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Hematopoietic Stem Cell Transplantation

A Global Perspective

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HEMATOPOIETIC STEM CELL transplantation (HSCT) has become the standard of care for many patients with defined congenital or acquired disorders of the hematopoietic system or with chemosensitive, radiosensitive, or immunosensitive malignancies.¹⁻³ Over the last 2 decades, HSCT has seen rapid expansion in use and a constant evolution in its technology. Novel indications are currently under evaluation.^{4,5} Bone marrow is supplemented as a stem cell source by peripheral blood or cord blood. More than 14 million typed volunteer donors or cord blood units from the many registries worldwide provide stem cells for patients without family donors. Novel conditioning regimens with lower intensity have expanded the use of HSCT to older patients and to those with comorbidities.⁶⁻⁹

Context Hematopoietic stem cell transplantation (HSCT) requires significant infrastructure. Little is known about HSCT use and the factors associated with it on a global level.

Objectives To determine current use of HSCT to assess differences in its application and to explore associations of macroeconomic factors with transplant rates on a global level.

Design, Setting, and Patients Retrospective survey study of patients receiving allogeneic and autologous HSCTs for 2006 collected by 1327 centers in 71 participating countries of the Worldwide Network for Blood and Marrow Transplantation. The regional areas used herein are (1) the Americas (the corresponding World Health Organization regions are North and South America); (2) Asia (Southeast Asia and the Western Pacific Region, which includes Australia and New Zealand); (3) Europe (includes Turkey and Israel); and (4) the Eastern Mediterranean and Africa.

Main Outcome Measures Transplant rates (number of HSCTs per 10 million inhabitants) by indication, donor type, and country; description of main differences in HSCT use; and macroeconomic factors of reporting countries associated with HSCT rates.

Results There were 50 417 first HSCTs; 21 516 allogeneic (43%) and 28 901 autologous (57%). The median HSCT rates varied between regions and countries from 48.5 (range, 2.5-505.4) in the Americas, 184 (range, 0.6-488.5) in Asia, 268.9 (range, 5.7-792.1) in Europe, and 47.7 (range, 2.8-95.3) in the Eastern Mediterranean and Africa. No HSCTs were performed in countries with less than 300 000 inhabitants, smaller than 960 km², or having less than US \$680 gross national income per capita. Use of allogeneic or autologous HSCT, unrelated or family donors for allogeneic HSCT, and proportions of disease indications varied significantly between countries and regions. In linear regression analyses, government health care expenditures ($r^2=77.33$), HSCT team density (indicates the number of transplant teams per 1 million inhabitants; $r^2=76.28$), human development index ($r^2=74.36$), and gross national income per capita ($r^2=74.04$) showed the highest associations with HSCT rates.

Conclusion Hematopoietic stem cell transplantation is used for a broad spectrum of indications worldwide, but most frequently in countries with higher gross national incomes, higher governmental health care expenditures, and higher team densities.

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Still, HSCT remains associated with significant morbidity and mortality and represents one example of high-cost, highly specialized medicine. It requires significant infrastructure and a network of specialists from all fields of medicine. Hence, information on indications, use of specific technologies, and trends in the application of HSCT is essential for correct patient counseling and for health care agencies to prepare the necessary infrastructure and to avoid planning errors.¹⁰⁻¹³ In addition, HSCT is no longer limited to countries with abundant resources. For selected indications, HSCT might represent the most cost-effective therapy in some countries.¹⁴ An assessment of global HSCT activity is warranted.

In view of the increasing numbers of transplant teams and HSCTs worldwide and the increasing awareness of the need for a global perspective for all cell, tissue, and organ transplants by the

World Health Organization,¹⁵ the recently founded Worldwide Network for Blood and Marrow Transplantation decided to collect standardized HSCT activity data on a global level. Results of the first worldwide HSCT survey are presented herein.

METHODS

Study Design

This is a retrospective survey among all HSCT teams known to the investigators, which was organized by the Worldwide Network for Blood and Marrow Transplantation through established international and regional organizations. The study was approved by the ethics committee of the University of Basel; and the need for informed consent of patients was waived because no individualized data was transferred to the investigators.

The main outcome measures were the determination of transplant rates

(number of HSCTs per 10 million inhabitants) by indication, donor type, and country on a global level. Secondary outcomes were the description of the main differences in HSCT use and the key macroeconomic factors of the reporting countries and regions associated with their transplant rates.

Participating Groups, Continents, Countries, and Teams

There were 1327 teams in 71 reporting countries over 5 continents (see eTable at <http://www.jama.com>) that provided information on numbers of HSCT for 2006 by indication and donor type (TABLE 1).¹⁶ They were subdivided into 4 regions: (1) the Americas (the corresponding World Health Organization regions are North and South America), (2) Asia (Southeast Asia and the Western Pacific Region, which includes Australia and New Zealand), (3) Europe (which includes Tur-

Table 1. Hematopoietic Stem Cell Transplants Worldwide in 2006^a

	Allogeneic Donor			Autologous Donor (n = 28 901)	Total (N = 50 417)
	Family (n = 11 928)	Unrelated (n = 9588)	Total (n = 21 516)		
Leukemia	8122 (68.1)	7088 (73.9)	15 210 (70.7)	1839 (6.4)	17 049 (33.8)
Acute myeloid leukemia	3907 (48.1)	3119 (44.0)	7026 (46.2)	1372 (74.6)	8398 (49.3)
Acute lymphoblastic leukemia	1799 (22.1)	1850 (26.1)	3649 (24.0)	216 (11.7)	3865 (22.7)
Myelodysplastic, myeloproliferative syndromes	1151 (14.2)	1248 (17.6)	2399 (15.8)	60 (3.3)	2459 (14.4)
Chronic myeloid leukemia	877 (10.8)	519 (7.3)	1396 (9.2)	14 (1.0)	1410 (8.3)
Chronic lymphocytic leukemia	336 (4.1)	269 (3.8)	605 (4.0)	175 (9.5)	780 (4.6)
Other leukemia	52 (1.0)	83 (1.2)	135 (1.0)	2 (<1.0)	137 (1.0)
Lymphoproliferative disorders	2088 (17.5)	1414 (14.7)	3502 (16.3)	23 990 (83.0)	27 492 (54.5)
Plasma cell disorders	546 (26.1)	287 (20.3)	833 (23.8)	11 877 (49.5)	12 710 (46.2)
Hodgkin disease	270 (12.9)	235 (16.6)	505 (14.4)	3275 (13.7)	3780 (13.7)
Non-Hodgkin lymphoma	1109 (53.1)	708 (50.1)	1817 (51.9)	7943 (33.1)	9760 (35.5)
Other lymphoma (type unknown)	163 (8.0)	184 (13.0)	347 (10.0)	895 (4.0)	1242 (5.0)
Solid tumors	113 (1.0)	40 (<1.0)	153 (<1.0)	2772 (9.6)	2925 (5.8)
Neuroblastoma	22 (19.5)	8 (20.0)	30 (19.6)	615 (22.2)	645 (22.1)
Germinal cancer	3 (3.0)	2 (5.0)	5 (3.3)	518 (18.7)	523 (17.9)
Breast cancer	13 (11.5)	4 (5.0)	17 (11.1)	273 (9.8)	290 (10.0)
Ewing sarcoma	17 (15.0)	6 (20.0)	23 (15.0)	176 (6.3)	199 (6.8)
Other	58 (51.3)	20 (50.0)	78 (51.0)	1190 (42.9)	1268 (43.4)
Nonmalignant disorders	1512 (12.7)	884 (9.0)	2396 (11.1)	197 (1.0)	2593 (5.1)
Bone marrow failures	879 (58.1)	457 (52.0)	1336 (55.8)	0	1336 (51.5)
Hemoglobinopathies	348 (23.0)	54 (6.1)	402 (16.8)	3 (1.5)	405 (15.6)
Immune deficiencies	216 (14.3)	241 (27.3)	457 (19.1)	3 (1.5)	460 (17.7)
Inherited diseases of metabolism	63 (4.0)	122 (13.8)	185 (7.7)	2 (1.0)	187 (7.2)
Autoimmune disorders	6 (<1.0)	10 (1.1)	16 (1.0)	189 (96.0)	205 (8.0)
Other	93 (1.0)	162 (2.0)	255 (1.2)	103 (<1.0)	358 (1.0)

^aValues are expressed as number (column percentage of total and within subgroup). Percentages may not equal 100% due to rounding.

key and Israel), and (4) the Eastern Mediterranean and Africa.

Data were provided by the Asian Pacific Blood and Marrow Transplant Group, the Australian Bone Marrow Transplant Recipient Registry, the Canadian Blood and Marrow Transplant Group, the Center for International Blood and Marrow Transplantation, the Sociedade Brasileira de Transplante de Medula Ossea, the Eastern Mediterranean Blood and Marrow Transplant Group, and the European Group for Blood and Marrow Transplantation (see eTable at <http://www.jama.com>).¹⁷⁻²⁰

Collection System and Data Validation

Data were obtained from mandatory reporting systems of initial transplant data (Australian Bone Marrow Transplant Recipient Registry, Canadian Blood and Marrow Transplant Group, and Center for International Blood and Marrow Transplantation) or collected on separate survey data forms from individual centers or national registries (Asian Pacific Blood and Marrow Transplant Group, European Group for Blood and Marrow Transplantation, Eastern Mediterranean Blood and Marrow Transplant Group, and Sociedade Brasileira de Transplante de Medula Ossea).

Data were validated by several independent methods. The data were first confirmed by the reporting team, which received a computer printout of the entered data. Selective comparison also was used with Med-A data sets in the European Group for Blood and Marrow Transplantation Promise data system or by cross-checking with national registries. Onsite visits of selected teams were part of the quality-control program within the Center for International Blood and Marrow Transplantation and the European Group for Blood and Marrow Transplantation.

Based on quality controls and contacts with regulatory agencies or national offices, response rates of allogeneic HSCT was greater than 95% in Australia, Brazil, Canada, Europe, Japan, Korea, Malaysia, New Zealand,

Taiwan, and the United States. No formal response rate can be evaluated for the other participating countries; there is no formal regulatory framework for cross-confirmation. Concerning autologous HSCT, the response rate in Europe was greater than 90% and it can be estimated to be between 80% and 90% for Australia, Brazil, Canada, Europe, Japan, Korea, Malaysia, New Zealand, Taiwan, and the United States. For autologous HSCT, no formal framework exists to capture nonreporting teams and to validate response rates with accuracy.

Definitions

This Worldwide Network for Blood and Marrow Transplantation survey focused on the numbers of patients treated for the first time with HSCT in 2006. Information on additional transplants (eg, retransplants or multiple HSCTs²¹) was not included.

Transplant rates were computed as the number of HSCTs per 10 million inhabitants.²¹ Transplant rates refer to the number of transplants in a given country compared with its own population, without adjustments for patients who cross borders and receive a HSCT in a foreign country. Population data were obtained from the US census office.

Team density refers to the number of transplant teams per 1 million inhabitants.²² The definition of a team followed the principles of the Foundation for the Accreditation of Cellular Therapy and the Joint Accreditation Committee of the International Society for Cellular Therapy and the European Group for Blood and Marrow Transplantation.

Transplant rates within the reporting participating countries were compared with a range of macroeconomic health care indicators: gross national income per capita; total health care expenditures; governmental health care expenditures; adult, infant and maternal mortality rate; number of hospital beds per capita; cesarean delivery rates; human developmental index, which is a composite index reflecting the devel-

opmental status of all countries in the world in a scale from 0 to 1.0; and team density, which indicates the number of transplant teams per 1 million inhabitants. Data were obtained from the World Bank, the World Health Organization, and the United Nations. Data from 2006 were used for all comparisons whenever possible.

Statistical Analysis

The association of the macroeconomic factors with HSCT rates was estimated by single linear and multiple linear regression analysis, using the least squares method. The linear relationship, positive or negative, between the macroeconomic factors and HSCT rates after transformation was measured using the *t* statistic; a level of 5% was considered significant. The goodness of fit was measured using the coefficient of determination (r^2). For the single and multiple linear regression analyses, the dependent variables were transformed to point out the linear associations. In the multiple regression analyses, all factors were assessed for their multicollinearity. Taiwan and Hong Kong were excluded from the multiple economic comparisons because of missing information on governmental health care expenditures. Cesarean delivery rates were included in the single linear analyses but not the multiple regression analyses, because data from too many countries were missing.

The *t* test was used to evaluate if the 4 world regions had a significant difference in the relative proportion of main indications and donor type (allogeneic vs autologous, unrelated vs family donors); $P = .05$ was considered significant. All statistical analyses were performed with EVIEWS version 5.1 (Quantitative Micro Software, Irvine, California).

RESULTS

A total 50 417 first HSCTs were reported for 2006; 21 516 allogeneic (43%) and 28 901 autologous (57%) (Table 1). The main indications were lymphoproliferative disorders (27 492

patients [54.5%]; 3502 allogeneic [13%] and 23 990 autologous [87%]); leukemias (17 049 patients [33.8%]; 15 210 allogeneic [89%] and 1839 autologous [11%]); solid tumors (2925 patients [5.8%]; 153 allogeneic [5%] and 2772 autologous [95%]); nonmalignant disorders (2593 patients [5.1%]; 2396 allogeneic [92%] and 197 autologous [8%]), and other nonspecified disorders (358 patients; 1%).

The most frequent malignant disease for an allogeneic HSCT was acute myeloid leukemia (n = 7026; 33%), the most frequent nonmalignant disease was bone marrow failure syndrome (n = 1336; 6%), and the most frequent indication for an autologous HSCT was a plasma cell disorder (n = 11 877; 41%).

Most of the 50 417 HSCTs were performed in Europe with 24 216 (48%) (median [range], 255 [6-4619] per country) followed by the Americas with 17 875 (36%) (median [range], 61 [8-15 082] per country), Asia with 7096 (14%) (median [range], 139 [5-3823] per country), and the Eastern Mediterranean and Africa with 1230 (2%) (median [range], 63 [10-360] per country). The absolute numbers of HSCTs in the participating countries ranged from 15 082 in the United States to 5 in Vietnam.

Transplant Rates in 2006

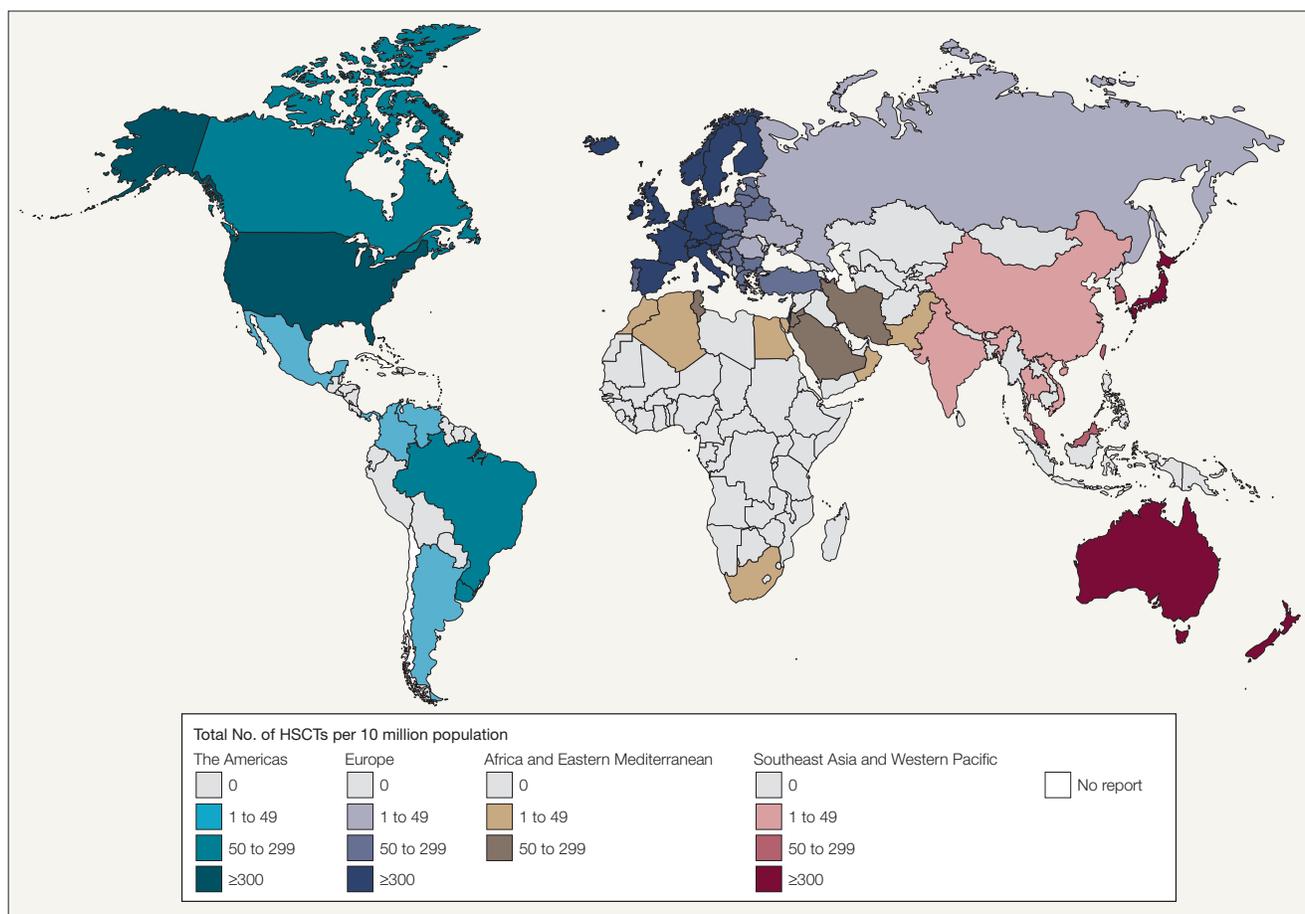
The median HSCT rates varied between the continental regions and between participating countries from 48.5

(range, 2.5-505.4) in the Americas, 184 (range, 0.6-488.5) in Asia, 268.9 (range, 5.7-792.1) in Europe, and 47.7 (range, 2.8-95.3) in the Eastern Mediterranean and Africa (FIGURE 1). Transplant rates for allogeneic HSCT ranged from 434.9 in Israel to 0.2 in Vietnam. Transplant rates for autologous HSCT ranged from 500 in Iceland to 0.3 in Mexico.

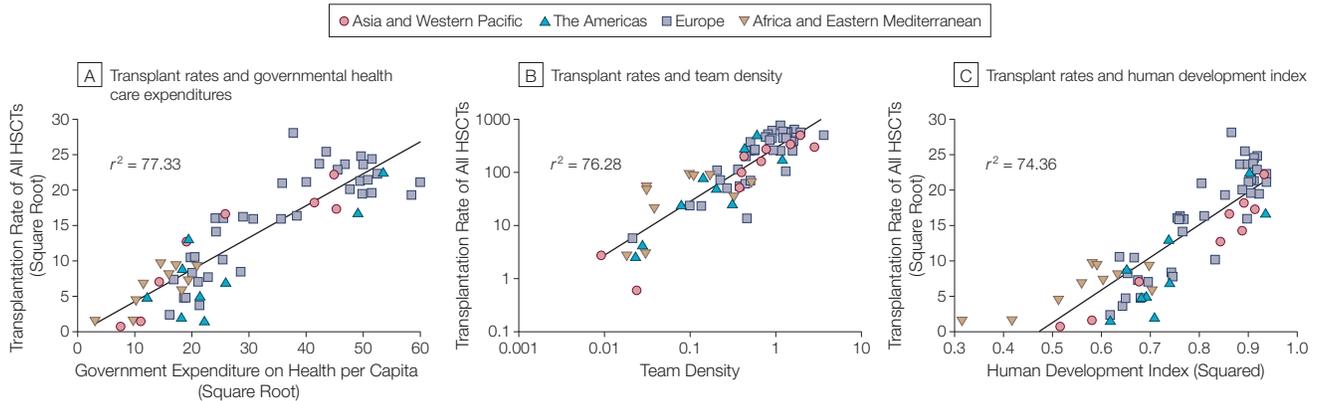
Regional Differences in Donor Type and Main Indications

Overall, there were more autologous HSCTs (n = 28 901; 57%) than allogeneic HSCTs (n = 21 516; 43%) (TABLE 2). Most of the autologous HSCTs occurred in the Americas and Europe. In other regions, allogeneic HSCTs were more common (Asia:

Figure 1. Global Distribution of Hematopoietic Stem Cell Transplantations (HSCTs) in 2006



Regions are colored by World Health Organization regional office code (see text) (<http://www.who.int/about/regions/en/>). Transplant rates indicate the number of first HSCTs per 10 million inhabitants in 2006 and are allogeneic and autologous by continental region.

Figure 2. Macroeconomic Factors and Transplant Rates

Transplant rates indicate the number of first hematopoietic stem cell transplantations (HSCTs) per 10 million inhabitants. Team density indicates the number of transplant teams per 1 million inhabitants. See "Methods" section for explanation of the human development index. Interactive graphs are available at <http://www.jama.com>.

HSCT rates. The second factor, team density (TD), increased R^2 to 79.83%, and the third factor, gross national income (GNI) per capita, added another 4.41% of explanation. All other factors, including the human development index, became insignificant, mainly due to multicollinearity with gross national income per capita, meaning that several factors did correlate highly with each other. Therefore, the equation of the multiple regressions was

$$\sqrt{TR} = c_1\sqrt{GOV} + c_2\ln(TD) + c_3\ln(GNI) + \epsilon$$

Hence, the combined explanatory content was $R^2=84.24$.

COMMENT

This first report by the Worldwide Network for Blood and Marrow Transplantation documents the current state of HSCT on a global level. It describes the achievements, illustrates the major differences, and points to the key needs. Transplant activity is concentrated in countries with higher governmental health care expenditures, higher gross national income per capita, and higher team density. Hence, availability of resources, governmental support, and access to a transplant center are the key factors related to regional HSCT activity. However, disease prevalence can

differ between regions and could contribute to differences in HSCT rates; those data were not included in this report.

The close link of HSCT rates with gross national income per capita was recognized many years ago; HSCT is an expensive procedure with a substantial investment for a single patient.²¹ No HSCTs were performed in countries with less than US \$700 gross national income per capita. However, gross national income per capita explained only parts of the variations. Therefore, we were specifically interested in other macroeconomic factors associated with HSCT rates. These factors were chosen with intention. They were either directly linked to availability of resources (gross national income per capita, health care expenditures), to governmental support (governmental health care expenditures), or to the overall infrastructure in a country (human development index). Others reflect quality measures of the health care system (mortality rates) or indicate potential overuse of the health care system (hospital beds, cesarean delivery). Of all macroeconomic factors, this study identified governmental health care expenditures as the most closely associated factor with HSCT rates.

Our study could not assess the role of the health care system in the partici-

pating countries because there is no globally accepted definition available. Definitive explanations cannot be given, but some assumptions can be made. The cost-effectiveness of HSCT compared with conventional treatment has at least recently been discussed for patients with chronic myeloid leukemia in middle-income countries.^{14,23} Transplant rates were strongly associated with team density. There was no indication for saturation in this association. Hence, a minimum number of transplant teams per inhabitants must be available so that patients have sufficient access. It does not appear that transplant teams overuse their infrastructure.^{22,24} None of the other traditional health care indicators or the composite human development index provided a higher explanatory content or added information in the multiple regression analyses.

There were significant differences between the regions concerning indications and donor type, with fewer autologous HSCTs in Asia and the Eastern Mediterranean and Africa than in the Americas and Europe. There were more unrelated donors for HSCTs in the Americas, Asia, and Europe than in the Eastern Mediterranean and Africa; the highest proportion of unrelated donors for HSCTs was in Japan. There also were more HLA identical sibling donor HSCTs for congenital disorders or

for aplastic anemia in countries with limited resources. A matched sibling donor HSCT might represent the most efficient way of therapy for a patient with aplastic anemia, thalassemia, or severe combined immunodeficiency in a country with some but still limited resources. No induction, consolidation chemotherapy is needed as would be the case for patients with acute leukemia.^{15,23}

There are some limitations of this study that warrant caution in interpretation. The organizations collecting the data had neither legal enforcement to obtain nor the possibility to control all data locally for accuracy and completeness. Cross-checks with national organizations indicate that the report covers nearly 100% of all HSCTs within their country. A few countries choose not to report any data. Most missing information relates to numbers of autologous HSCTs because they are performed in some countries outside of the realm of national transplant organizations and in nonuniversity institutions. Despite these limitations, the main observations of this study regarding the main indications, donor type, transplant rates, and associations with macroeconomic factors should remain valid. Finally, we had neither information on outcome of the transplant procedures nor on correctness of the indication; this is beyond the scope of this study and would require a much longer follow-up time.²⁴

This study was in part triggered by the increasing awareness by scientific and health care organizations, including the World Health Organization, to address key aspects of cell, tissue, and organ transplantation on a global level. In contrast to solid organ transplantation, HSCT faces limitations other than donor organ shortage.²⁵ Patients are in need of a closely matched donor, family or unrelated donor, but there are many unrelated donor registries and public cord blood banks throughout the world. In 2008, there were, for the first time, more unrelated donor HSCTs than family donor HSCTs reported to the European survey and more unrelated

HSCTs across than within borders. In addition to traditional HSCT, novel treatment forms with hematopoietic stem cells for nonhematopoietic use or transplantation of nonhematopoietic stem cells for organ and tissue repair are under investigation.²⁶⁻²⁹ The challenges with these new forms of therapy have recently been addressed; stem cell tourism has become a topic of concern.³⁰ Information on the current status of HSCT use has become a necessity for correct patient counseling and health care planning.

In conclusion, this global overview on HSCT activity demonstrates that it is an accepted therapy worldwide, with different needs and priorities in different regions. Transplant activity is concentrated in countries with higher health care expenditures, higher gross national income per capita, and higher team density; hence, the availability of resources, governmental support, and access to a transplant center determine regional HSCT activity.

Author Contributions: Dr A. Gratwohl had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: A. Gratwohl, Bouzas, Yoshimi, Szer, Niederwieser, Horowitz, Kodera.

Acquisition of data: Baldomero, Aljurf, Pasquini, Bouzas, Yoshimi, Lipton, Horowitz, Kodera.

Analysis and interpretation of data: A. Gratwohl, Baldomero, Bouzas, Yoshimi, Szer, Schwendener, M. Gratwohl, Frauendorfer, Niederwieser, Horowitz, Kodera.

Drafting of the manuscript: A. Gratwohl, Pasquini, Bouzas, Yoshimi, Szer, Niederwieser, Kodera.

Critical revision of the manuscript for important intellectual content: Baldomero, Aljurf, Bouzas, Yoshimi, Szer, Lipton, Schwendener, M. Gratwohl, Frauendorfer, Niederwieser, Horowitz, Kodera.

Statistical analysis: Pasquini, Bouzas, Yoshimi, Schwendener, M. Gratwohl, Frauendorfer, Kodera.

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Study supervision: A. Gratwohl, Pasquini, Bouzas, Yoshimi, Lipton, Kodera.

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Disclaimer: 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 US government.

Online-Only Material: eTable and interactive graphs are available at <http://www.jama.com>.

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