Quantitative and qualitative differences in use and trends of hematopoietic stem cell transplantation: a Global Observational Study

by Alois Gratwohl, Helen Baldomero, Michael Gratwohl, Mahmoud D Aljurf, Luis Fernando Bouzas, Mary Horowitz, Yoshihisa Kodera, Jeff Lipton, Minako Iida, Marcelo C Pasquini, Jakob Passweg, Jeff Szer, Alejandro Madrigal, Karl Frauendorfer, and Dietger Niederwieser

Haematologica 2013 [Epub ahead of print]

doi:10.3324/haematol.2012.076349

Publisher's Disclaimer.
E-publishing ahead of print is increasingly important for the rapid dissemination of science. Haematologica is, therefore, E-publishing PDF files of an early version of manuscripts that have completed a regular peer review and have been accepted for publication. E-publishing of this PDF file has been approved by the authors. After having E-published Ahead of Print, manuscripts will then undergo technical and English editing, typesetting, proof correction and be presented for the authors’ final approval; the final version of the manuscript will then appear in print on a regular issue of the journal. All legal disclaimers that apply to the journal also pertain to this production process.

Haematologica (pISSN: 0390-6078, eISSN: 1592-8721, NLM ID: 0417435, www.haematologica.org) publishes peer-reviewed papers across all areas of experimental and clinical hematology. The journal is owned by the Ferrata Storti Foundation, a non-profit organization, and serves the scientific community with strict adherence to the principles of open access publishing (www.doaj.org). In addition, the journal makes every paper published immediately available in PubMed Central (PMC), the US National Institutes of Health (NIH) free digital archive of biomedical and life sciences journal literature.

Support Haematologica and Open Access Publishing by becoming a member of the European Hematology Association (EHA) and enjoying the benefits of this membership, which include free participation in the online CME program.
Quantitative and qualitative differences in use and trends of hematopoietic stem cell transplantation: a Global Observational Study

Alois Gratwohl,1 Helen Baldomero,1 Michael Gratwohl,2 Mahmoud Aljurf,3 Luis Fernando Bouzas,4 Mary Horowitz,5 Yoshihisa Kodera,6 Jeff Lipton,7 Minako Iida,8 Marcelo C. Pasquini,5 Jakob Passweg,1 Jeff Szer,9 Alejandro Madrigal,10 Karl Frauendorfer,2 Dietger Niederwieser,11 for the Worldwide Network of Blood and Marrow Transplantation WBMT

1The European Group for Blood and Marrow Transplantation (EBMT) Transplant Activity Survey Office, University Hospital, Basel, Switzerland; 2Institute for Operations Research and Computational Finances, University of St. Gallen, Switzerland; 3The Eastern Mediterranean Blood and Marrow Transplant Group (EMBMT), King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia; 4The Sociedade Brasileira de Transplante de Medula Ossea (SBTMO), Instituto Nacional de Cancer, Rio de Janeiro, Brazil; 5The Center for International Blood and Marrow Transplant Research (CIBMTR), Medical College of Wisconsin, Milwaukee, USA; 6Aichi Medical University, School of Medicine, Japan; 7The Canadian Blood and Marrow Transplant Group (CBMTG), Princess Margaret Hospital, Toronto, Canada; 8The Asian Pacific Blood and Marrow Transplant Group (APBMT) Data Centre, Aichi Medical University, School of Medicine, Japan; 9The Australasian Bone Marrow Transplant Recipient Registry (ABMTRR), Royal Melbourne Hospital, Parkville, Victoria, Australia; 10The Anthony Nolan Trust, The Royal Free Hampstead NHS Trust, London, UK, and 11Hematology-Oncology Department, University Hospital, Leipzig, Germany

Correspondence
Alois Gratwohl, Hematology, WBMT activity survey office, University Hospital Basel, Switzerland
Petersgraben 4, CH 4031 Basel, Switzerland. Phone: international + 41.612653203.
Fax: international + 41.61.2652735. E-mail: baldomero@uhbs.ch
ABSTRACT

Fifty five years after the first publication, hematopoietic stem cell transplantation has become an accepted treatment option for defined hematological and non-hematological disorders. There is considerable interest in understanding differences of its use and trends on a global level and of the macroeconomic factors associated with these differences.

Data on HSCT numbers for the 2006-2008 3-years period were obtained from WBMT member registries and from transplant centers in countries without registries. Population and macroeconomic data were collected from the World Bank and from the International Monetary Fund. Transplant rates were analyzed by indication, donor type, country, and World Health Organization (WHO) regional offices areas and related to selected health care indicators using single and multiple linear regression analyses.

A total of 146,808 patients were reported by 1,411 teams from 72 countries over 5 continents. Annual number of transplants increased worldwide with the highest relative increase in the Asia Pacific region. Transplant rates increased preferentially in high (p=0.02), not in low or medium income countries. Allogeneic transplants increased for myelodysplasia, chronic lymphocytic leukemia, acute leukemias, and nonmalignant diseases but decreased for chronic myelogenous leukemia. Autologous transplants increased for autoimmune and lymphoproliferative diseases but decreased for leukemias and solid tumors. Transplant rates (p< 0.01), donor type (p< 0.01) and disease indications (p < 0.01) differed significantly between countries and regions. Transplant rates were associated with Gross National Income/capita (p < 0.01) but showed a wide variation of explanatory content by donor type, disease indication and WHO region.

HSCT activity increases worldwide. The preferential increase in high income countries, the widening gap between low and high income countries and the significant regional differences suggest that different strategies are required in individual countries to foster HSCT as an efficient and cost effective treatment modality.

Key words: Hematopoietic stem cell transplantation, autologous, allogeneic, global perspective, transplant rates, leukemia, lymphoma, solid tumors, non-malignant disorders, unrelated donors.

DOI: 10.3324/haematol.2012.076349
INTRODUCTION

Quantitative differences in transplant rates of hematopoietic stem cell transplantation (HSCT) have been well described in the recent past: more patients are transplanted in countries with a higher national income. HSCT requires a specific infrastructure, depends on a network of specialists and remains associated with significant morbidity and mortality; it is a prime example of costly specialized medicine. Broader use of HSCT has therefore long been limited to high income countries (1, 2). This has changed over the last decade, for several reasons. Transplantation of autologous or allogeneic bone marrow, peripheral blood or cord blood stem cells has become treatment of choice for many patients with defined severe congenital or acquired disorders of the hematopoietic system. Unrelated donor registries have expanded to more than 20 million HLA-typed (Human Leukocyte Antigen) volunteer donors worldwide and increased the likelihood to find a suitable matched donor. Results have improved, including those for elderly patients and for those with co morbidities. As a consequence, novel indications are being explored and transplant numbers have increased worldwide (3-9).

Furthermore, the World Health Organization (WHO) has recognized transplantation as an important global task. Transplantation of cells, tissues and organs has extended the lifespan of hundreds of thousands of patients worldwide and enhanced their quality of life; it has become standard of care for many patients with single organ failure and should no longer be restricted to affluent countries or individuals. The guiding principles of the WHO declare regulation of transplantation on a national level as a governmental responsibility. Regulation includes harmonized data collection on use and outcome as an essential tool to improve results and to achieve efficient and cost effective use of resources (10, 11). Information on use and trends is therefore a prime prerequisite for any health care agency. The Worldwide Network for Blood and Marrow Transplantation (WBMT), an umbrella organization of HSCT and a non-governmental organization recognized by WHO has taken up the task of facilitating HSCT. It previously identified availability of resources, governmental support and access of patients to the therapy as key factors associated with quantitative differences in transplant rates (12). It presents now an in-depth assessment of factors associated with qualitative differences in use and trends on a global level.

METHODS

Study design

This retrospective survey followed the principles of the WBMT through data collection by its network of international or regional member organizations (12). Main outcome measures were the assessment of transplant rates by indication and donor type for each country, the changes
over the three years period from 2006 to 2008 and their associations with defined macroeconomic factors.

**Data collection and validation**

Data were obtained from 1,411 teams in 72 countries over 5 continents on their numbers of HSCT performed in the years 2006, 2007 and 2008 by indication and donor type (Table 1). Data were reported via the mandatory worldwide compatible reporting system of initial transplant data (ABMTRR, CBMTG, and CIBMTR) or by a separate survey data form (APBMT, EBMT, EMBMT, and SBTMO) (9, 13-16).

Data were pooled, validated through confirmation by the reporting team, which received a computer printout of the entered data, by selective comparison with MED-A data sets in the EBMT ProMISE data system or by crosschecking with National Registries. Double reporting was excluded. Onsite visits of selected teams are part of the quality control program within CIBMTR and EBMT teams.

**Definitions**

*Transplant rates*

Transplant rates were computed as the number of patients treated with a first HSCT per 10 million inhabitants (2). Patients with a re-transplant or a second or third HSCT were not included.

Population data and data on Gross National Income/capita (GNI/cap), Health Care Expenditures/cap, Governmental Health Care Expenditures, and World Bank Category (by GNI/cap) were obtained from the World Bank (www.worldbank.org) and from the International Monetary Fund (www.imf.org).

*World Health Organization regional offices areas*

The allocation of individual countries to a region followed the WHO regional offices classification (www.who.int/about_regions/en/) and the previously reported restriction to four regions (11): 1) the Americas; 2) Asia; 3) Eastern-Mediterranean and Africa; and 4) Europe (Figure 1).

**Statistical analysis**

The association of macroeconomic factors with HSCT rates and the changes from 2006 to 2008 were estimated by single and multiple linear regression analyses using the least squares method. The significance of relationships was measured using \( \tau \) statistics; a level of 5% was considered significant. The goodness of fit was calculated using the coefficient of
determination \( (R^2) \), the square of the Pearson’s correlation coefficient. For single and multiple regression analyses, the dependent variables were transformed to be closer to an underlying linear model. For the multiple regression analyses, all factors were assessed for their multicollinearity.

The t test was used to evaluate significant differences between the WHO regions. All statistical analyses were performed with EViews version 5.1 (Quantitative Micro Software, Irvine, California).

**RESULTS**

**Numbers of HSCT for the years 2006-2008, indications, donor type and stem cell source**

There were 146,808 patients (45% allogeneic and 55% autologous) with HSCT during this three years period (Table 1). The analysis showed substantial heterogeneity in indication and donor type by WHO region. Main indications were *lymphoproliferative disorders* with 53%; *leukemias* 36%; *solid tumors* 5% and *non-malignant disorders and others* 6%. There was, however, a distinctly different pattern for allogeneic and autologous HSCT. Main indications for allogeneic HSCT were leukemias (72%), lymphoproliferative disorders (15%) and non malignant disorders (12%), while main indications for autologous HSCT were lymphoproliferative disorders (84%), solid tumors (9%) and non malignant disorders (1%; see Table 1).

Information on stem cell source was available on a total of 142,822 patients. Peripheral blood was used predominantly in related and unrelated HSCT (64%) and in autologous HSCT (98%). Bone marrow remained an important source for allogeneic HSCT (26%), specifically for *non malignant disorders* (56%); its use was minimal for autologous HSCT (2%). Allogeneic HSCT (in patients with information on stem cell source available) were performed from family donors in 51% (43% matched, 7% mismatched/haplo, 0.5% twins and 0.43% cord blood) and from unrelated donors in 49%. Of the 49% unrelated HSCT, 54% were obtained from peripheral blood, 27% from bone marrow and 19% from cord blood.

The highest number of HSCT was reported from Europe (51% of which 39% allogeneic HSCT) followed by the Americas (29%; 46% allogeneic HSCT), Asia (18%; 60% allogeneic HSCT) and Eastern Mediterranean/Africa (3%; 63% allogeneic HSCT) as shown in Table 1. The distribution was asymmetric concerning the proportion of autologous and allogeneic HSCT with a significant difference between America and Europe from Asia and Eastern Mediterranean/Africa \( (p < 0.05) \) and concerning the repartition of main indications with a higher proportion of non malignant indications in Eastern Mediterranean/Africa \( (p< 0.01) \) and a higher proportion of acute leukemia in Asia \( (p< 0.01) \). This asymmetric distribution was primarily influenced by the World Bank category of the participating countries (Figure 2). Low income countries preferentially used
allogeneic compared to autologous HSCT, low and middle income countries preferentially used family donors compared to unrelated donors and showed a higher proportion of non malignant indications.

Transplant rates

Over the three years period the average absolute number of HSCT in the participating countries ranged from 1 (Philippines) to 11,228 HSCT (USA; Figure 1). Transplant rate ranged from 0.1 to 732 per 10 million inhabitants (median 119) for total HSCT, from 0 to 397 (median 49) for allogeneic and from 0 to 412 (median 81) for autologous HSCT. There were no autologous or allogeneic transplants in countries with less than 300,000 inhabitants or with a GNI/cap below $US 690; there were no unrelated donor transplants in countries with a GNI/cap below $US 850.

Transplant rates were significantly associated with common health care indicators, lnGNI/cap ($R^2 = 61\%$) (Figure 3), Health Care Expenditures/capita ($R^2 = 64\%$) or Governmental Health Care Expenditures/capita ($R^2 = 63\%$) (Data not shown). These associations were similar for 2006, 2007 and 2008. They differed significantly for donor types, indications and by the World Health Organization regions.

The association was stronger and with a greater explanatory content for autologous ($R^2 = 55\%$) than allogeneic HSCT ($R^2 = 49\%$) as shown for lnGNI/cap (Figure 3a). Explanatory content was higher for unrelated than for family donor HSCT. It was highest for acute leukemia ($R^2 = 49\%$), lower for non malignant disorders ($R^2 =15\%$) (Figure 3b) and nonexistent for non malignant disorders with HSCT from family donors ($R^2 = 4\%$).

Unrelated donor transplant rates were also associated with lnGNI/cap ($R^2 = 48\%$), with the presence of an unrelated donor registry in the respective country ($R^2=30\%$) and the number of donors in the respective donor registry ($R^2=15\%$). The combined effect of these three factors in a multiple regression reached an extent of even $R^2=59$. If only countries performing unrelated donor transplants were included in the analysis, explanatory content reached $R^2=72\%$ (Figure 3c). Unrelated cord blood transplant rates were weakly associated with lnGNI/cap ($R^2 = 24\%$) and with the presence of a cord blood bank in the respective country ($R^2=10\%$). The 264 family donor cord blood transplants were minimally associated (lnGNI/cap: $R^2=5\%$). The three factors lnGNI/cap, presence of an unrelated donor registry and the number of donors in the respective donor registry exerted as well a combined effect on total transplant rates ($R^2=63\%;$ all regions combined) but to a different extent in the different regions. Associations with lnGNI/cap were strongest in the Americas ($R^2=94\%$), followed by Asia ($R^2=67\%$), Europe ($R^2=57\%$) and the Eastern Mediterranean /Africa region ($R^2=25\%$).
Trends 2006 to 2008

Numbers of HSCT increased from 46 563 HSCT in 2006 to 51 536 HSCT in 2008 (+ 10%). The increase in reporting teams from 1327 teams in 2006 to 1407 in 2008 (+6%) was one reason, but even more was the increase of the median number of transplants/year (+26.3%) performed at each center [38 (range 3-180), to 46 (3-421) and 48 (1-389) in 2006, 2007 and 2008 respectively]. Changes differed between regions as well as for main indications, donor types and stem cell sources (Figure 4).

Relative increase was greater for related and unrelated allogeneic (+17%) than for autologous HSCT (+ 5%; see Figure 4A). The highest increase in absolute and relative numbers was observed in the Asia/Western Pacific region (see Figure 4B; +39%) for allogeneic (+50%) and autologous (+22%) HSCT, followed by Europe (+6%) for allogeneic (+10%) and autologous (+3%) HSCT, Americas (4%) for allogeneic (+9%) and autologous (+1%) HSCT, and EMRO/Africa (+19) for allogeneic (+11%) and autologous (+34%) HSCT. The relative increase in HSCT numbers was higher in low income countries (Figure 4C) but not in absolute numbers and in transplant rates (see below). The increase in HSCT numbers was predominantly accounted for by unrelated donor HSCT for patients with leukemia in America and Europe, by family donor HSCT for patients with non-malignant disorders in Asia and EMRO/Africa.

Numbers of autologous HSCT increased for for lymphoproliferative disorders (+8%) and decreased for leukemia (-15%) and solid tumors (-2%) as shown in Figure 4D. Numbers of allogeneic HSCT increased for leukemia (+20%) and non malignant disorders (+26%; Figure 4E) with divergent trends for myelodysplasia (+26%), acute myeloid leukemia (+23%), acute lymphoblastic (+27%) leukemias and chronic lymphocytic (+24.6%) leukemia than for chronic myeloid leukemia (-17%). The numbers of allogeneic HSCT increased for bone marrow failure syndromes (+21%) and other non-malignant disorders (+27%). Changes in use of stem cell source are shown in Figure 4F with the highest relative but not absolute increase in cord blood HSCT. The relatively higher increase in transplant numbers in countries with lower income ($R^2 = 11\%$) did not translate into a higher increase in transplant rates. In contrast transplant rates were weakly but positively associated with lnGNI/cap ($R^2 = 3\%$) (Figure 3d). Linear trend analysis confirms this with a positive and increasing linear trend ($p=0.02$, total HSCT) for the absolute number of HSCT in high income countries but none for the middle ($p=0.57$) and low ($p=0.35$) income countries. The trend was most clearly underpinned for unrelated donor HSCT for acute leukemia in high income countries ($p=0.004$). There was no association of increase or decrease in transplant rates with change in lnGNI/cap over time ($R^2 = 1\%$).

DISCUSSION

DOI: 10.3324/haematol.2012.076349
This global analysis shows that availability of resources impacts on use of HSCT in a quantitative and qualitative way. Transplant rates are higher in high income countries but the difference is not the same for all indications or all donor types. High income countries use autologous and allogeneic HSCT for more indications. They are more likely to use autologous than allogeneic HSCT and unrelated donors than family donors. Transplant rates for autologous HSCT are more likely to be influenced by GNI/cap as illustrated by the higher explanatory content for autologous HSCT. Countries with limited resources in contrast preferentially restrict use of HSCT to allogeneic transplants with stem cells from family donors for non malignant indications or chronic leukemia. The previously described differences between the WHO regional offices areas (11) might therefore rather reflect the differences in resources than in opinions. It is comforting to observe the continued increase in transplant numbers in low income countries; it remains of concern that transplant rates increased to a greater extent in high income compared to middle or low income countries: the gap remains widening.

Transplant rates were associated with GNI/cap for all indications and all donor types but with vast differences in explanatory content and impact. How can these findings be interpreted? A high explanatory content with a strong impact can be considered as a situation with increasing demand without saturation: more patients with acute leukemia will be transplanted in the coming years if the necessary resources, money and donors can be made available. A low explanatory content with a weak impact indicates a different situation. Transplant rates are no longer driven by a higher national income alone. Other factors than availability of resources must come into play. It could relate to different beliefs of the medical community on the value of a given therapy in different countries. However, the focus on matched family donor transplant for non malignant disorders and chronic leukemia in lower income countries is suggestive for prioritization in a cost effectiveness approach. HSCT might be less expensive and equally effective as lifelong treatment with supportive care or expensive drugs in selected patients. There is no need for intensive high cost pre-treatment as is the case for patients with acute leukemia and, the search for a matched family donor requires minimal resources (17-21).

Economic aspects of HSCT with its patient centered approach have traditionally concentrated on costs of the individual procedure for an individual patient. (17, 22-24). Studies on macroeconomic aspects or on cost effectiveness in individual countries have gained broader acceptance only recently (11, 21, 22, and 25). They were triggered in part by some rapid changes in use of HSCT, such as for breast cancer or chronic myeloid leukemia (18, 26) and by the raising awareness of the disturbing gap between unlimited requests and limited resources in any health care system (27, 28). Availability of resources, governmental support and access to therapy were identified as factors associated with use; availability of resources, evidence, external regulations and positive or negative expectations of transplant physicians as factors associated with diffusion (11, 25). These previous findings and the observations in this report
form an objective basis for recommendations or guidelines by professional organizations. They point to the different requirements within high or low income countries, hence different cost effectiveness considerations (20, 21, 26-28). Unrelated donor transplant rates were associated with GNI/cap, the presence of an unrelated donor registry and the number of registered donors. The association is likely reciprocal; high income countries perform more HSCT in general and are more likely to invest in an unrelated donor registry. Competent authorities will have to balance the advantages and costs of establishing and maintaining a national donor registry with its own local HLA-haplotype distribution with alternative strategies (24, 29, 30). The even representation of unrelated HSCT in high income countries documents the functioning worldwide exchange of graft material.

Some caveats remain. Data for this survey were collected for the years 2006 to 2008. Patterns might have changed since; differences in indications might reflect different disease prevalence or missing information. Some congenital non malignant disorders such as immune deficiency syndromes or hemoglobinopathies are highly present in some and absent in other countries (31, 32). Evidently, a few teams known to have performed HSCT did choose not to report (13). Data reporting is mandatory by law in some, limited to allogeneic HSCT or even absent in other countries. The discrepancy between performed and reported HSCT might be higher for autologous than for allogeneic HSCT (9, 14-16). There is, however, no indication for a systematic bias and more recent data from the European survey are consistent with a widening gap (13).

The report gives no information on outcome. This requires additional time and another framework. Outcome is influenced by many factors, including the disease, the pre-treatment, patient and donor characteristics, transplant techniques, the transplant team, its quality management system or the income of the respective country (3, 5, 33-36). Combined analyses on use and outcome are needed to ascertain that those patients with the highest need and the best likelihood to profit from a transplant procedure are selected within a given country. Transplant organizations and competent authorities worldwide are currently challenged to implement the WHO guiding principles. The present data provide a platform to begin with. They indicate that one size will not fit all. Regulatory aspects and recommendations on therapy should not only be transparent and consistent but as well be targeted according to the specific cost effectiveness considerations and needs in the individual countries (36, 37).

ACKNOWLEDGEMENTS

The cooperation of all participating teams, countries and organizations with their staff (see
supplementary Table 1) is greatly appreciated. Specifically the following: ABMTRR, APBMT: Minako Iida MD, Ph.D., Aichi Medical School, CBMTG, CIBMTR: Kathy Sobocinski M.S. and Xiaobo Zhong, M.S., Medical College of Wisconsin, EBMT: Co-ordination offices in Barcelona, Paris and London and the Austrian Registry (ASCTR), the Czech BMT Registry, the French Registry (SFGM), the German Registry (DRST), the Italian Registry (GITMO), the Dutch Registry (HOVON), the Spanish BMT Registry (GETH), the Swiss Registry (SBST, the Turkish BMT Registry and the British Registry (BSBMT), EMBMT, SBTMO.

Funding

Funding was solely to support the study; no individual payment was made to any of the persons involved in the study. The activity survey office is in part supported by the Swiss National Research Foundation NFP 63.

CIBMTR is supported by Public Health Service Grant/Cooperative Agreement U24-CA76518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI) and the National Institute of Allergy and Infectious Diseases (NIAID); a Grant/Cooperative Agreement 5U01HL069294 from NHLBI and NCI; a contract HSHS234200637015C with Health Resources and Services Administration (HRSA/DHHS); two Grants N00014-06-1-0704 and N00014-08-1-0058 from the Office of Naval Research; and grants from AABB; Aetna; American Society for Blood and Marrow Transplantation; Amgen, Inc.; Anonymous donation to the Medical College of Wisconsin; Astellas Pharma US, Inc.; Baxter International, Inc.; Bayer HealthCare Pharmaceuticals; Be the Match Foundation; Biogen IDEC; BioMarin Pharmaceutical, Inc.; Biovitrum AB; Blood Center of Wisconsin; Blue Cross and Blue Shield Association; Bone Marrow Foundation; Canadian Blood and Marrow Transplant Group; CaridianBCT; Celgene Corporation; CellGenix, GmbH; Centers for Disease Control and Prevention; Children’s Leukemia Research Association; ClinImmune Labs; CTI Clinical Trial and Consulting Services; Cubist Pharmaceuticals; Cylex Inc.; CytoTherm; DOR BioPharma, Inc.; Dynal Biotech, an Invitrogen Company; Eisai, Inc.; Enzon Pharmaceuticals, Inc.; EBMT; Gamida Cell, Ltd.; GE Healthcare; Genentech, Inc.; Genzyme Corporation; Histogenetics, Inc.; HKS Medical Information Systems; Hospira, Inc.; Infectious Diseases Society of America; Kiadis Pharma; Kirin Brewery Co., Ltd.; The Leukemia & Lymphoma Society; Merck & Company; The Medical College of Wisconsin; MGI Pharma, Inc.; Michigan Community Blood Centers; Millennium Pharmaceuticals, Inc.; Miller Pharmacal Group; Milliman USA, Inc.; Miltenyi Biotec, Inc.; National Marrow Donor Program; Nature Publishing Group; New York Blood Center; Novartis Oncology; Oncology Nursing Society; Osiris Therapeutics, Inc.; Otsuka America Pharmaceutical, Inc.; Pall Life Sciences; Pfizer Inc; Saladax Biomedical, Inc.; Schering Corporation; Society for Healthcare Epidemiology of America; StemCyte, Inc.; StemSoft
Software, Inc.; Sysmex America, Inc.; Teva Pharmaceutical Industries; THERAKOS, Inc.; Thermogenesis Corporation; Vidacare Corporation; Vion Pharmaceuticals, Inc.; ViraCor Laboratories; ViroPharma, Inc.; and Wellpoint, Inc. The views expressed in this article do not reflect the official policy or position of the National Institute of Health, the Department of the Navy, the Department of Defense, or any other agency of the U.S. Government.

EBMT is supported by grants from the corporate members: Amgen Europe, Gilead Sciences UK, Miltenyl Biotec GmbH, Merck Sharp and Dohme, Celgene International SARL, Astellas, Fresenius Biotech GmbH, CaridianBCT Europe NV, Therakos, Cephalon, Gentium SpA, Genzyme, Pierre Fabre Médicament, Alexion Europe – Pfizer, Exem Consulting, Chugai sanofi-aventis, Novartis, Hospira, MacoPharma and Millennium

Support from corporate members was solely for keeping the infrastructure of the organizations. The funding organizations and sponsors of the organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Authorship and Disclosures

Contributions to the manuscript are as follow:

Design: AG; DN; KF

Contributing data and data analysis: HB; AG; DN; KF; MG; MA; LFB; MH; YK; JL; MI; MCP; JP; JS; AM; KF

Manuscript processing: AG; DN; MG; MA; LFB; MH; YK; JL; MI; MCP; JP; JS; AM; KF; HB; AG; DN; KF

There are no conflicts of interest pertinent to this manuscript to declare by any of the authors.
REFERENCES


19) Saussele S, Lauseker M, Gratwohl A, Beelen DW, Bunjes D, Schwerdtfeger R et al. Allogeneic hematopoietic stem cell transplantation (allo SCT) for chronic myeloid

20) Gajewski JL, Robinson P. Do affluent societies have the only options for the best therapy? Leukaemia. 2007;21(3):387-8.


31) Wang W.C. Sickle cell anemia and other sickling syndromes. In "Wintrobe’s clinical


Table 1: Population description of patients with HSCT by WHO regional offices area from 2006 to 2008

<table>
<thead>
<tr>
<th></th>
<th>East Mediterranean / Africa</th>
<th>SE Asia/ Western Pacific</th>
<th>Americas</th>
<th>Europe</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td><strong>Donor type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allogeneic HSCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family donor</td>
<td>2474</td>
<td>99</td>
<td>7944</td>
<td>51</td>
<td>10034</td>
</tr>
<tr>
<td>Unrelated donor</td>
<td>35</td>
<td>1</td>
<td>7603</td>
<td>49</td>
<td>9429</td>
</tr>
<tr>
<td>Total **</td>
<td>1477</td>
<td>37</td>
<td>23007</td>
<td>54</td>
<td>45714</td>
</tr>
<tr>
<td><strong>Main Indications Allogeneic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Leukaemias</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Leukemia</td>
<td>1059</td>
<td>73</td>
<td>9585</td>
<td>79</td>
<td>9619</td>
</tr>
<tr>
<td>Chronic Leukemia</td>
<td>276</td>
<td>19</td>
<td>1086</td>
<td>9</td>
<td>1827</td>
</tr>
<tr>
<td>MDS/MPS</td>
<td>120</td>
<td>8</td>
<td>1455</td>
<td>12</td>
<td>2174</td>
</tr>
<tr>
<td><strong>Lymphoproliferative disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>68</td>
<td>69</td>
<td>1280</td>
<td>87</td>
<td>2729</td>
</tr>
<tr>
<td>Plasma cell disorders</td>
<td>31</td>
<td>31</td>
<td>183</td>
<td>13</td>
<td>685</td>
</tr>
<tr>
<td><strong>Non malignant disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow failure</td>
<td>468</td>
<td>50</td>
<td>1094</td>
<td>63</td>
<td>1247</td>
</tr>
<tr>
<td>Other non malignant</td>
<td>460</td>
<td>50</td>
<td>653</td>
<td>37</td>
<td>945</td>
</tr>
<tr>
<td><strong>Solid tumors</strong></td>
<td>928</td>
<td>37</td>
<td>1747</td>
<td>11</td>
<td>2192</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>24</td>
<td>1</td>
<td>79</td>
<td>1</td>
<td>172</td>
</tr>
<tr>
<td><strong>Main Indications Autologous</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lymphoproliferative disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>734</td>
<td>61</td>
<td>4279</td>
<td>52</td>
<td>9719</td>
</tr>
<tr>
<td>Plasma cell disorders</td>
<td>479</td>
<td>39</td>
<td>3877</td>
<td>48</td>
<td>10304</td>
</tr>
<tr>
<td><strong>Solid tumors</strong></td>
<td>101</td>
<td>7</td>
<td>1347</td>
<td>13</td>
<td>1951</td>
</tr>
<tr>
<td><strong>Leukemias</strong></td>
<td>153</td>
<td>10</td>
<td>717</td>
<td>7</td>
<td>852</td>
</tr>
<tr>
<td>Acute Leukemia</td>
<td>129</td>
<td>84</td>
<td>694</td>
<td>97</td>
<td>816</td>
</tr>
<tr>
<td>Chronic Leukemia</td>
<td>10</td>
<td>7</td>
<td>14</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>MDS/MPS</td>
<td>14</td>
<td>9</td>
<td>9</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td><strong>Non malignant disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow failure</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Other non malignant</td>
<td>10</td>
<td>100</td>
<td>88</td>
<td>100</td>
<td>153</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>0</td>
<td>0</td>
<td>76</td>
<td>1</td>
<td>27</td>
</tr>
</tbody>
</table>

*column percentages; **row percentages; MDS/MPS, myelodysplastic syndrome/myeloproliferative syndrome
Legend to the Figures

**Figure 1:** Transplant rates for the total number of HSCT in participating countries by WHO regional offices area for the years 2006-2008. Regions are colored by WHO regional offices area code (see text). Shades of colors reflect transplant rates (numbers of HSCT, allogeneic and autologous combined, by 10 million inhabitants).

**Figure 2:** Indications and donor types of 146,808 HSCT by World Bank category in the years 2006-2008. The figure reflects the relative proportions of allogeneic (blue) or autologous (red) HSCT (left three columns), of allogeneic donor type [family donor (green) or unrelated donor (blue)] (central left three columns), main indications allogeneic HSCT (central right three columns), and main indications autologous HSCT (right three columns; for color code see figure) by low, middle of high income World Bank category. For definitions see methods section.

NM, non malignant disorders; ST, solid tumors; LPD, lymphoproliferative disorders; Leuk, leukemia;

**Figure 3:** Transplant rates and Gross National Income per capita (GNI/cap)

Figure 3a) Transplant rates for allogeneic and autologous HSCT by WHO regional offices area, donor type and GNI/cap. Symbols reflect transplant rates (TR; numbers of HSCT by 10 million inhabitants) in participating countries and the respective lnGNI/cap. Colors indicate WHO region (see figure 1); squares indicate allogeneic, triangles autologous HSCT. Vertical lines separate countries by World Bank category.

Figure 3b) Transplant rates for allogeneic HSCT for acute leukemia and non malignant disorders by WHO regional offices areas and GNI/cap. Symbols reflect transplant rates (TR; numbers of HSCT by 10 million inhabitants) in participating countries and the respective lnGNI/cap. Colors indicate WHO regional offices areas (see figure 1); squares indicate acute leukemia, triangles non malignant disorders. Vertical lines separate countries by World Bank category.

Figure 3c) Unrelated donor transplant rates by WHO regional offices areas, GNI/cap and presence of an unrelated donor registry. Symbols represent transplant rates; open symbols indicate absence of, full symbols presence of an unrelated donor registry and size of symbols numbers of its registered donors. Colors indicate WHO region (see figure 1). Only countries with unrelated donor HSCT are included.
Figure 3d) Change in transplant rates (all transplants) from 2006 to 2008 by GNI/cap and WHO regional offices areas. Symbols represent increase or decrease in transplant rates (TR) from 2006 to 2008; colors indicate WHO regional offices areas (see figure 1).

**Figure 4:** Total HSCT in 2006 and relative increase or decrease (in %) in 2007 and 2008 according to (A) donor type, (B) WHO region, (C) World Bank Category (high, medium and low income by GNI/capita), (D) autologous transplant indication, (E) allogeneic transplant indication and (F) allogeneic stem cell source
METHODS

Study design

This retrospective survey followed the principles of the WBMT through data collection by its network of international or regional member organizations (12). Main outcome measures were the assessment of transplant rates by indication and donor type for each country, the changes over the three years period from 2006 to 2008 and their associations with defined macroeconomic factors.

Data collection and validation

Data were obtained from 1,411 teams in 72 countries over 5 continents on their numbers of HSCT performed in the years 2006, 2007 and 2008 by indication and donor type (Table 1). They were contributed by the Asian Pacific Blood and Marrow Transplant Group APBMT, the Australasian Bone Marrow Transplant Recipient Registry ABMTRR, the Canadian Blood and Marrow Transplant Group CBMTG, the Center for International Blood and Marrow Transplantation CIBMTR, the Sociedade Brasileira de Transplante de Medula Ossea SBTMO, the Eastern Mediterranean Blood and Marrow Transplant Group EMBMT and the European Group for Blood and Marrow Transplantation EBMT. Data were reported via the mandatory worldwide compatible reporting system of initial transplant data (ABMTRR, CBMTG, and CIBMTR) or by a separate survey data form (APBMT, EBMT, EMBMT, and SBTMO) (9, 13-16).

Data were pooled, validated through confirmation by the reporting team, which received a computer printout of the entered data, by selective comparison with MED-A data sets in the EBMT ProMISE data system or by crosschecking with National Registries. Double reporting was excluded. Onsite visits of selected teams are part of the quality control program within CIBMTR and EBMT teams.

Definitions

Transplant rates

Transplant rates were computed as the number of patients treated with a first HSCT per 10 million inhabitants (2). Patients with a re-transplant or a second or third HSCT were not included. Transplant rates were computed by donor type, irrespective of stem cell source. This did relate to cord blood transplants as well. There was no adjustment for patients who crossed borders and received their HSCT in a foreign country.

Population data and data on Gross National Income/capita (GNI/cap), Health Care
Expenditures/cap, Governmental Health Care Expenditures, and World Bank Category (by GNI/cap) were obtained from the World Bank (www.worldbank.org) and from the International Monetary Fund (www.imf.org).

World Health Organization regional offices areas

The allocation of individual countries to a region followed the WHO regional offices classification (www.who.int/about/regions/en/) and the previously reported restriction to four regions (11): 1) the Americas (the corresponding WHO regional offices areas are North and South America); 2) Asia (South-East Asia and Western Pacific Region which includes Australia and New Zealand); 3) Eastern-Mediterranean and Africa; and 4) Europe (which includes Turkey and Israel; Figure 1).

Statistical analysis

The association of macroeconomic factors with HSCT rates and the changes from 2006 to 2008 were estimated by single and multiple linear regression analyses using the least squares method. The significance of relationships was measured using τ statistics; a level of 5% was considered significant. The goodness of fit was calculated using the coefficient of determination (R²), the square of the Pearson’s correlation coefficient. For single and multiple regression analyses, the dependent variables were transformed to be closer to an underlying linear model. For the multiple regression analyses, all factors were assessed for their multicollinearity.

The t test was used to evaluate significant differences between the WHO regions. All statistical analyses were performed with EViews version 5.1 (Quantitative Micro Software, Irvine, California).