

# TRAPIANTO ALLOGENICO E AUTOLOGO SU PAZIENTI EMATOLOGICI

## Il trapianto di cellule staminali emopoietiche, rappresenta in casi selezionati, l'atto conclusivo di un complesso percorso terapeutico in pazienti in terapia oncologica.

Il midollo osseo è un tessuto spugnoso contenuto all'interno delle ossa, in prevalenza di quelle piatte e corte, che ha la funzione di produrre tutte le cellule del sangue e precisamente i globuli rossi senza i quali l'ossigeno non arriva dai polmoni ai vari organi, le piastrine necessarie alla coagulazione del sangue e i globuli bianchi detentori della immunità che ci difende da quanto è estraneo al nostro organismo e in particolare dalle infezioni e dai tumori.

Tutte queste cellule derivano da una sola, chiamata cellula staminale emopoietica che, attraverso successive e ripetute divisioni, dà luogo alle cellule mature prima ricordate e cioè ai globuli rossi, ai globuli bianchi e alle piastrine. Queste cellule staminali sono contenute in prevalenza nell'interno del midollo osseo, ma sono presenti anche nel sangue periferico e nel sangue del cordone ombelicale al momento della nascita.

La tecnica del trapianto consiste nell'asportare e conservare in modo adeguato tali cellule, quindi reinfonderle al malato al momento opportuno; in altre parole il cosiddetto trapianto di midollo osseo è in realtà un trapianto di cellule staminali emopoietiche totipotenti che abitualmente sono estratte dal midollo osseo ma che possono essere recuperate anche dal sangue periferico e dal cordone ombelicale. Deriva da quanto detto, che è più esatto il termine "trapianto di cellule staminali emopoietiche" che non quello di "trapianto di midollo osseo".

Le cellule staminali di cui sopra si reinfondono al paziente allo stesso modo di una trasfusione di sangue e hanno la meravigliosa capacità di raggiungere attraverso la circolazione del sangue gli spazi midollari dove sistemarsi, accasarsi (homing) e ricostruire il midollo osseo. Appare chiaro a questo punto che gli spazi dove queste cellule nuove si devono "accasare" devono essere vuoti e quindi è necessario che prima di reinfonderle, il midollo del malato sia stato svuotato del suo contenuto cellulare, sia stato cioè distrutto da un trattamento chemioterapia e/o radioterapico che va sotto il nome di "condizionamento". Si tratta di una terapia molto aggressiva, che rappresenta il primo dei rischi e delle difficoltà che il malato che viene trapiantato deve affrontare ma che abitualmente supera facilmente.

La chemioradioterapia di condizionamento non serve solo per fornire lo spazio midollare necessario all'impianto e allo sviluppo delle cellule staminali emopoietiche normali trapiantate ma anche a distruggere le cellule anormali responsabili della malattia.

Le malattie, abitualmente mortali in passato, che traggono beneficio dalla strategia terapeutica trapiantologica, ottenendo la guarigione in una percentuale variabile a seconda del tipo di malattia e dell'età del paziente dal 30% al 90% sono:

malattie neoplastiche del sangue rappresentate da:

- Leucemia acuta mieloide e linfocitica
- Leucemia cronica mieloide
- Sindromi mielodisplastiche (leucemia refrattaria con eccesso di blasti; leucemia refrattaria con eccesso di blasti in trasformazione, leucemia acuta mieloide secondaria)
- Disturbi linfoproliferativi (leucemia linfatica cronica, linfomi non di Hodgkin, linfomi di Hodgkin, mieloma multiplo).

malattie da immunodeficienza o da errori congeniti e precisamente

- Sindrome da immunodeficienza severa (SCID = Severe Immunodeficiency Disease)
- Leucemia aplastica severa
- Talassemia o anemia mediterranea
- Anemia di Fanconi e anemia di Brockman – Diamond
- Errori congeniti del metabolismo
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La novità degli ultimi anni è però rappresentata dall'applicazione di tale strategia terapeutica a tumori non del sangue ma di altri organi, i cosiddetti tumori solidi e principalmente a quelli della mammella, dell'ovaio, del testicolo, al neuroblastoma, al tumore a piccole cellule del polmone ecc. Queste neoplasie che non intaccano abitualmente il midollo osseo sono molto sensibili alla chemioterapia e possono quindi essere trattate con dosi molto alte, la cosiddetta terapia sovramassimale che di solito è molto efficace, ma sfortunatamente non distinguendo tra cellule normali e cancerose non distrugge solo le cellule del cancro ma anche molte di quelle normali, comprese le cellule del midollo osseo; solo provvedendo a rimpiazzare il midollo osseo con il trapianto, il paziente può ricevere queste grandi ed efficaci dosi di terapia, altrimenti mortali. Particolarmente estesa ed interessante la casistica riguardante il carcinoma della mammella, soprattutto negli Stati Uniti d'America, ma ormai anche in Europa. 1 paziente che è opportuno sottoporre a tale trattamento sono quelli dal II stadio in su e i risultati sono davvero incoraggianti in quanto la

sopravvivenza libera da malattia a lunga scadenza (6 anni e oltre) raggiunge il 60% nel II stadio, il 50% nel III stadio e nell'infiammatorio, attestandosi intorno al 20% nel IV.

Infine, si è visto che il trapianto autologo di cellule staminali emopoietiche dà risultati esaltanti anche in malattie autoimmuni a grave prognosi quali il lupus erimatoso sistemico (LES) o fortemente invalidanti quali l'artrite reumatoide e la sclerosi multipla. In quest'ultima affezione si ottengono risultati veramente buoni per cui malati costretti su una sedia a rotelle riprendono spesso e per molti anni la loro normale funzione motoria.

### VARI TIPI DI TRAPIANTO DI CELLULE STAMINALI EMOPOIETICHE

La **prima distinzione** va fatta sulla base dell'organo di provenienza delle cellule staminali emopoietiche: tali cellule si possono infatti estrarre dal midollo osseo, attraverso una serie di punture midollari a livello delle ossa del bacino eseguite in anestesia generale, ovvero ottenerle dal sangue periferico mediante l'aferesi nel quale caso tutto si riduce ad inserire in vena ad ogni braccio del donatore un ago: il sangue prelevato da un braccio passa attraverso l'apparecchiatura dell'aferesi, capace di rimuovere e conservare le cellule staminali, e ritorna al donatore (senza le cellule staminali) attraverso l'ago posto nell'altro braccio. Sono necessarie più sedute per avere cellule staminali sufficienti ma il procedimento è indolore e può essere eseguito anche su pazienti non ricoverati. Fra l'altro la raccolta di cellule staminali del sangue periferico può rendere possibile un trapianto autologo in un paziente non idoneo a subire l'espianto di midollo osseo. Tuttavia, possono essere necessari giorni o anche settimane di raccolta per avere sufficienti cellule staminali per il trapianto, mentre la raccolta del midollo osseo può essere completata in appena due ore. Le cellule staminali sono conservate a  $-180^{\circ}\text{C}$ .

Infine le cellule staminali emopoietiche possono provenire dal sangue del cordone ombelicale in cui sono molto abbondanti, tali cellule si estraggono dal cordone, con il consenso della madre, subito dopo il parto e vengono, dopo opportuna preparazione preservata a  $-180^{\circ}\text{C}$ .

La **seconda distinzione** va fatta a seconda del donatore e in questo senso ci sono tre tipi di trapianto di cellule staminali emopoietiche: **autologo**, **singenerico** e **allogenerico**.

Nel trapianto **autologo**, si è donatori di se stessi. Il midollo osseo prelevato dal malato (espianto) viene sottoposto a congelamento per il tempo necessario (criopreservato) e quindi restituito (trapiantato) dopo alte dosi di chemioterapia, radioterapia o entrambe. Il midollo osseo può essere purificato prima di essere reinfuso, per ridurre il più possibile le cellule malate che potrebbe ancora contenere. Il trapianto autologo è il tipo più comune di trapianto. Viene effettuato con frequenza doppia rispetto all'allogenerico e al singenerico. Proprio perché il donatore e il ricevente sono la stessa persona, molte delle complicanze associate al trapianto allogenerico (come il rigetto o la sindrome da trapianto contro ospite) vengono evitate.

Nel trapianto **singenerico**, il donatore è un gemello identico. Questa è una situazione ideale, perché donatore e ricevente hanno lo stesso tipo di tessuto. In realtà, questi trapianti sono rari (<1%), perché le persone con gemelli identici, sono molte poche ed inoltre, in questo tipo di trapianto spesso non si ottiene l'attecchimento e si ha la recidiva della malattia per la quale il trapianto era stato effettuato.

Nel trapianto **allogenerico**, il midollo osseo del paziente è ricostituito mediante la reinfusione di cellule staminali emopoietiche di un donatore sano compatibile. Il motivo per cui il donatore delle cellule staminali, in questo tipo di trapianto, deve essere compatibile deriva dal fatto che il tessuto midollare fa parte del sistema immunitario, e produce cellule capaci di riconoscere sostanze estranee all'organismo umano. I tessuti di ogni persona possiedono sostanze con caratteristiche molecolari proprie chiamate marcatori (markers); di origine genetica sono simili alle impronte digitali e si trovano soprattutto sui globuli bianchi. Questi markers costituiscono il sistema degli antigeni umani (Human Leucocyte Antigen - HLA system)- uniti in coppie sono denominati loci e sono ereditati uno dal padre e uno dalla madre. Più sono simili fra donatore e ricevente, maggiore sarà la probabilità di successo del trapianto. Infatti se il sistema HLA è differente da quello del donatore, il sistema immunitario dell'ospite riconosce, attraverso i marcatori HLA, il nuovo midollo osseo come estraneo, lo attacca e lo distrugge (non attecchimento), oppure, e questa è la situazione più comune, è il midollo osseo del donatore a riconoscere gli antigeni dei tessuti dell'ospite come estranei, rivoltarsi contro di loro, attaccandoli. Questa situazione è chiamata: sindrome da trapianto contro l'ospite. Per evitare questo tipo di complicazioni, è necessario trovare un donatore il cui midollo sia il più possibile simile a quello del ricevente, cioè compatibile. La ricerca comincia con la propria famiglia, innanzi tutto con i fratelli e le sorelle. Il 30-40% di coloro che hanno bisogno di un BMT hanno una sorella o un fratello compatibili. Se la tipizzazione HLA non rileva la compatibilità tra fratelli, la ricerca si sposta sui genitori e poi su tutta la famiglia; cugini e zii. Se anche questi parenti risultano non compatibili la ricerca si allarga a tutta la popolazione per trovare un donatore non parente. E' infatti possibile trovare un donatore compatibile, tra persone estranee attraverso i registri dei donatori di midollo osseo. Statisticamente le probabilità variano, a seconda della frequenza nella popolazione degli antigeni HLA del paziente, da un minimo di 115000 a 111 milione, cioè per alcuni riceventi è possibile trovare un donatore compatibile su 5000 donatori mentre per altri si trova solo all'interno di un pool di 1 milione di donatori volontari.

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# PICO

**P** (paziente o popolazione): pazienti con trapianto di midollo osseo

**I** (intervento): Re-infuse cellule staminali emopoietiche attraverso CVC

**C** (controintervento): Confronto tra trapianto allogenico e autologo

**O** (outcome): Vantaggi o svantaggi di tali re-infusioni

## **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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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 outcomes<sup>1</sup>.

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 research<sup>2</sup>.

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)<sup>3</sup>. 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 density<sup>4</sup>. 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  $\geq 5$  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<sup>7, 12</sup>. 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 settings<sup>12</sup>. 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

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carried out in 15 Western European countries with a population of 381 million, equating to 446 HSCT per 10 million population<sup>13</sup>. In comparison, in the 9 EMBMT countries with a collective population of 367 million in the same year<sup>14</sup>, 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 low<sup>4</sup>.

Factors that may contribute to differences in HSCT activity have been elucidated<sup>15–16</sup>. Allo-HSCT is an expensive procedure and various factors can affect total cost<sup>17</sup>. Gross national income, team density and healthcare expenditure have been shown to have an impact on transplant numbers<sup>18</sup>.

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<sup>15, 19</sup>. 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-SCTs<sup>20</sup>. Data from the United States as reported to CIBMTR also demonstrate an excess of ASCT over allo-HSCT<sup>21</sup>. 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<sup>22–23</sup>.

#### **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%)<sup>20</sup>. 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 published<sup>24</sup>.

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

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indication for allo-HSCT in 30% of all transplants, and their respective experience has been reported<sup>25, 26</sup>. 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)<sup>20</sup>.

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<sup>21, 27, 28</sup>. 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 year<sup>20</sup>. 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<sup>29, 30</sup>. 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 GVHD<sup>31–33</sup>.

While there has been an increase in the use of cord blood as a stem cell source - a trend observed in Europe<sup>34</sup> - 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 nonumbilical 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 transplant<sup>4</sup>.

### **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 in 2007, and has been reported to be as high as 71% in some European countries<sup>20,28</sup>. 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

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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 are adequate numbers of transplant physicians and nurses to deal with increasing transplant demands<sup>35</sup>.

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