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

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ABSTRACT

Fifty-five years after publication of the first hematopoietic stem cell transplantation this technique has become an accepted treatment option for defined hematologic and non-hematologic disorders. There is considerable interest in understanding differences in its use and trends on a global level and the macro-economic factors associated with these differences. Data on the numbers of hematopoietic stem cell transplants performed in the 3-year period 2006-2008 were obtained from Worldwide Network for Blood and Marrow Transplantation member registries and from transplant centers in countries without registries. Population and macro-economic 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 regional offices areas and related to selected health care indicators using single and multiple linear regression analyses. Data from a total of 146,808 patients were reported by 1,411 teams from 72 countries over five continents. The annual number of transplants increased worldwide with the highest relative increase in the Asia Pacific region. Transplant rates increased preferentially in high income countries (P=0.02), not in low or medium income countries. Allogeneic transplants increased for myelodysplasia, chronic lymphocytic leukemia, acute leukemias, and non-malignant 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) aand 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 World Health Organization region. Hematopoietic stem cell transplantation activity is increasing 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 hematopoietic stem cell transplantation as an efficient and cost-effective treatment modality.

Introduction

Quantitative differences in 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 the treatment of choice for many patients with defined severe congenital or acquired disorders of the hematopoietic system. Registers of unrelated donors have expanded to include more than 20 million human leukocyte antigen (HLA)-typed volunteer donors worldwide and increased the likelihood of finding a suitable matched donor. Results have improved, including those for elderly patients and for those

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with co-morbid conditions. 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 on 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 now presents an in-depth assessment of factors associated with *qualitative* differences in use and trends on a global level.

Design and 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] The main outcome measures were the assessment of transplant rates by indication and donor type for each country, the changes over the 3-year period from 2006 to 2008 and their associations with defined macro-economic factors.

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

	East Mediterranean/ Africa		SE Asia/ Western Pacific		Americas		Europe		Total	
	N.	%	N.	%	N.	%	N.	%	N.	%
Donor type*										
Allogeneic HSCT	2509	63	15547	60	19463	46	28707	39	66226	45
Family donor	2474	99	7944	51	10034	52	14523	51	34975	53
Unrelated donor	35	1	7603	49	9429	48	14184	49	31251	47
Autologous HSCT	1477	37	10384	40	23007	54	45714	61	80582	55
Total **	3986	3	25931	18	42470	29	74421	50	146808	100
Main indications allogeneic*										
Leukemias	1455	58	12126	78	13620	70	20476	71	47677	72
Acute leukemia	1059	73	9585	79	9619	71	14271	70	34534	72
Chronic leukemia	276	19	1086	9	1827	13	2259	11	5448	11
MDS/MPS	120	8	1455	12	2174	16	3946	19	7695	16
Lymphoproliferative disorders	99	4	1463	9	3414	18	4868	17	9844	15
Lymphoma	68	69	1280	87	2729	80	3347	69	7424	75
Plasma cell disorders	31	31	183	13	685	20	1521	31	2420	25
Non-malignant disorders	928	37	1747	11	2192	11	2954	10	7821	12
Bone marrow failure	468	50	1094	63	1247	57	1359	46	4168	53
Other non-malignant	460	50	653	37	945	43	1595	54	3653	47
Solid tumors	3	0	132	1	65	0.3	199	1	399	0.6
Other	24	1	79	1	172	1	210	1	485	1
Main indications autologous*										
Lymphoproliferative disorders	1213	82	8156	79	20023	87	37999	83	67391	84
Lymphoma	734	61	4279	52	9719	49	18994	50	33726	50
Plasma cell disorders	479	39	3877	48	10304	51	19005	50	33665	50
Solid tumors	101	7	1347	13	1951	8	4260	9	7659	9
Leukemias	153	10	717	7	852	4	2926	6	4648	6
Acute leukemia	129	84	694	97	816	96	2453	84	4092	88
Chronic leukemia	10	7	14	2	22	3	353	12	399	9
MDS/MPS	14	9	9	1	14	2	120	4	157	3
Non malignant disorders	10	1	88	1	154	1	453	1	705	1
Bone marrow failure	0	0	0	0	1	1	3	1	4	0.5
Other non-malignant	10	100	88	100	153	99	450	99.3	701	99
Other	0	0	76	1	27	0.1	76	0.1	179	0.2

*Column percentages; **row percentages; MDS/MPS, myelodysplastic syndrome/myeloproliferative syndrome.

Data collection and validation

Data were obtained from 1,411 teams in 72 countries over five continents on the 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 cross-checking 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 (GNI)/capita, health care expenditures/capita, governmental health care expenditure, and World Bank Category (by GNI/capita) 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] (i) the Americas; (ii) Asia; (iii) Eastern-Mediterranean and Africa; and (iv) Europe (Figure 1).

Statistical analysis

The association of macro-economic 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 statistically significant. The goodness of fit was calculated using the coefficient of determination (R^2), the square of 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, CA, USA).

Results

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

During the 3-year period considered, 146,808 patients underwent a first HSCT (45% allogeneic and 55% autologous) (Table 1). The analysis showed substantial hetero-

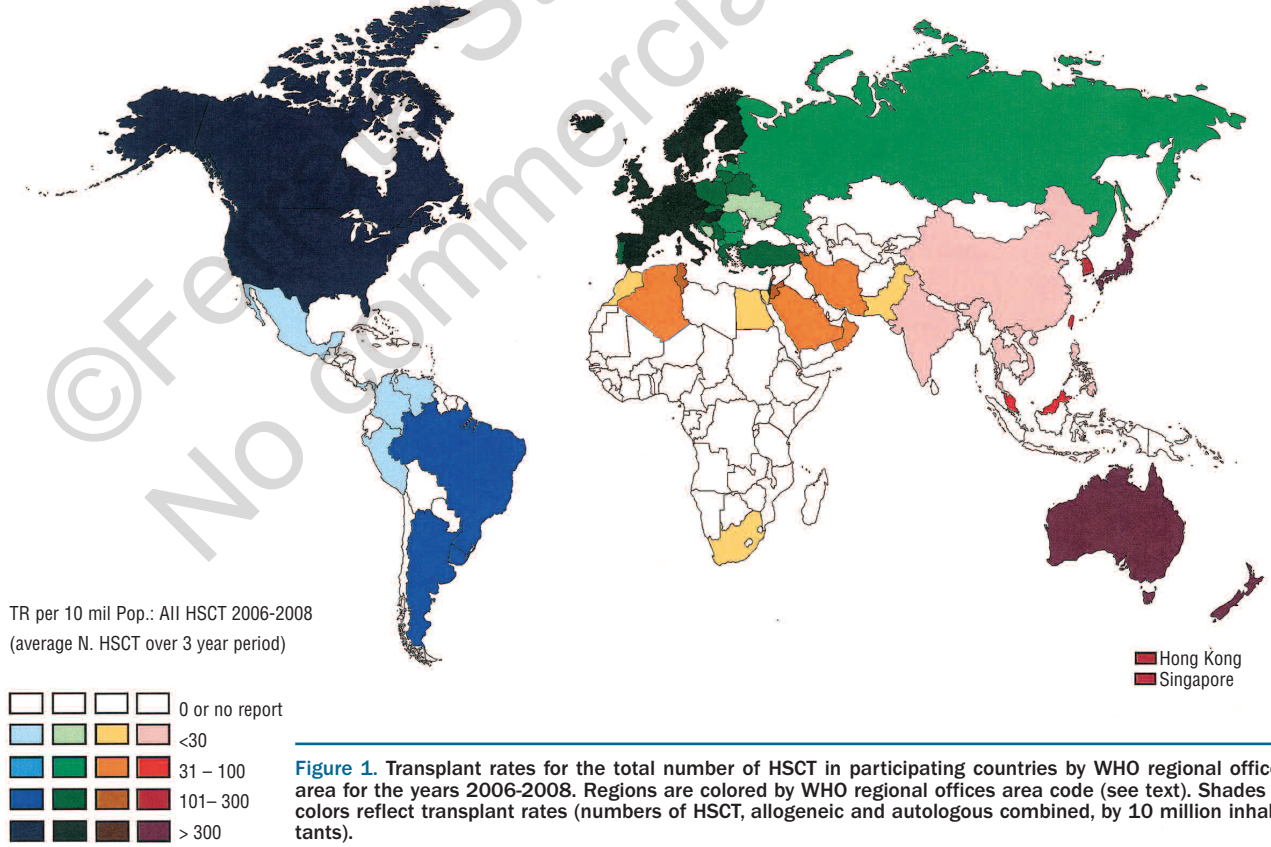

Figure 1. Transplant rates for the total number of HSCT in participating countries by WHO regional offices area for the years 2006-2008. Regions are colored by WHO regional offices area code (see text). Shades of colors reflect transplant rates (numbers of HSCT, allogeneic and autologous combined, by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

geneity in indication and donor type by WHO region. The main indications were lymphoproliferative disorders (53%) and leukemias (36%), followed by solid tumors (5%) and non-malignant disorders and others (6%). There was, however, a distinctly different pattern for allogeneic and autologous HSCT. The main indications for allogeneic HSCT were leukemias (72%), lymphoproliferative disorders (15%) and non-malignant disorders (12%), while the main indications for autologous HSCT were lymphoproliferative disorders (84%), solid tumors (9%) and non-malignant disorders (1%) (Table 1).

Information on stem cell source was available for 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 for whom information on stem cell source was available) were performed from family donors in 51% of cases (43% matched, 7% mismatched/haploidentical, 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 the pattern in America and Europe being significantly different from that in Asia and Eastern Mediterranean/Africa ($P<0.05$) and concerning the repartition of main indications with a higher proportion of non-malignant indications in the Eastern Mediterranean/Africa region ($P<0.01$) 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 HSCT 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 3-year period studied, the average absolute number of HSCT in the participating countries ranged from 1 (Philippines) to 11,228 (USA) (Figure 1). The 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 HSCT and from 0 to 412 (median 81) for autologous HSCT. There were no autologous or allogeneic transplants in countries with fewer than 300,000 inhabitants or with a GNI/capita below $US 690; there were no

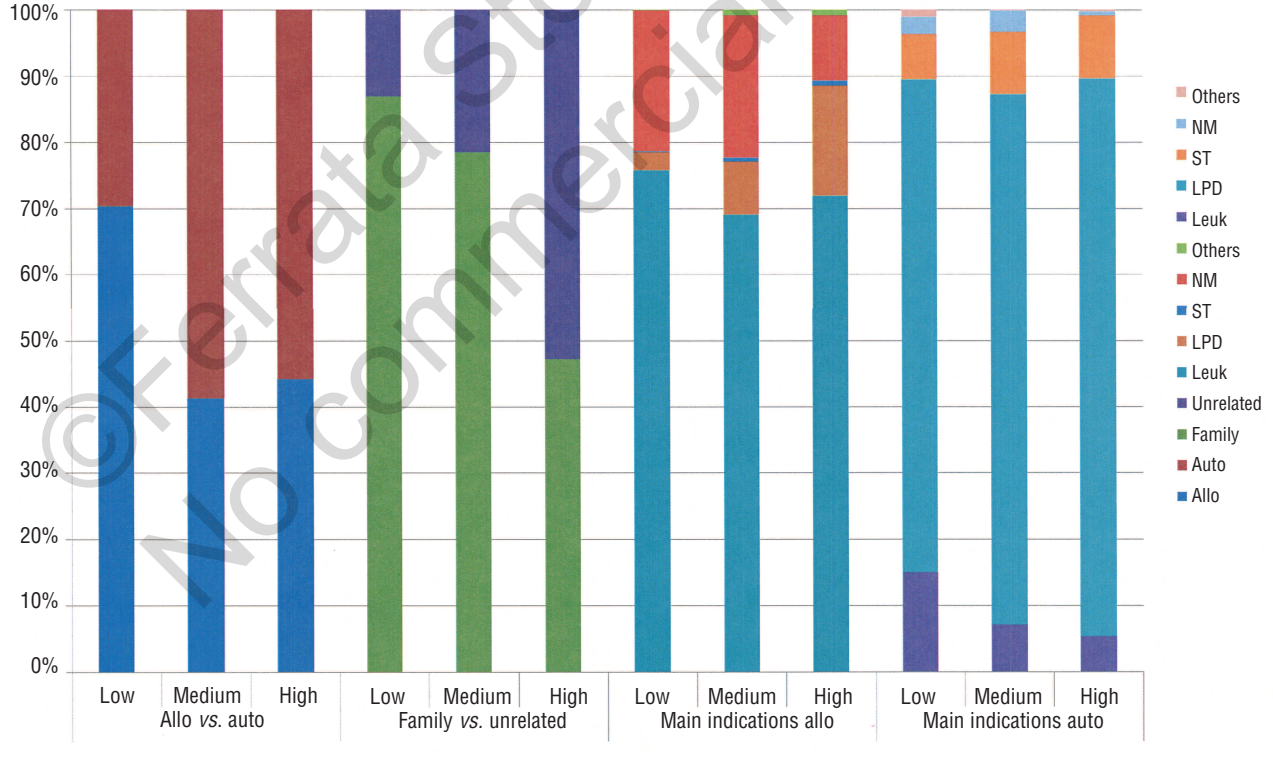

Figure 2. Indications and donor types of 146,808 HSCT by World Bank category in the years 2006-2008. The figure reflects the relative proportions of allogeneic (blue) or autologous (red) HSCT (left three columns), of allogeneic donor type [family donor (green) or unrelated donor (blue)] (central left three columns), main indications for allogeneic HSCT (central right three columns), and main indications for autologous HSCT (right three columns; for color code see figure) by low, middle of high income according to World Bank category. For definitions see the *Design and Methods* section. NM: non-malignant disorders; ST: solid tumors; LPD: lymphoproliferative disorders; Leuk: leukemia.

unrelated donor transplants in countries with a GNI/capita below $US 850.

Transplant rates were significantly associated with common health care indicators, lnGNI/capita (R^2 = 61%) (Figure 3), health care expenditure/capita (R^2 = 64%) or governmental health care expenditure/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 WHO regions.

The association was stronger and with a greater explanatory content for autologous HSCT (R^2 = 55%) than for allogeneic HSCT (R^2 = 49%) as shown for lnGNI/capita (Figure 3A). Explanatory content was higher for unrelated donor 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 non-existent for non-malignant disorders with HSCT from family donors (R^2 = 4%).

Unrelated donor transplant rates were also associated with lnGNI/capita (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 even R^2 =59%. If only countries performing unrelated donor transplants were included in the analysis, the explanatory content reached R^2 =72% (Figure 3C). Unrelated cord blood transplant rates were weakly associated with lnGNI/capita (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/capita: R^2 =5%). The three factors lnGNI/capita, presence of an unrelated donor registry and the number of donors in the respective donor registry also exerted 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/capita 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 from 2006 to 2008

The numbers of HSCT increased from 46,563 in 2006 to 51,536 in 2008 (+10%). The increase in reporting teams from 1,327 in 2006 to 1,407 in 2008 (+6%) was one rea-

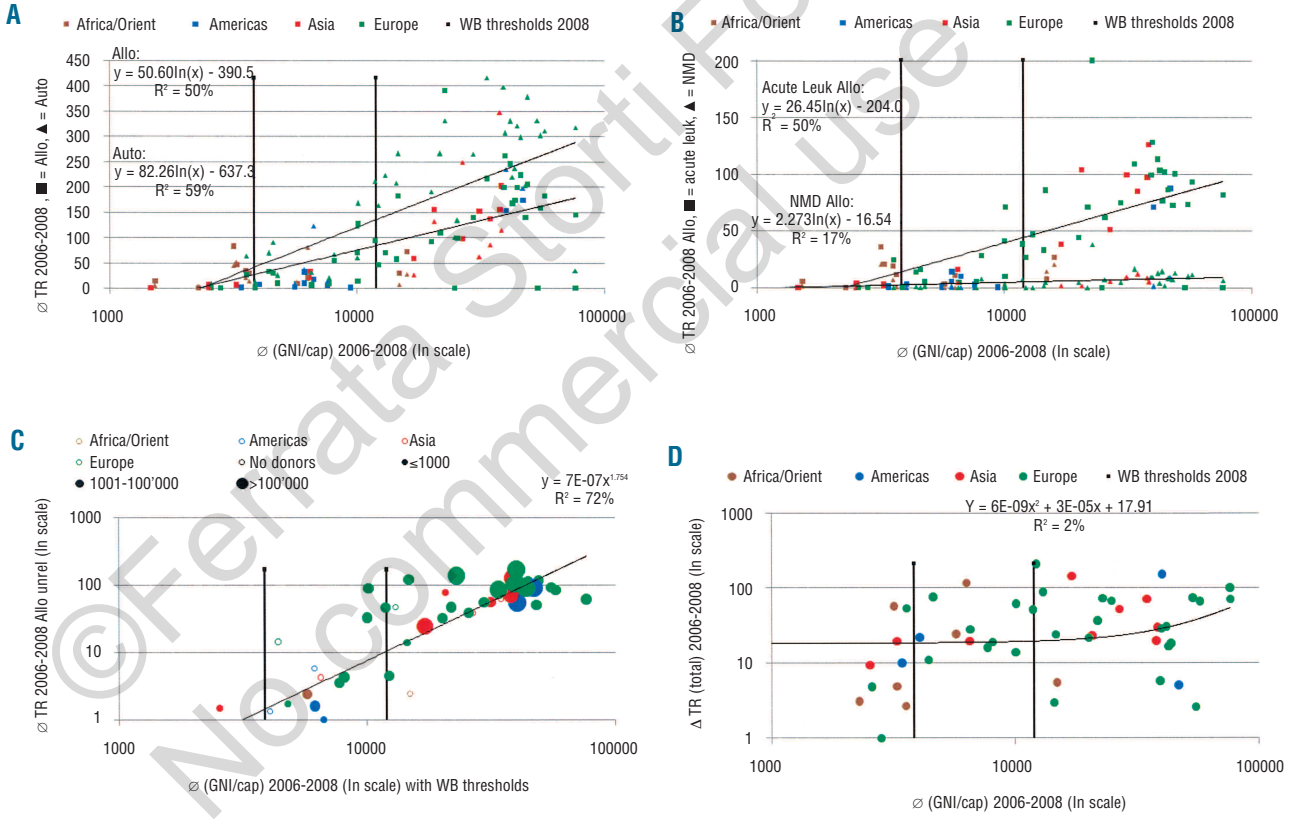

Figure 3. Transplant rates and Gross National Income per capita (GNI/cap). (A) Transplant rates for allogeneic and autologous HSCT by WHO regional offices area, donor type and GNI/cap. Symbols reflect transplant rates (TR; numbers of HSCT by 10 million inhabitants) in participating countries and the respective lnGNI/cap. Colors indicate WHO region (see Figure 1); squares indicate allogeneic HSCT, triangles autologous HSCT. Vertical lines separate countries by World Bank (WB) category. (B) 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. (C) 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 an unrelated donor registry, full symbols the presence of such a 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. (D) 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).

son, 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).

The relative increase was greater for related and unrelated allogeneic HSCT (+17%) than for autologous HSCT (+5%; Figure 4A). The greatest increase in absolute and relative numbers was observed in the Asia/Western Pacific region (+39%; Figure 4B) for both allogeneic (+50%) and autologous (+22%) HSCT, followed by Europe (+6% overall; allogeneic +10%, autologous +3%), the Americas (+4% overall; allogeneic +9%, autologous +1%, and the Eastern Mediterranean/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 or 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, and by family donor HSCT for patients with non-malignant disorders in Asia and the Eastern Mediterranean /Africa.

The numbers of autologous HSCT increased for lymphoproliferative disorders (+8%) and decreased for leukemia (-15%) and solid tumors (-2%) as shown in Figure 4D. The 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 leukemia (+27%) and chronic lymphocytic lymphocytic (+24.6%), which all increased, compared to chronic myeloid leukemia (-17%), for which fewer allogeneic HSCT were performed. 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 incomes (R^2 = 11%) did

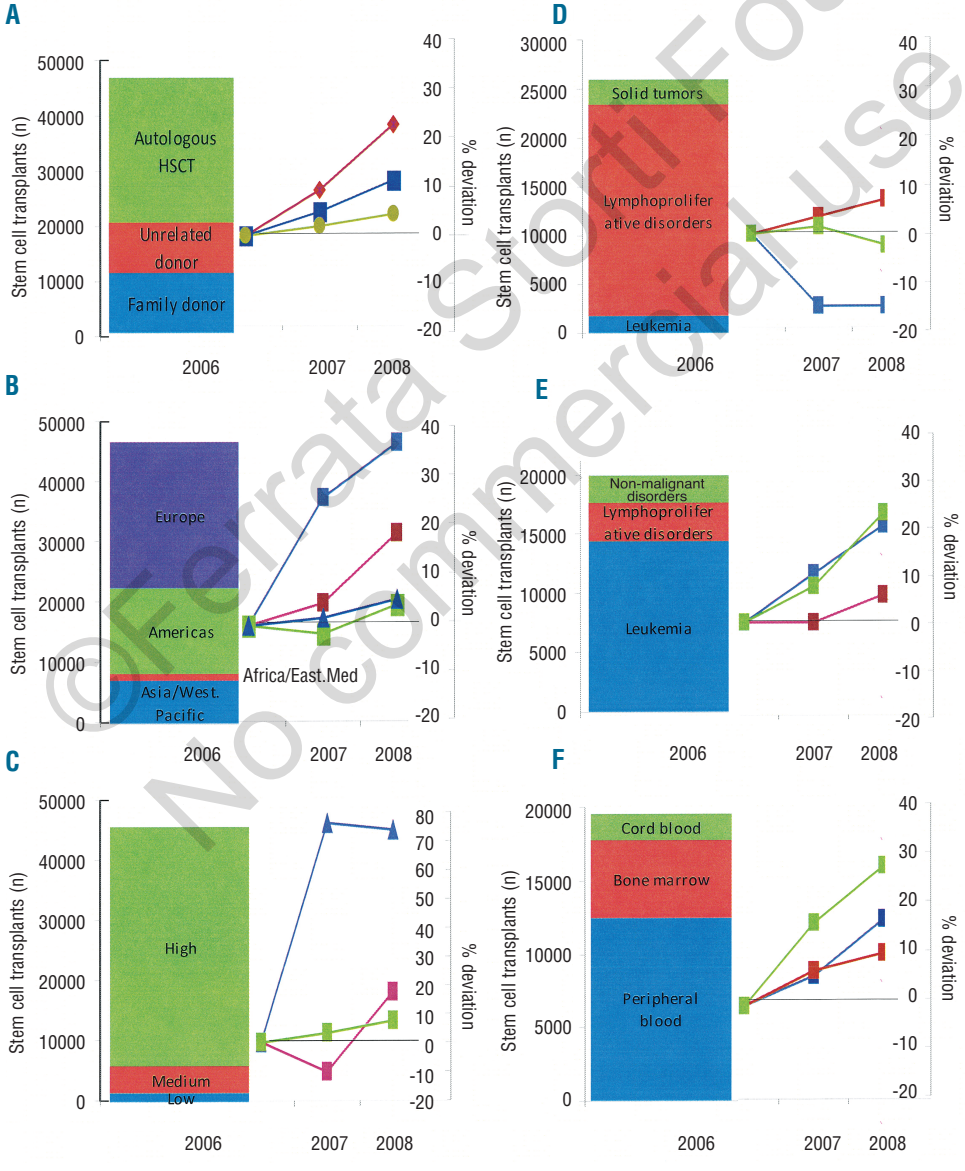

Figure 4. Total HSCT in 2006 and relative increase or decrease (in %) in 2007 and 2008 according to (A) donor type, (B) WHO region, (C) World Bank Category (high, medium and low income by GNI/capita), (D) autologous transplant indication, (E) allogeneic transplant indication and (F) allogeneic stem cell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

not translate into a greater increase in transplant rates. In contrast transplant rates were weakly but positively associated with lnGNI/capita (R^2 = 3%) (Figure 3D). Linear trend analysis confirmed this with there being 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/capita over time (R^2 = 1%).

Discussion

This global analysis shows that availability of resources has quantitative and qualitative impacts on the use of HSCT. 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/capita, as illustrated by the higher explanatory content for autologous HSCT. In contrast, countries with limited resources preferentially restrict the 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, reflect differences in resources rather than in opinions. It is comforting to observe the continued increase in transplant numbers in low income countries, but it remains a concern that transplant rates increased to a greater extent in high income than in middle or low income countries and the gap between the countries is widening.

Transplant rates were associated with GNI/capita 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. Factors other than availability of resources must come into play. One factor could be related to different beliefs of the medical community on the value of a given therapy in different countries. However, the focus on transplantation from matched family donors for non-malignant disorders and chronic leukemia in lower income countries is suggestive of 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]

The 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 macro-economic aspects or on cost-effectiveness in individual countries have gained broader acceptance only recently.[11,21,22,25] They were triggered in part by some rapid changes in the use of HSCT, such as for breast cancer or chronic myeloid leukemia[18,26] and by the rising 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/capita, 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 prevalences or missing information. Some congenital non-malignant disorders such as immune deficiency syndromes or hemoglobinopathies are highly present in some countries and absent in others.[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 countries, limited to allogeneic HSCT in other countries and not required in other countries. The discrepancy between performed and reported HSCT might be higher for autologous HSCT 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]

This report gives no information on outcome. Such a report would require additional time and another framework. Outcome is influenced by many factors, including the disease, the pre-treatment, characteristics of the patients and donors, transplant techniques, the transplant team, its quality management system and the income of the country in which the transplants take place.[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 of benefiting 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 should also be well targeted according to specific cost-effectiveness considerations and needs in the individual countries.[36,37]

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