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Trends of Hematopoietic stem cell transplantation in the Eastern Mediterranean region, 1984–2007

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Abstract

Hematopoietic stem cell transplantation (HSCT) activity was surveyed in the 9 countries in the WHO Eastern Mediterranean (EM) region that are reported to carry out transplants. Between the years of 1984 and 2007, 7933 transplants were reported. The total number of HSCT per year has continued to increase, with a plateau in allogeneic HSCT (allo-HSCT) between 2005 and 2007. Overall, a greater proportion of transplants were allogeneic HSCT (allo-HSCT) (n=5761, 77%) compared to autologous HSCT (ASCT) (n=2172, 23% ASCT). Of 5761 allo-HSCT, acute leukemia constituted the main indication (n=2124, 37%). There was a relatively high proportion of allo-HSCT for bone marrow failure (n=1001, 17%) and hemoglobinopathies (n=885, 15%). The rate of unrelated donor transplants remained low, with only 2 non-umbilical cord matched unrelated donor (MUD) allo-HSCT reported. One hundred umbilical cord (UCB) transplants were reported (0.017% of allo- HSCT). Peripheral blood stem cells (PBSC) were the main source of graft in allo-HSCT, and PBSC increasingly constitutes the main source of stem cells. Reduced intensity conditioning was utilized in 5.7% of allografts over the surveyed period. ASCT numbers continue to increase. There has been a shift in the indication for ASCT from acute leukemia to lymphoproliferative disorders (45%) followed by myeloma (26%). The survey reflects transplantation activity according to the unique health settings of this region. Notable differences

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Conflict of Interest: None declared

in transplant practices as reported to the European Group for Blood and Marrow Transplantation (EBMT) over recent years are addressed.

Keywords

Hematopoietic stem cell transplantation; EMRO; stem cell source; conditioning

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a potentially curative therapeutic modality for many hematological and, increasingly, non-hematological conditions. The last few decades have witnessed significant developments in conditioning techniques, better donor selection, and post-transplant care, all of which have contributed to improvements in outcomes¹.

Data pertaining to transplantation are captured by a number of international registries, including the European Group for Blood and Marrow Transplantation (EBMT), International Bone Marrow Transplant Registry (IBMTR), World Bone Marrow Transplant Group (WBMT), and Asia-Pacific Bone Marrow Transplant Group (APBMT), among others. In addition to informing the transplant community of outcomes, risk factors and efficacy of HSCT in given diseases, the information thus obtained also assists transplant physicians in planning the various components of transplant programs and directing research².

The East Mediterranean Blood and Marrow Transplantation (EMBMT) group was conceived in 2007 and represents the nine countries that have an active transplant program from among the 17 WHO East Mediterranean Regional Organization (EMRO) nations (Table 1)³. We have recently reported on special issues pertaining to HSCT in the region such as the prevalence of hemoglobinopathies, CMV seropositivity, prevalence of hepatitis B and resource limitations. The report also provided a regional overview of economic status in terms of GNI, transplant rates and team density⁴. In this report, we present a survey of HSCT activity pertaining to allo-HSCT and ASCT activity as reported to the EMBMT. A comparison was also made between transplant practices in the EMBMT survey for 2007 and HSCT activity reported to the EBMT for the same year

Methods

The participating centers were identified by means of a database that was established following initial meetings between teams. An active program was identified as one that consistently carried out 5 cases per year for at least 3 consecutive years. The EMBMT holds a directory of participating centers, with the names and addresses of participating centers and named transplant physicians with their contact details. Countries with an active transplant program were Egypt, Iran, Jordan, Lebanon, Morocco, Oman, Pakistan, Saudi Arabia (KSA), and Tunisia.

An electronic data capture sheet was sent via email to each of these members where the following fields of information were sought for allo-HSCT and ASCT transplants: indication of transplant (including stage of disease); conditioning in allo-HSCT HSCT (conventional vs. RIC); source of stem cells (Related BM vs. Related PBSC vs. Cord vs. MUD).

The data was sought for each year since the inception of the respective transplant program. For transplant by indication, only the first transplant was reported to avoid re-reporting.

Data from different participating centers within a country was aggregated to present national data. The data was tabulated at the office of the EMBMT. No remuneration was offered to participating centers. The European Bone Marrow Transplant (EBMT) Group Activity Survey was utilized as a template for analysis of the activity data and supplementary data was obtained from EBMT as needed. The reported data was also matched with submitted data for the Center for International Blood and Marrow Transplant Research (CIBMTR) for CIBMTR reporting centers. A comparison was also made between transplant practices in the EMBMT survey for 2007 and HSCT activity reported to the EBMT for the same year.

RESULTS

OVERALL TRANSPLANT ACTIVITY

Countries identified with an active transplant program were Egypt, Iran, Jordan, Lebanon, Morocco, Oman, Pakistan, Saudi Arabia (KSA), and Tunisia. Of 17 active teams in 9 countries, completed data capture sheets were received from all except 2 teams (Makassed General Hospital, Lebanon and Bismilah Taqi Institute, Pakistan). Information on the type of conditioning was not available from two countries (Tunisia, Iran). Information on the source of stem cells was incomplete from two countries (Pakistan, Tunisia).

A total of 7933 first transplants were reported between the periods of 1984–2007, of which 2172 (27%) were ASCT and 5761 (73%) were allo-HSCT transplants (Table 1). There was an increase in overall transplant activity from 12 transplants in 1984 to 1097 in 2007 (Figure 1). Over the survey period the mean year-on-year increase in transplant activity was 24%, with a significant increase in activity in the period 1996–2007.

ALLOGENEIC TRANSPLANTATION

A total of 5761 allo-HSCT procedures were carried out, starting with 12 in 1984 to 684 per year in 2007. Except for Morocco, where all reported transplants were ASCT, and Tunisia, where 50% of transplants were ASCT, in the remaining countries the majority of the transplants were allo-HSCT (Fig 2). There was significant variation in total allo-SCT number between countries and in the increase in numbers over the 24 year period (Table 1, Figure 3). Over 2005–2007, overall allo-HSCT numbers showed a plateau, though numbers in Iran and Pakistan continue to rise.

Indication for Allogeneic Transplantation—Of the 5761 allo-HSCT, a major indication was acute leukaemia (n=2124, 36.8%) (Table 3). Acute myeloid leukemia (AML) accounted for 1260 (21%) allo-HSCTs with 924 transplants in 1st complete remission (CR1) (16%), and 336 (5%) beyond CR1. Acute lymphoblastic leukemia (ALL) in all stages accounted for 864 (15%) allo-HSCT. Other major indications were bone marrow failure (BMF), both congenital and acquired, (n=1001, 17%), followed by chronic myeloid leukemia (CML) in both chronic phase and beyond (n=948, 16%). There was a recent reduction in allo-HSCT for CML (Figure 5). There was a large proportion of patients who received transplants for hemoglobinopathies (n=885, 15%), especially in Iran and Egypt that both have a high carrier rate of B-thalassemia^{7, 12}. Other diagnoses were the indication for allo-HSCT in the remaining 15% of reported cases, and indications remained relatively stable (Figure 4).

Conditioning Regimes—Conditioning information was sought for all allo-HSCTs. Of the 8 countries performing allo-HSCT transplants, data were returned from 5. Of all 5761 allo-HSCT, 3483 (60.4%) were carried out with conventional conditioning regimes, 333 (5.7%) utilized RIC was utilized. Conditioning regime was unknown in 1945 (33.7%) allografts.

RIC transplants, though not carried out prior to 1999, are being carried out increasingly and accounted for conditioning in 51 transplants in 2007 (Figure 6). Over the survey period, the mean annual proportion of RIC HSCT was 13.4% of allo-HSCTs where conditioning information was available.

Stem Cell Source—The main source of stem cells was peripheral blood (PB) (2688 allo-HSCTs, 47%) followed by bone marrow (BM) (2523 allo-HSCTs, 44%). There was a shift from BM to PBSC especially in the years after 2000 (Figure 7). There were variations between countries in the use of BM vs. PBSC. In KSA, related BM was used in 1815 (86%) of allo-HSCT over the surveyed period, while in Egypt, BM was the source in only 31 (3%), with PBSC being used in 97% of allo-HSCT. In the other countries surveyed, PB was used more frequently than BM.

Umbilical cord blood (UCB) transplantations were first carried out in the region in 1998. Overall, 100 transplants (2% of allografts) have been carried out with UCB as a source of stem cell. There were 6 co-infusions of BM with PB (5/6) and UCB (1/6). Only two (0.003%) non-UCB matched unrelated donor (MUD) allo-SCTs were reported to have been performed.

AUTOLOGOUS TRANSPLANTATION

A total of 2172 ASCT procedures were carried out in the period 1985–2007. There was an increase in procedures from 1 in 1985 to 413 in 2007 with a continuing increase in transplant procedures year on year. There was a 25% increase in ASCT activity from 2006 to 2007 (Figure 1).

Indication for Autologous transplantation—Of the 2172 total ASCT, the main indications were myeloma (n=55, 26%), Hodgkin's lymphoma (n=539, 25%), non-Hodgkin's Lymphoma (n=451, 20%), and AML in CR1 (n=261, 12%), with other indications comprising the remaining 35% of ASCTs (Table 4). There was a reduction in the proportion of ASCTs carried out for acute leukemia and myelodysplasia from a median of 70.5% (range 50–100%) in the years 1988–1996, to 21% (10–46%) in the years 1997–2007 (Figure 8).

A total of 32 ASCTs were carried out between the years of 1996 and 2001 for breast cancer; none were reported for this indication after 2001. ASCT procedures were carried out in a total of 134 (6%) cases for other non-haematological malignancies.

Stem Cell Source—Peripheral blood was the main source of stem cells in 1875 (86%) ASCTs; bone marrow accounted for 223 (10%), and in 11 (1%) both PBSC and BM stem cells were infused. The source of stem cells was not known in 65 (3%) ASCTs.

DISCUSSION

This is the activity first survey of the EMBMT, which presents the analysis of transplant activity in the WHO EMRO region between the years 1984–2007. Individual country reports have previously been published highlighting unique HSCT settings¹². The data here illustrate the increasing transplant activity in the region over the years and the trends in indication for HSCT, both allo-HSCT and ASCT, conditioning regimes and sources of stem cells.

The overall number of transplants in the EMRO region of 7984 allo-HSCT and ASCT transplants over a span of 24 years is significantly lower as a cumulative number compared to annual numbers in Western Europe over a single year. In 2003, 17020 first HSCTs were

carried out in 15 Western European countries with a population of 381 million, equating to 446 HSCT per 10 million population¹³. In comparison, in the 9 EMBMT countries with a collective population of 367 million in the same year¹⁴, 704 HSCTs were carried out, or 19 per 10 million population. However, transplant numbers, especially ASCT, in the region continue to increase at a steady rate and have yet to plateau, though transplant rates remain low⁴.

Factors that may contribute to differences in HSCT activity have been elucidated^{15–16}. Allo-HSCT is an expensive procedure and various factors can affect total cost¹⁷. Gross national income, team density and healthcare expenditure have been shown to have an impact on transplant numbers¹⁸.

Though there appears to be a degree of correlation between GNI and SCT per 10 million inhabitants, this does not always hold true, and various other unexplained factors are likely contribute to a higher or lower than expected HSCT rate in any given country (Figure 9). There may be a number of reasons for discrepancies in transplant rates in countries with similar GNI, including infrastructure and sociopolitical factors^{15, 19}. Data for patients referred overseas for HSCT were not available for the purposes of the study, though such referral practices may go some way in fulfilling transplant requirements, especially in the few countries with higher GNI.

Allo-HSCT vs. ASCT

There has been a steady increase in the number of allo-HSCT transplants being performed with a mean year-on-year rise of 20%. There was no significant overall increase over the period 2005–07, possibly as a reflection of the saturation of available services or other local factors.

The majority (73%) of all transplant procedures over the survey period were allo-HSCT, and this was true for each year surveyed (mean 74%, range 63% to 100%). In 2007, 63% of procedures were allo-HSCT, representing a gradual trend towards an increase in the proportion of ASCT transplants. This is in contrast to activity reported from EBMT, where in 2007 ASCTs comprised the majority of transplant activity with 15491 (61%) ASCTs vs. 10072 (39%) allo-SCTs²⁰. Data from the United States as reported to CIBMTR also demonstrate an excess of ASCT over allo-HSCT²¹. A possible explanation for the excess allo-HSCTs may be that the Eastern Mediterranean region consists of communities of large families with high population growth, which certainly increases the likelihood of finding a full matched sibling donor. Demographic information of the transplanted population in the EMRO region would be required to investigate this regional difference further.

Consistent with practices worldwide, there have been no ASCTs for breast cancer following 2001, after studies failed to show a survival benefit in these patients^{22–23}.

Indications and Diseases

The main indications for allo-HSCT remain acute leukemias and bone marrow failure syndromes. In 2007, allo-HSCT for bone marrow failure syndromes was proportionally a more common indication for HSCT in the EMBMT data (n=106, 15% of allo-HSCT) as compared to EBMT data (n=523, 5%)²⁰. Whether this is due to differences in the incidence of diseases or other causes remains to be determined, though data on large cohorts of patients with inherited BMF in the Middle East have been published²⁴.

In our survey, hemoglobinopathies were the indication for allogeneic HSCT in 874 cases, comprising 15.2 % of all allo-HSCT. There was considerable variability in the proportion transplanted for this indication. In both Iran and Pakistan, hemoglobinopathies were the

indication for allo-HSCT in 30% of all transplants, and their respective experience has been reported^{25, 26}. In 2007, 102 of 684 (14.9%) transplants were carried out in the EM region for this indication. In contrast, this was an indication in only 2.7 % of transplants reported to EBMT in 2007 (Table 2)²⁰.

There has been a worldwide decline in the use of HSCT for the treatment of CML in first chronic phase (CP1) with the advent of imatinib mesylate^{21, 27, 28}. While this recent reduction is observed in our survey, it is noteworthy that CML still constituted an indication for allo-HSCTs in 8.7% (n=60) cases in 2007 compared to 0.4% for 2007 in the EBMT survey for that year²⁰. This may be partly due to limited access to tyrosine kinase inhibitors in some countries, but may also reflect demographic differences that were not included in this activity survey.

Stem cell source trends

The trend towards increased use of PBSC in both allo-HSCT and ASCT is consistent with practice as reported by the National Marrow Donor Program (NMDP) and EBMT activity surveys^{29, 30}. In our survey, in 2007, 65% of all allo-HSCT were PB derived, followed by related BM (25%) and UCB (4%). PBSC are logistically less burdensome to procure and entail a lower likelihood of complications for donors, obviating the need for general anesthesia. The increasing trend has not been influenced by evidence to suggest a higher incidence of GVHD³¹⁻³³.

While there has been an increase in the use of cord blood as a stem cell source - a trend observed in Europe³⁴ - and while there are established cord banks in the region, these provide a source of stem cells in only a minority (2%) of transplants (Figure 7). Unrelated donor transplants are exceedingly uncommon in the EMBMT region and only 2 non-umbilical cord matched unrelated donor transplants have been reported. This is in marked contrast to data reported to the EBMT, where in 2007, 4752 HSCT (47%) were carried out with an unrelated donor source (Table 2). Larger family sizes and the higher probability of finding an HLA-matched sibling donor; the possibility of a parent being a match due to consanguinity and inter-marriage and the availability of HLA-matched non-sibling related donors all contribute to reducing the need for a UCB or MUD transplant⁴.

Conditioning trends

Though complete data pertaining to conditioning were lacking, most of the reported allo-HSCTs were carried out with conventional conditioning, with RIC being used in no more than 20% of transplants in any given year. In contrast, the EBMT survey demonstrated that RIC was utilized in 36% of all allo-HSCT HSCT in 2007, and has been reported to be as high as 71% in some European countries^{20,28}. The increase RIC HSCT in our survey in the years between 1999 and 2001 corresponds temporally to a similar rise in this practice as reported to EBMT, though the numbers in our survey are smaller. Data regarding the indications for RIC transplants per se were not requested in our survey. Further studies including demographic information regarding the age and/or comorbidities of patients may help in elucidating the reason for this discrepancy between EBMT and EMBMT data with regards RIC allo-SCT. The disparity may also be a reflection of the differences in proportions of indications for HSCT in the registries.

CONCLUSIONS

This report demonstrates the unique transplantation needs and activity for a region where transplant numbers continue to rise. We also demonstrate that there is a marked difference in transplantation indications as reported to EMBMT as compared to with data reported to

EBMT with relatively larger proportions of SCTs being carried out for hemoglobinopathies and bone marrow failure syndromes in the former. Further retrospective studies focusing on these conditions may be a valuable contribution of the EMBMT to the international HSCT community. A further contrast requiring study is the higher proportion of allo-HSCT vs. ASCT, and reduced utilization of alternate donors and of RIC transplants, although data for the latter was incomplete. The current survey did not study patient demographics or outcomes, as these data were not sought for the purposes of this activity survey. It is important to note that given that a number of countries comprising the EMBMT report to EBMT (Iran, KSA, Lebanon, Tunisia) and CIBMTR (Egypt, Iran, Pakistan Saudi Arabia) in 2007, differences in HSCT activity between the registries, while reflecting regional differences, represent data as made available to the registries.

The increasing rates of transplant will require adequate planning for resources in the future; not least with regards ensuring that there is adequate numbers of transplant physicians and nurses to deal with increasing transplant demands³⁵.

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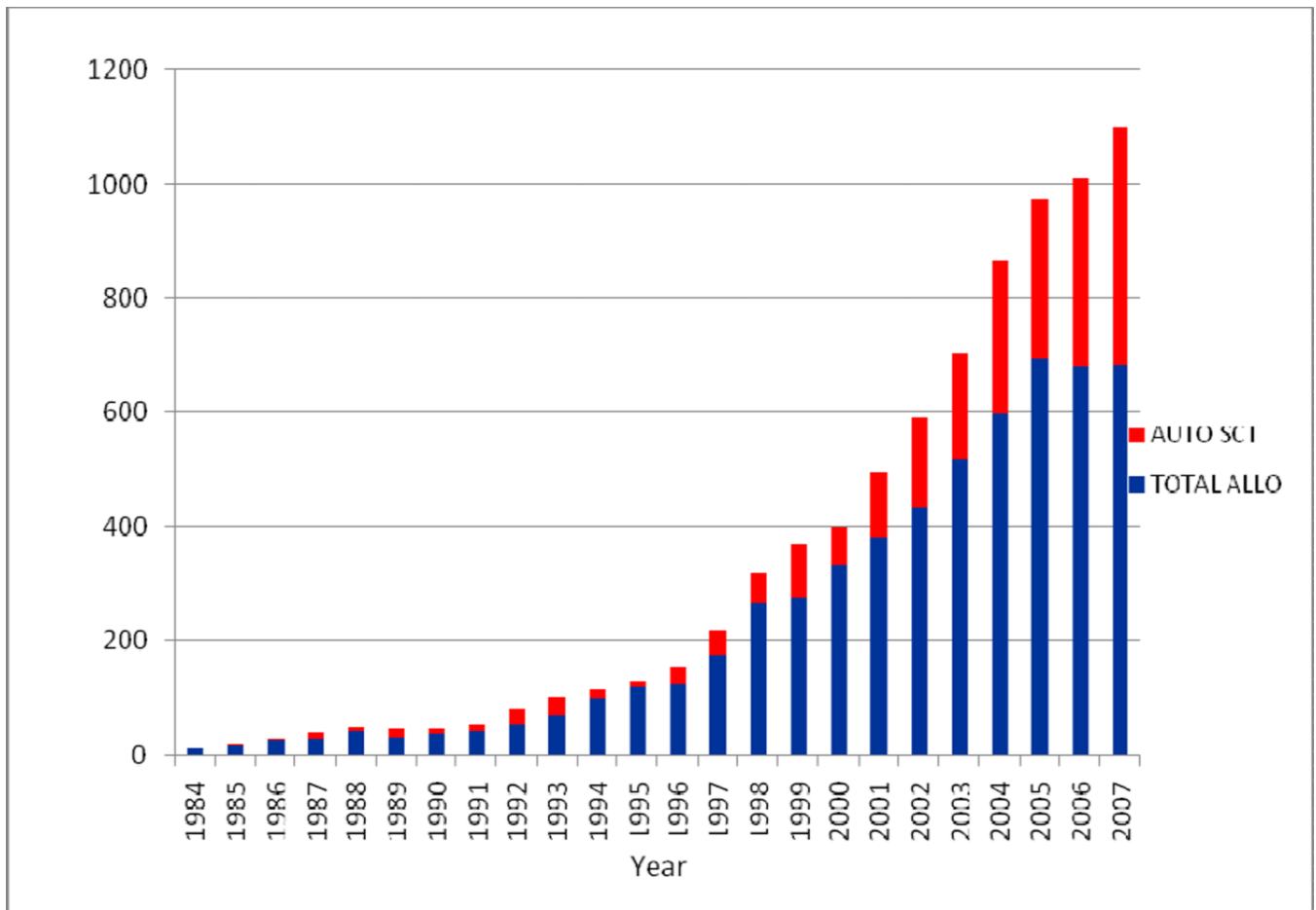


Figure 1.

Trends in total numbers of autologous and allogeneic transplant procedures 1984–2007

Abbreviations: Auto SCT= autologous hematopoietic stem cell transplantation; allo = allogeneic hematopoietic stem cell transplantation

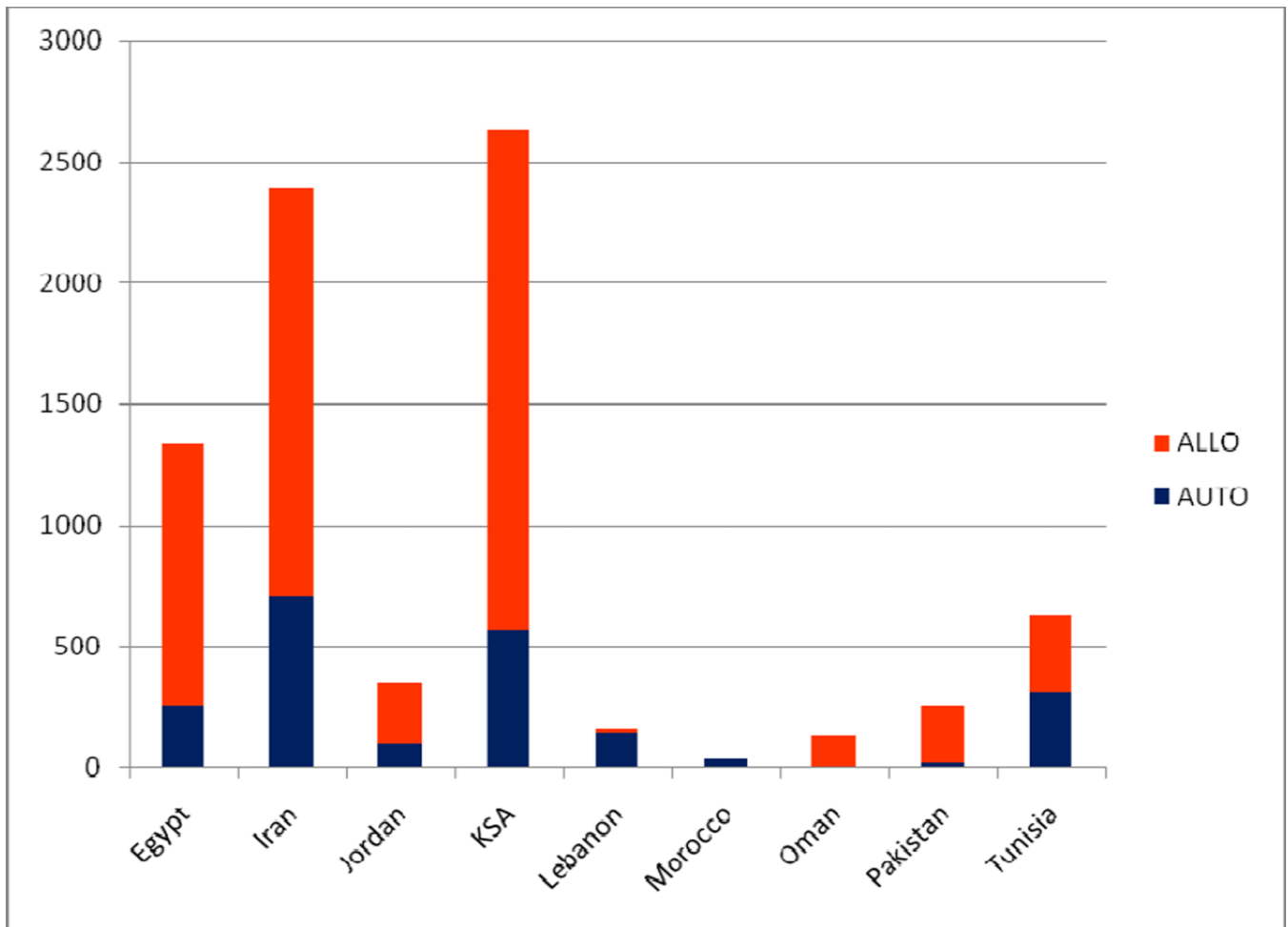


Figure 2.
Overall autologous and allogeneic hematopoietic stem cell transplant numbers 1984–2007
by country.
Abbreviations: KSA= Kingdom of Saudi Arabia

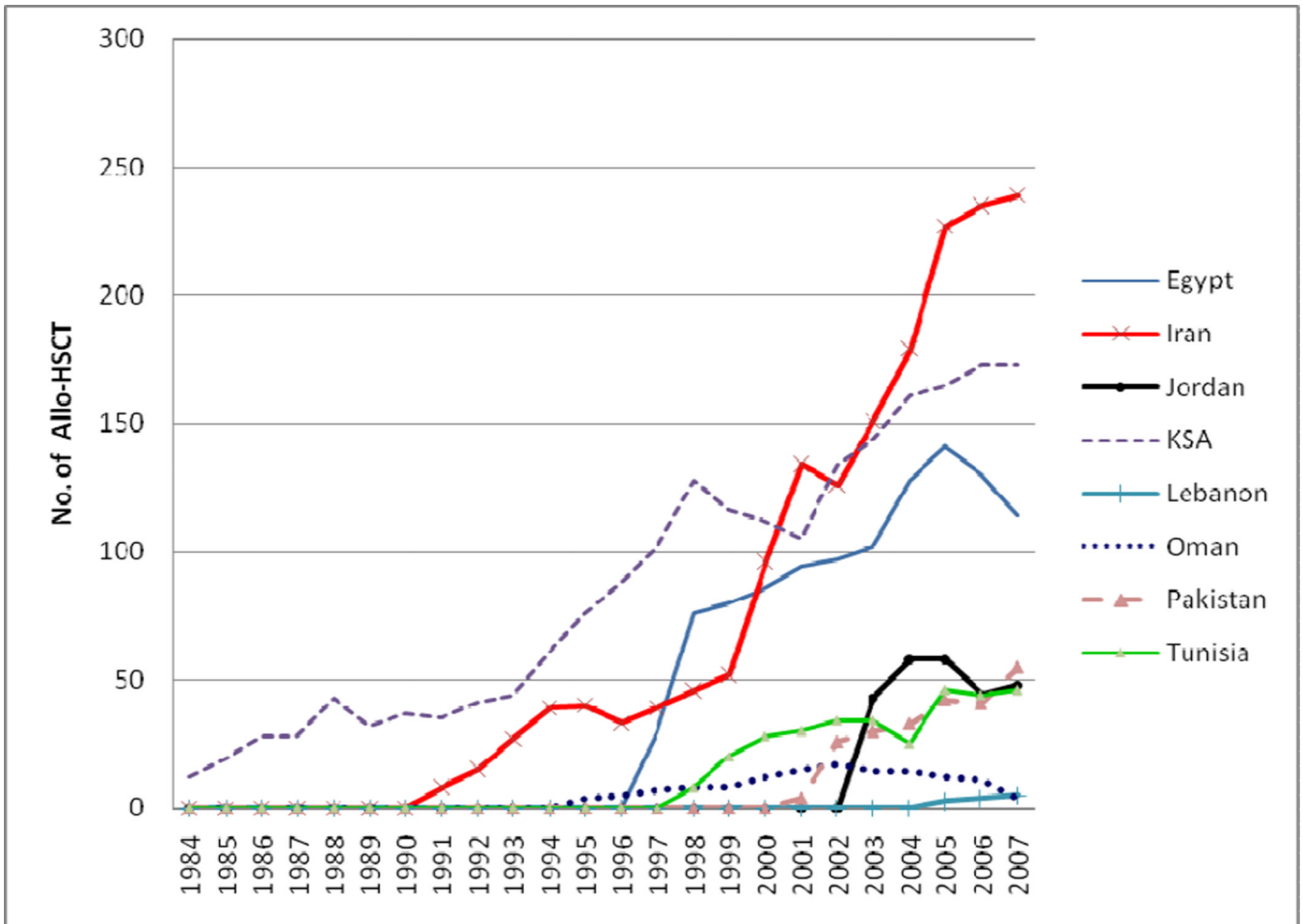


Figure 3. Trends in total numbers first allo-HSCT activity 1984–2007 by country reported to EMBMT
Abbreviations: KSA= Kingdom of Saudi Arabia

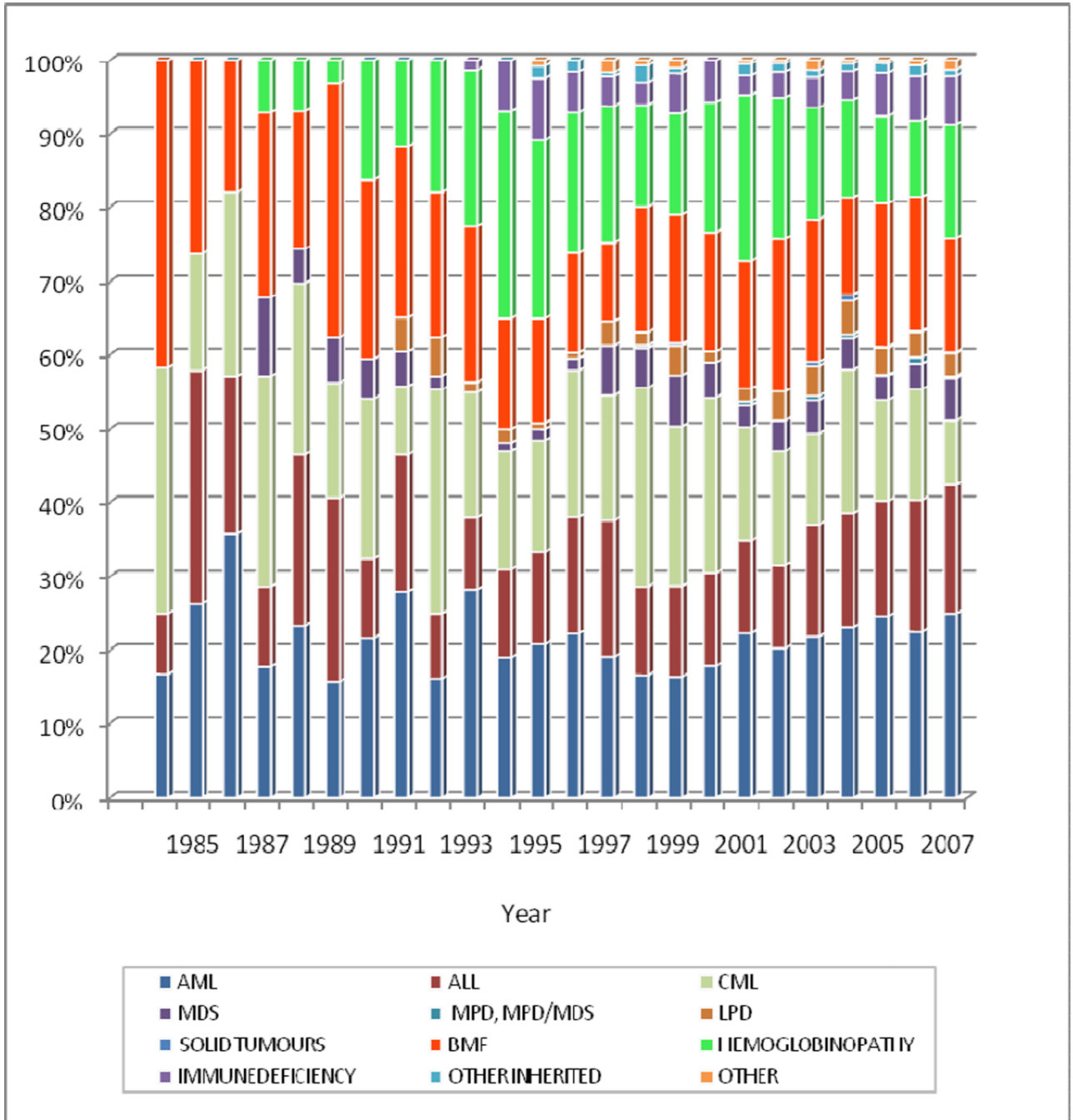


Figure 4. Trends in Allo- HSCT in EM region by disease indication 1984–2007, expressed as percentage of annual transplants. Abbreviations: AML= acute myeloid leukemia; ALL=acute lymphoblastic leukemia; CML= chronic myeloid leukemia; MDS=myelodysplasia; MPD= myeloproliferative disorder; LPD= lymphoproliferative disorders; BMF=bone marrow failure

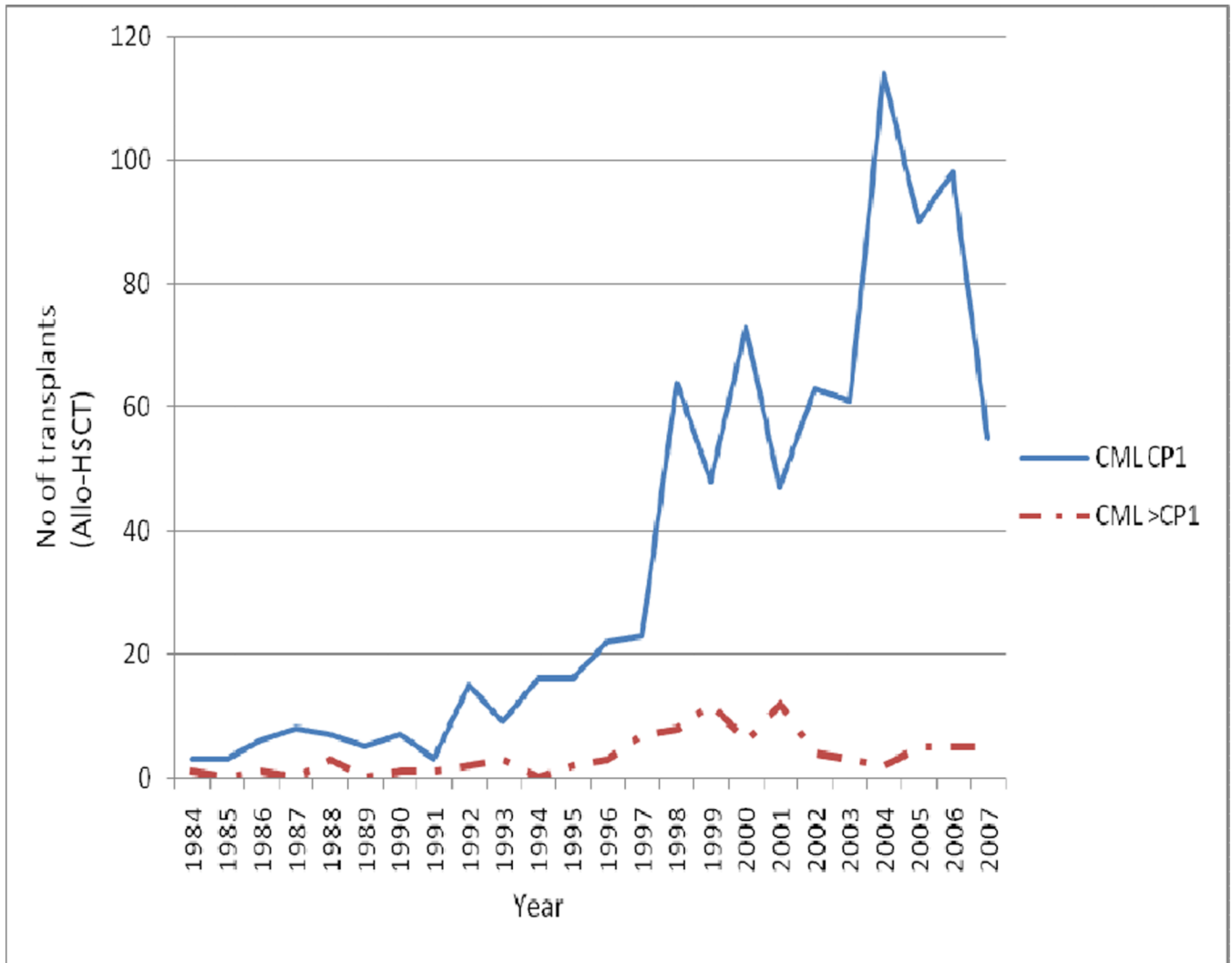


Figure 5.
Trends in Allo- HSCT for CML in 1st chronic phase (CP1) and beyond (>CP1).

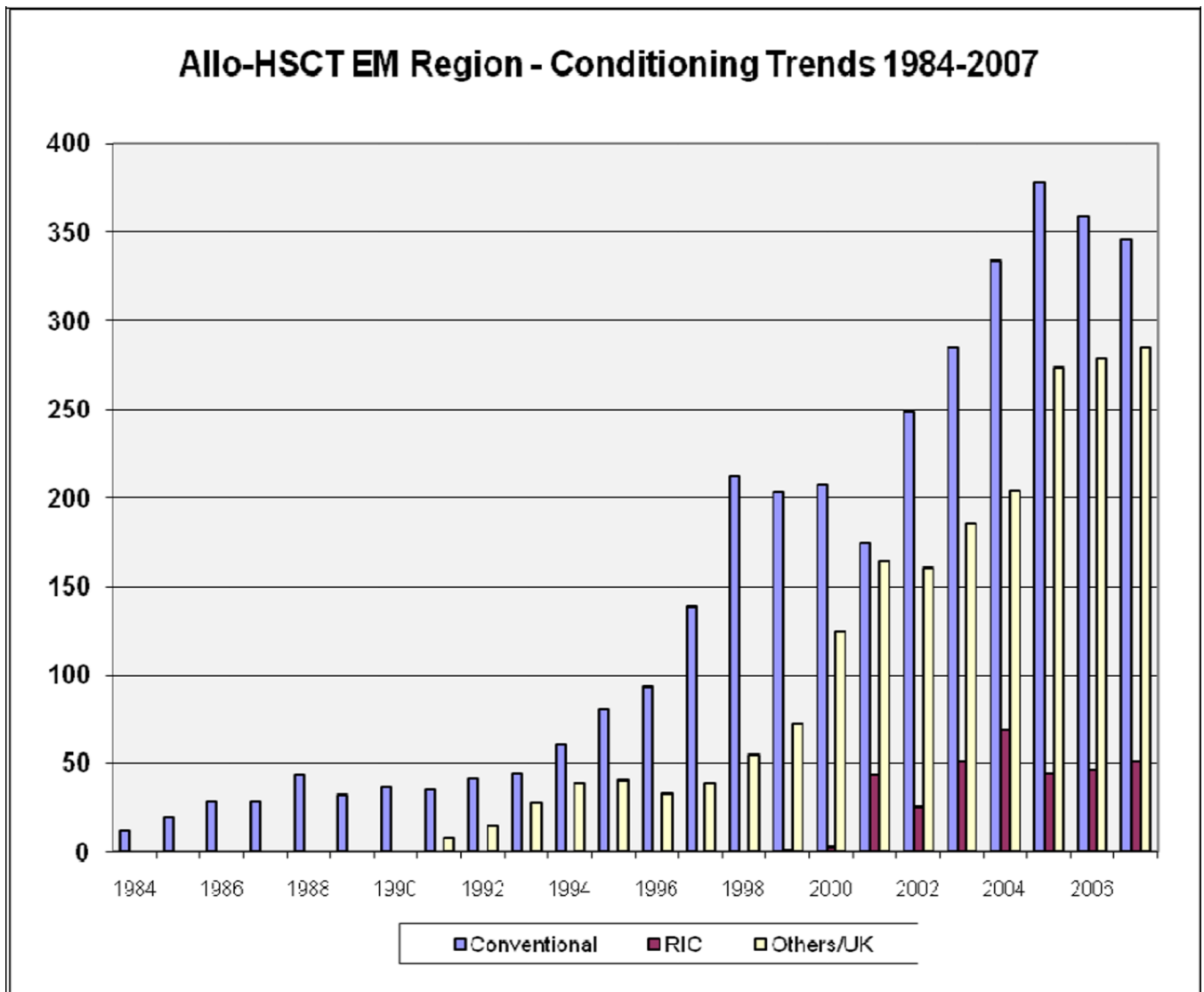


Figure 6.
 Total numbers of allo-HSCT by conditioning.
 Abbreviations: RIC=reduced intensity conditioning; UK=unknown

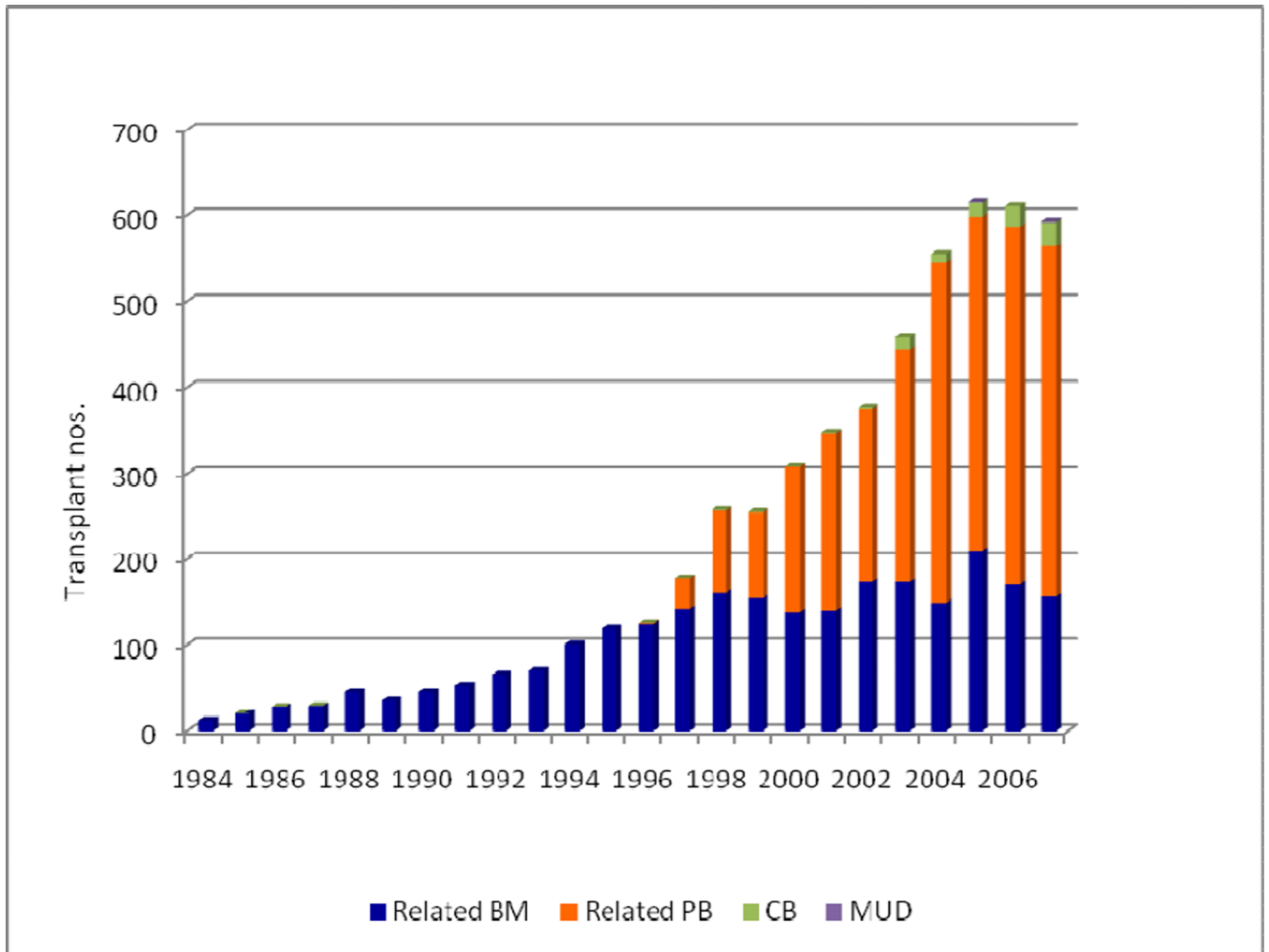


Figure 7.

Trends in stem cell source for allo-HSCT 1984–2007.

Abbreviations: BM=bone marrow; PB=peripheral blood; CB= cord blood; MUD= matched unrelated donor

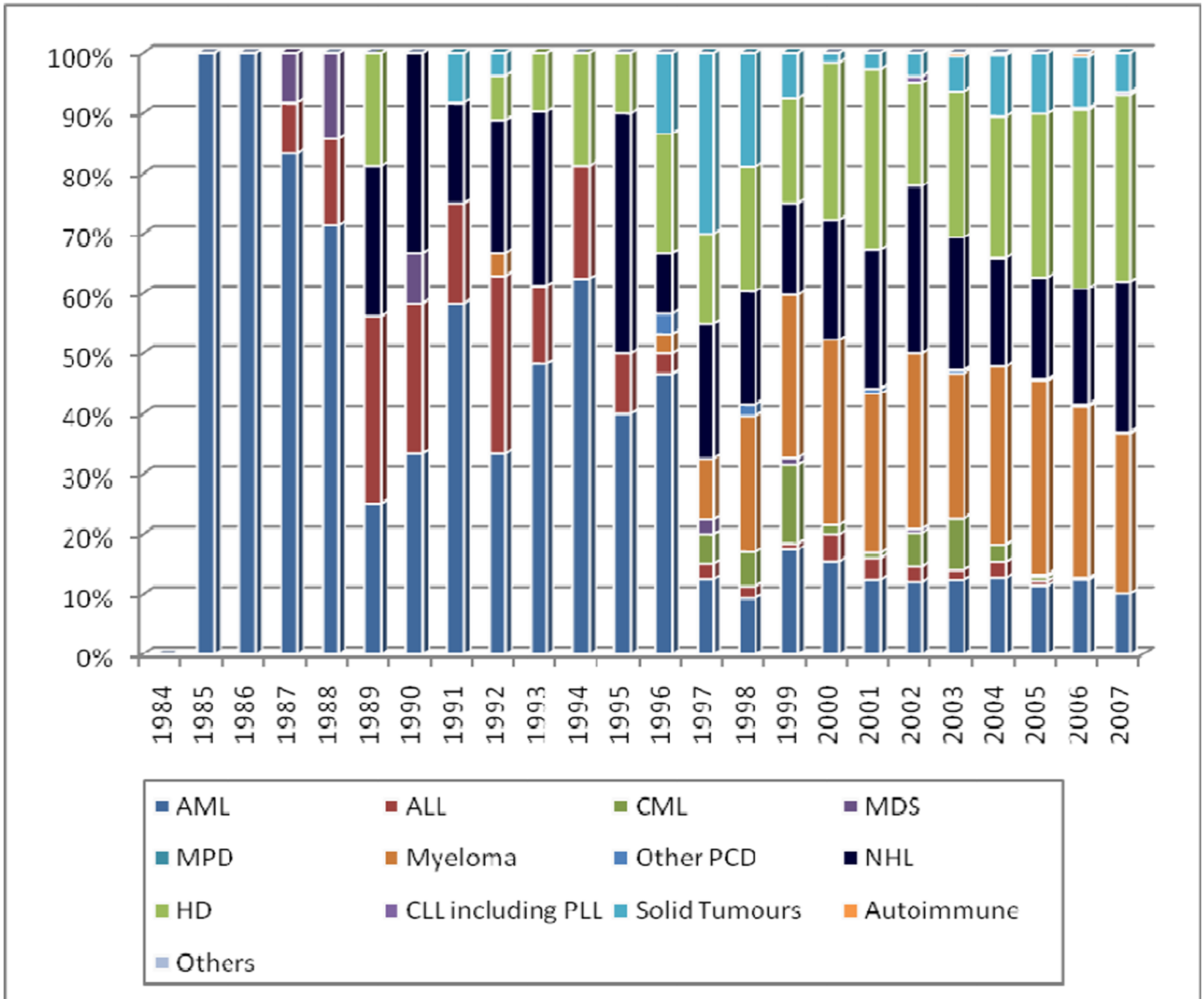


Figure 8.

Trends in autologous HSCT in EM region by disease indication 1984–2007, expressed as percentage of annual transplants.

Abbreviations: (Abbreviations: AML= acute myeloid leukemia; ALL=acute lymphoblastic leukemia; CML= chronic myeloid leukemia; MDS=myelodysplasia; MPD= myeloproliferative disorder; PCD= plasma cell disorders; NHL=non-Hodgkins lymphoma; HD=Hodgkin’s disease; CLL=chronic lymphocytic leukemia; PLL=prolymphocytic leukemia)

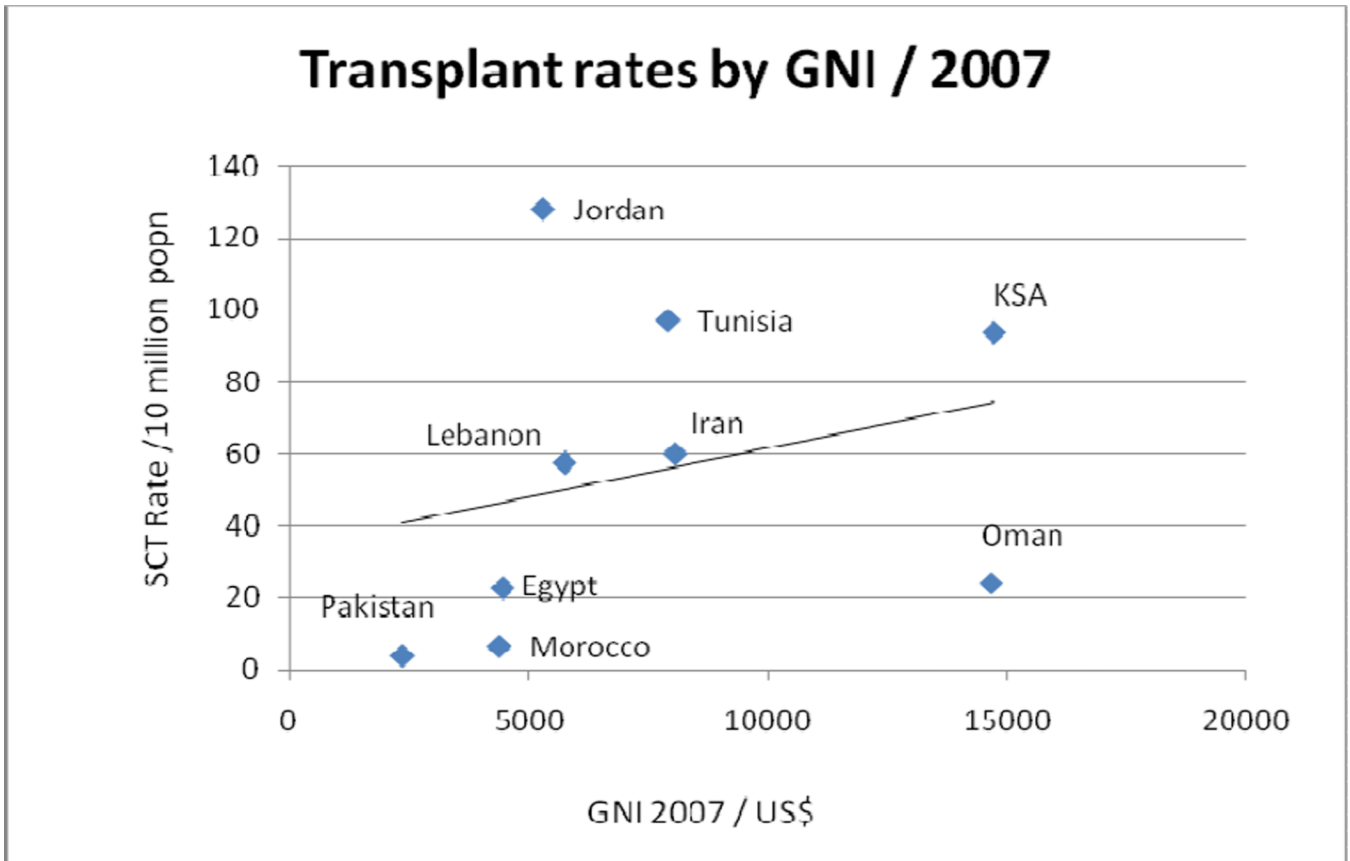


Figure 9.

Correlation of gross national income (US\$) per capita in 2007 of countries reporting to EMBMT against transplant rates

Abbreviations: SCT=stem cell transplant; GNI=gross national income; KSA=Kingdom of Saudi Arabia

Table 1

Overall transplant activity in countries of the Eastern Mediterranean region that reported to EMBMT.

Country*	Age of Program (yrs)		No. of procedures		All HSCT
	ASCT	Allo-HSCT	ASCT	Allo-HSCT	
Egypt	10	10	259	1078	1337
Iran	16	16	705	1686	2391
Jordan	4	4	101	251	352
KSA	21	22	572	2057	2629
Lebanon	9	2	147	12	159
Morocco	3	NA	38	0	38
Oman	3	12	7	131	138
Pakistan	6	6	26	231	257
Tunisia	8	19	317	315	632
Total no. of transplants :			2172	5761	7933

* EMRO countries that do not have a transplant program, or which were not reported to the EMBMT to have performed 5 HSCT for 3 years were: Afghanistan, Bahrain, Djibouti, Iraq, Kuwait, Libya, Qatar, Somalia, Sudan, Syria, United Arab Emirates, Yemen.

Abbreviations: ASCT= autologous hematopoietic stem cell transplantation; allo-HSCT = allogeneic hematopoietic stem cell transplantation; KSA= Kingdom of Saudi Arabia

Table 2

Comparison of HSCT activity reported to EMBMT and EBMT for 2007

	EMBMT -2007 activity	EBMT – 2007 activity
Total 1 st Transplants in 2007	1097	25563
Population of reporting countries *	383 million	988 million **
Teams	17	613
Allo vs auto (%)	684 vs 413 (63 vs 37)	10072 vs 15491 (39 vs 71)
1 st Transplants in 2006 vs 2007	1012 vs 1097	25050 vs 25563
• % increase	8%	2%
• ASCT '06 vs '07 (% rise)	330 vs 413 (25%)	15389 vs 15491 (1%)
• Allo-HSCT '06 vs '07 (% rise)	682 vs 684 (0.2%)	9661 vs 10072 (4%)
Indications, Allo n (% of allo)		
• Acute leukemia	289 (42%)	5050 (50%)
• CML	60 (8.7%)	434 (0.4%)
• BMF - all	106 (15.5%)	523 (5.2%)
• Hemoglobinopathy	102 (15%)	254 (2.5%)
• Others		
Indications – Auto n(% of ASCT)		
• Myeloma	110 (26.6%)	6234 (40%)
• HD	128 (30.9%)	1830 (11.8%)
• NHL	103(24.9%)	4639 (29.9%)
• Solid tumours	27 (6.5%)	1425 (9.2%)
Conditioning Allo-HSCT (includes 2 nd transplants)		
Conventional %	347/684 (50.7%)	64%
RIC %	51/684 (7.4%)	36%
Unknown	286/684 (41.8%)	
Stem cell source % allo n=683)		
BM-related	156 (24.8%)	1382 (13.7%)
PB related	408 (64.8%)	3889 (38.6%)
Cord	28 (4.4%)	585 (6%)
MUD – non-cord	1 (0.1%)	4216 (42%)
Unknown	54 (7.9%)	

* Countries that reported to both registries for the year include Iran, Saudi Arabia, Tunisia,,and Lebanon.

** Includes 106 million population from Iran, Saudi Arabia, Tunisia,,and Lebanon.

Abbreviations: (Abbreviations: CML= chronic myeloid leukemia; BMF= bone marrow failure; NHL=non-Hodgkins lymphoma; HD=Hodgkin's disease; BM=bone marrow; PB=peripheral blood; MUD= matched unrelated donor; RIC=reduced intensity conditioning)