	EBMT report 2009 (Europe and 6 affiliated EMRO countries)[13]	EM-BMT 2009 (including the 6 affiliated EMRO countries)
Number of teams	647	14
Countries	48	10
Average Teams/country	14	1.4
Team Density /10 M inhabitant	7.6*	0.3*
Rate of HSCT /10 M population	467	28.7
Total first Transplants	**28 033**	**1322**
Allo-HSCT	11 442 (41%)	839 (63.5%)
Auto-HSCT	16 591 (59%)	483 (36.5%)
Main indications of HSCT		
Non-malignant	5.5%	27.9%
Malignant disorders	95%	72.1%
Leukemias (% of total)	8752 (31.2%) Allo; 8022(92%) vs. Auto, 730 (8%)	426 (32.2%) Allo, 407 (95.5%) vs. Auto, 19(4.5%)
Lymphomas/myeloma	16 196 (57.7%) Allo, 1901 (12%) vs. Auto, 14 295 (88%)	427 (32.3%) Allo, 10 (2.3%) vs. Auto, 417 (97.7)%
Solid tumors	1454 (5.2%) Allo, 6% vs. Auto, 94%	42 (3.2%) Auto, 100%
Conditionings for allo-HSCT	**NA**	**791**
Conventional	61%	645 (81.5%)
Reduced intensity conditioning	39%	101 (12.8%)
Unknown/others	0%	45 (5.6%)
Stem cell source for allo-HSCT	**11 442**	**863**
Bone marrow	2 569 (22%)	254 (29.4%)
Peripheral blood	8 119 (71%)	541 (62.7%)
CBT	754 (7%)	42 (4.9%)
Donor source in allo-sources	**11 442**	**863**
Identical sibling PB/BM	4 856 (42%)	821 (95.1 %%)
Unrelated donor HSCT	5 167 (45%)	0 (0%)
Cord blood HSCT	701 (6%)	42 (4.9%)
Other family	702 (6%)	NA
Stem cell source for autologous		
Bone marrow	1%	2.6%
Peripheral blood	99%	97.4%

NA: not available; Auto: autologous HSCT; Allo: allogeneic hematopoietic SCT; *estimated based on 2009 census[26]

due to substantial variation in acceptance among centers and across years, center capacity, team size, as well as national rate and burden of diseases.[48] Shortage of well qualified transplant physicians and nurses may be an impending challenge that is underestimated and contribute significantly to such stagnation.[49]

Numerical performance in this study is meant to measure only the number of Allo-HSCTs performed by the centers in any year, although it may also be suggested by parameters including the rate of increase in the number of transplants, the increased spectrum of indications, and the diversity in the types of transplants as well as the conditioning regimens. It is clear that larger centers with >50 transplants/year (**Table 1**) have reached a plateau of their numerical performance over the last 5 years which could be attributed to the accumulated number of patients with late transplant complications without further expansion of the infrastructure. Also, the slow shift towards RIC which does not need inpatient prolonged admission has further complicated the situation. Further adjustment of the transplant rate per year per the rising population census indicates clearly that such plateau is false and the actual rate is indeed slowly decreasing, if compared to the progressive rise of the population census creating a gap between the "center" rate of allogeneic transplants and the "national' needs for transplants. Further details captured about staff resources, center facilities, center transplant bed capacity and utilization of beds by other non-transplant activities like leukemia induction should be collected for better analysis of data and use for constructing a model of improvement.[49,50]

Because the activity survey does not provide information on the outcome or the clinicopathologic features of transplanted patients or their detailed management, it would be difficult to draw quality data assessment as such. It would also be impossible to compare performance based on absolute number of transplants per center or team. However, it may help provide a platform for institutional or regional health care planning. In particular, the center-based capacity data may represent the first descriptive analysis suggesting the sore need for expanding HSCT availability either by expansion of the current centers, opening new centers or changing the module of transplant.

There are prospective and progressive endeavors in the EMBMT group to study and work on the important unmet needs in the region. Because of the relatively "prioritized" eligibility in many EMBMT countries and literally unavailability in the remaining countries of the region, it would be highly imperative for the responsible bodies and governments in the region to conduct a survey of the number of transplants performed for EMRO patients outside the region as well as those who actually needed transplants whether transplants are done or not done.

On the other hand , collecting and analyzing data on the number of centers, transplant beds, full time equivalent (FTE) transplant physician positions[47] and BMT-qualified doctors who currently do not perform transplants may help redistribute resources for optimal utilization and national cost-saving.

It has also become clear from the current and previous studies that there is a great potential for further optimization of transplant utilization by initiating cord blood bank and registry and MUD bank and registry in the region with an expected better matching opportunities and cost-benefit ratios.

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