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One and a half million hematopoietic stem cell transplants: continuous and differential improvement in worldwide access with the use of non-identical family donors



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ABSTRACT

The Worldwide Network of Blood and Marrow Transplantation (WBMT) pursues the mission of promoting hematopoietic cell transplantation (HCT) for instance by evaluating activities through member societies, national registries and individual centers. In 2016, 82,718 first HCT were reported by 1,662 HCT teams in 86 of the 195 World Health Organization member states representing a global increase of 6.2% in autologous HCT and 7.0% in allogeneic HCT and bringing the total to 1,298,897 procedures. Assuming a frequency of 84,000/year, 1.5 million HCT were performed by 2019 since 1957. Slightly more autologous (53.5%) than allogeneic and more related (53.6%) than unrelated HCT were reported. A remarkable increase was noted in haploidentical related HCT for leukemias and lymphoproliferative diseases, but even more in non-malignant diseases. Transplant rates (TR; HCT/10 million population) varied according to region reaching 560.8 in North America, 438.5 in Europe, 76.7 in Latin America, 53.6 in South East Asia/Western Pacific (SEA/WPR) and 27.8 in African/East Mediterranean (AFR/EMR). Interestingly, haploidentical TR amounted to 32% in SEA/WPR and 26% in Latin America, but only 14% in Europe and EMR and 4.9% in North America of all allogeneic HCT. HCT team density (teams/10 million population) was highest in Europe (7.7) followed by North America (6.0), SEA/WPR (1.9), Latin America (1.6) and AFR/EMR (0.4). HCT are increasing steadily worldwide with narrowing gaps between regions and greater increase in allogeneic compared to autologous activity. While related HCT is rising, largely due to increase in haploidentical HCT, unrelated HCT is plateauing and cord blood HCT is in decline.

Introduction

Allogeneic and autologous hematopoietic stem cell transplantation (HCT) is considered a routine but complex therapy for patients with otherwise incurable chemo- and immune-sensitive malignant and non-malignant disorders.¹ The treatment is also used for replacing deficient hematopoietic cells or cellular components and more recently for repairing hematopoietic stem cells by gene editing. Despite its increasing applications and international expansion of access, allogeneic HCT is still associated with significant morbidity and mortality and remains an example of highly specialized, high-cost medicine. It requires extensive experience, significant infrastructure and a network of specialists from all fields of medicine. Over the last two decades in particular, allogeneic HCT has undergone a constant technological evolution, with decreasing transplant related-morbidity and mortality and expansion of the donor pool. This has been achieved by optimizing indications, by manipulating alloreactive immune reactions *ex vivo* and *in vivo* and by using novel reduced or minimal intensity conditioning regimens.² As a result, HCT is being offered to patients without a matched donor, to older patients and to those with comorbidities.³⁻⁵ The predominant autologous HCT transplant type, in contrast, relies exclusively on the high-dose preparative regimen for tumor eradication or for reshaping the immune system in autoimmune diseases.^{6,7} Patients' own hematopoietic stem cells are required to rebuild a normal hematopoietic system after the intensive preparative regimen. Missing graft-*versus*-host disease leads to extremely low mortality, but missing graft-*versus*-tumor effects to high relapse rates. It is not surprising that autologous HCT involves different treatment strategies and indications as compared to allogeneic HCT, but like allogeneic HCT it requires extensive experience, significant infrastructure and a network of specialists from all fields of medicine.

However, the increasing specialization and complexity of health care systems required, threaten global equity of access to HCT. The World Health Organization (WHO;

www.who.org) declared the transplantation of organs, cells and tissues a global priority and formed a task force to address quality, safety and equity of access. In order to achieve this, analysis of baseline global activity and evolving trends is essential.⁸ The Worldwide Network for Blood and Marrow Transplantation (WBMT; www.wbmt.org), is a non-governmental (NGO) umbrella organization in the field of HCT and in collaboration with the WHO, has taken up the challenge of collecting and disseminating global HCT activity data on a regular basis. Information on indications, the use of different technologies, donor types and trends over time provide a sound basis for physicians to provide appropriate patient counseling and for health care agencies to develop the necessary infrastructure. Informed by global activity survey data, the WBMT performs worldwide workshops to support the development of new HCT programs and to optimize existing programs. The ability to share accumulated experience covering a wide range of strategies, successes and pitfalls continues to be key in improving global HCT access for patients in need.

The first WBMT HCT activity report was based on the global HCT activity in 2006.⁸ This was followed by an updated report in 2010.⁹ After reaching the global milestone of one million HCT in 2012,¹⁰ the WBMT focused on analyzing major trends from 2006 onwards¹¹ and noted a narrowing of gaps in the African/East Mediterranean (AFR/EMRO) regions.¹²

The success of HCT depends on a number of factors including, the early and effective control of the underlying disease prior to HCT, risk of relapse of the underlying disease and donor characteristics. Over the past decade, the rapid evolution of molecular diagnostic and prognostic techniques has led to the emergence of more accurate prognostic tools and effective targeted molecular therapies for malignant hematological diseases.

We report on the global activity trends between 2014 and 2016 compared to 2006 with a specific focus on global trends in equity of access, in indications of HCT and in donor type.

Methods

Study design

In this retrospective observational survey we analyzed the worldwide HCT activity from the first published series of bone marrow transplants collected from the scientific literature and from member societies for very early transplants.¹¹ After 2006, activities were obtained annually through the WBMT network using a unified center-based reporting system. Information from 2016 onwards is given as prediction based on currently available incomplete and non-validated data.

Main outcome measures were the spread of HCT over time and transplant by donor type, country of origin, and WHO region. Secondary outcome measures were to document any trends in the number of HCT by donor type or region, to classify these trends, and quantify differences in the use of autologous or allogeneic HCT across indications and regions.

No individual patient data were used and no ethics committee approval was mandated. Outcome information is not available from our center-specific registry and we opted against the report of fragmented outcome information of just two developed regions (EBMT and CIBMTR).

Data collection and validation

Global transplant numbers by country of origin, year of transplant, disease and donor type (autologous vs. allogeneic) have been collected since 2006 (foundation year of the WBMT) in 194 WHO member states through the registries of the reporting member organizations, or national registries or transplant centers directly either in paper form or electronically using the standardized WBMT form. Detailed and validated information about main indication including stage of the disease, stem cell source, and allogeneic (family matched, family mismatched and unrelated) donor type were obtained for the years 2006 to 2016. Data were validated by a range of different independent systems; through confirmation by the reporting teams, following receipt of a computer print-out of the entered data, by selective comparison with MED-A/TED datasets in the EBMT or CIBMTR data system or by cross-checking for double reporting with national registries. Data were validated by onsite visits to selected teams to verify reported data as part of the quality control program within the European, North American, Latin American and Asia-Pacific organizations. On-site visits to selected teams were part of the quality-control accreditation program of JACIE (www.ebmt.org/jacie-accreditation) or FACT (www.factweb.org). Based on quality controls and contacts with regulatory agencies or national offices, the response rate for allogeneic HCT was estimated to be >95% and for autologous HCT 80–90%. The number of potential missing transplant numbers is estimated to be less than 5% for allogeneic HCT and less than 15% for autologous HCT. This number is much lower for Australia, Canada, Europe, Japan, and the USA. The survey focuses on the numbers of patients treated for the first time with HCT.

Participating hematopoietic cell transplantation (HCT) teams, groups, countries and continents

In 2016, 1,662 HCT teams in 86 countries over six WHO continental regions delivered HCT services globally [www.who.int/about/regions/en/]. These regions included the Americas (AMR/PAHO; WHO regions North-, Middle and South America and Canada); Asia (SEAR/WPR; WHO regions South East Asia and Western Pacific Region, which includes Australia and New Zealand); Europe (EUR; which includes Turkey and Israel) and AFR/EMR (WHO regions Africa and Eastern Mediterranean). For specific analyses AMR/PAHO activities were divided in North America and Latin-America and AFR/EMR in Africa and EMR. A

detailed list of organizations providing activity data and definitions used in the manuscript are reported in the *Online Supplementary Appendix*.

Statistical analysis

The data analysis was comprised of ordinary least squares regressions for trends, χ^2 tests for independent proportions of indications, and binomial tests for donor type. Calculations were done in Eviews⁹ and Excel 2010 (Microsoft).

Results

Total hematopoietic cell transplantations and overall trends

From 1957-2016, a total of 1,298,897 HCT (57.1% autologous) procedures were recorded. The cumulative numbers increased continuously from 10,000 in 1985, to 500,000 in 2005 and doubled to 1 million HCT by 2012. Projecting a frequency of at least 86,844 HCT for 2017 and 89,510 HCT for 2018 (incomplete and not validated data), a total of 1.5 million HCT worldwide was expected to be reached by 2019 (*Online Supplementary Figure S1*). The annual activity increased continuously from 46,563 in 2006 to 82,718 in 2016, amounting to a global increase of 77.6% since 2006, which was somewhat higher in allogeneic (89.0%) than in autologous HCT (68.9%, Table 1). The yearly increase was by a median of 5.9% for all HCT (allogeneic 6.8% and autologous 5.9%) to a total of 697,934 procedures (54% autologous) since 2006. The most frequent indications were lymphoproliferative disorders (LPD; n=370,884 HCT of which 88.4% were autologous) and leukemia (n=248,860 total of which 94.9% were allogeneic; see the *Online Supplementary Figure S2*). Global HCT team numbers plateaued in the last 4 years with a slight increase in 2016 (*Online Supplementary Figure S3*), while annual HCT numbers increased continuously. The increase was not a consequence of more reporting HCT teams, but of increased activity per HCT team. While the overall number of HCT per team was 35.1 in 2006, this reached 49.8 in 2016 (*Online Supplementary Figure S3*). Absolute numbers of all HCT per countries ranged from 0 to 19,505.

Hematopoietic cell transplantation teams activity in 2016

In 2016, the rates of HCT exceeded 80,000 HCT per year for the first time with 82,718 HCT (53.5% autologous) reported in the global HCT activity survey (Table 1). The majority of HCT were performed in Europe (45.2%) and in North America (24.4%), while SEAR/WPR contributed with 22.7%, Latin-America with 5.1% and AFR/EMR with 2.7%. The trends for TR were somewhat different, with rates highest in North America (561 TR), followed by Europe (439 TR), Latin America (77 TR), SEAR/WPR (54 TR), EMR (36 TR) and Africa (9 TR) (Figure 1). TR were higher for autologous than for allogeneic HCT in all regions except for SEAR/WPR, EMR and AFR. TR for allogeneic HCT ranged from 0.3 in Morocco to 414.0 in Israel (median 47.6); and for autologous HCT from 0.1 in Egypt to 705.9 in Iceland (median 99.1).

The number of HCT teams varied considerably across regions, with the highest numbers being in SEAR/WPR and Europe (Figure 2). In contrast, TD ranged from 0.05-29.4/country and was highest in Europe (7.7 TD) followed

Table 1. Global hematopoietic cell transplantation (HCT) activity in 2006, 2016 and changes according to disease indication, donor type and world region.

	Family			Unrelated			Allogeneic			Autologous			Total			
	2006	2016	Δ % (06-16)	2006	2016	Δ % (06-16)	2006	2016	Δ % (06-16)	2006	2016	Δ % (06-16)	2006	2016	Δ % (06-16)	2016 %
Leukemias	7,491	14,992	100	6,901	13,727	99	14,392	28,719	99.5	1,726	844	-51.1	16,118	29,563	83.4	35.7
AML	3,587	7,531	110	3,024	6,803	125	6,611	14,334	116.8	1,269	631	-50.3	7,880	14,965	89.9	18.1
ALL	1,679	3,965	136	1,809	2,930	62	3,488	6,895	97.7	209	155	-25.8	3,697	7,050	90.7	8.5
CML	826	624	-24	508	484	-5	1,334	1,108	-16.9	14	1	-92.9	1,348	1,109	-17.7	1.3
MDS/MPS	1,052	2,472	135	1,216	3,144	159	2,268	5,616	147.6	59	10	-83.1	2,327	5,626	141.8	6.8
CLL	295	220	-25	261	240	-8	556	460	-17.3	173	22	-87.3	729	482	-33.9	0.6
Other leukemias	52	180	246	83	126	52	135	306	126.7	2	25	1,150.0	137	331	141.6	0.4
LPD	1,863	2,023	9	1,356	1,949	44	3,219	3,972	23.4	21,655	39,878	84.2	24,874	43,850	76.3	53.0
Plasma cell disorders	490	312	-36	283	348	23	773	660	-14.6	10,675	23,701	122.0	11,448	24,361	112.8	29.5
HD/NHL	1,373	1,673	21	1,073	1,573	47	2,446	3,246	32.7	10,980	16,103	46.7	13,426	19,349	44.1	23.4
Lymphoma other/unknown	0	38		0	28		0	66		0	74		0	140		0.2
Solid tumors	110	47	-57	40	37	-7	150	84	-44.0	2,560	2,853	11.4	2,710	2,937	8.4	3.6
Non-malignant disorders	1,458	3,423	134	902	2,004	122	2,360	5,427	139.4	193	691	258.0	2,553	6,118	139.6	7.3
Bone marrow failures	840	1,775	111	452	909	101	1,292	2,684	107.7	0	6		1,292	2,690	108.2	3.3
Hemoglobinopathies	338	962	185	54	301	457	392	1,263	222.2	3	10	233.3	395	1,273	222.3	1.5
Immune deficiencies	206	472	129	239	500	109	445	972	118.4	3	15	400.0	448	987	120.3	1.2
Inherited diseases of metabolism	59	111	88	118	182	54	177	293	65.5	2	4	100.0	179	297	65.9	0.4
Autoimmune disorders	6	19	217	10	22	120	16	41	156.3	184	637	246.2	200	678	239.0	0.8
Other non-malignant disorders	9	84	833	29	90	210	38	174	357.9	1	19	1,800.0	39	193	394.9	0.2
Others	80	109	36	132	114	-14	212	223	5.2	96	27	-71.9	308	250	-18.8	0.3
EUR	4,906	7,074	44	4,222	8,348	98	9,128	15,422	69.0	15,088	21,946	45.5	24,216	37,368	54.3	45.2
North America	2,580	3,680	42.6	2,878	4,458	54.9	5,458	8,138	49.1	6,730	12,006	78.4	12,188	20,144	65.3	24.4
SEAR/WPR	1,948	7,392	279	2,110	4,513	114	4,058	11,905	193.4	3,038	6,884	126.6	7,096	18,789	164.8	22.7
Latin America	771	1,197	55.3	115	438	280.9	886	1,635	84.5	947	2,561	170.4	1,833	4,196	128.9	5.1
EMR/AFR	797	1,251	57	6	74	1,133	803	1,325	65.0	427	896	109.8	1,230	2,221	80.6	2.7
TOTAL	11,002	20,594	87.0	9,331	17,831	91.0	20,333	38,425	89.0	26,230	44,293	68.9	46,563	82,718	77.6	100

Δ (06/16) Difference from 2006 to 2016 in %; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; CML: chronic myeloid leukemia; MDS/MPS: myelodysplastic syndrome/myeloproliferative syndrome; CLL: chronic lymphocytic leukemia; LPD: lymphoproliferative disorders; EUR: Europe; SEAR/WPR: South East Asia Pacific Region/West Pacific Region; EMR/AFR: East Mediterranean Region/African Region.

by North America (6.0 TD), SEAR/WPR (1.9 TD), Latin America (1.6 TD), EMR (0.4 TD) and Africa (0.3 TD). Accordingly, the most HCT per team were performed in North America and EMR.

Trends in indications and hematopoietic cell transplantation type

All regions showed increases in activity compared to 2006 (range, 54.3% in EUR - 164.8% in SEAR/WPR) for both transplant types (range, autologous 45.5% in EUR - 126.6% in SEAR/WPR and allogeneic 49.1% North America - 193.4% SEAR/WPR; Table 1). Trends and increase in allogeneic and autologous HCT from 2006 to 2016 according to disease and regions are shown in Figure 3 and the *Online Supplementary Figure S4A and B*, respectively. The most common indications for autologous and allogeneic HCT (n=82,718) were lymphoproliferative diseases (53.0%), leukemias (35.7%), non-malignant disorders (7.3%) and solid tumors (3.6%; see Table 1).

Allogeneic hematopoietic cell transplantations

Leukemia is the most common indication for allogeneic HCT (n=28,719) and the most frequent single indication

acute myeloid leukaemia (AML) with a total of 14,334 HCT, followed by acute lymphoblastic leukemia (ALL; n=6895), myelodysplastic syndrome (MDS)/myeloproliferative neoplasms (MPS; n=5,616) and chronic myeloid leukemia (CML; n=1,108). Non-malignant disorders (n=5,427) with the subgroups bone marrow (BM) failure (49.5%), hemoglobinopathies (23.3%) and immunodeficiencies (17.9%) were identified as the second most common indication for allogeneic HCT. The third most common indication was lymphoproliferative disorder (LPD; n=3,972) of which 81.7% were Hodgkin disease (HD)/non-Hodgkin disease (NHL) and 16.6% plasma cell disorders (PCD).

Increases from 2006 were noted especially in non-malignant disorders (139.4%), leukemias (99.5%) with the subgroups MDS/MPS (147.6%), AML (116.8%) and LPD (23.4%). Declines were noted in CML (-16.9%) and chronic lymphocytic leukemia (CLL) (-17.3%; Table 1). HCT were performed predominantly in AML in first complete remission (CR1) (*Online Supplementary Figure S4A*) with a decline in procedures in non-CR1. In ALL CR1 was also more frequent than non-CR1. HCT for MDS and, to a lower extent MPN, increased steadily over the observa-

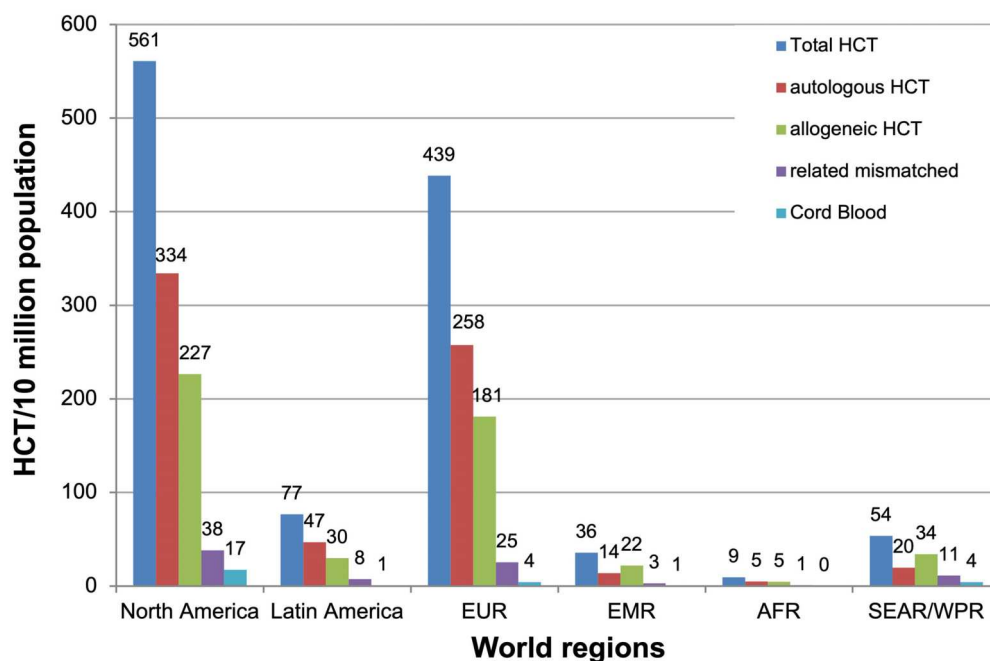


Figure 1. Transplant rates. Hematopoietic cell transplantation (HCT)/10 million population according to transplant type (autologous, allogeneic, related mismatched and cord blood) and world regions in 2016. EUR: Europe, EMR: East Mediterranean Region; AFR: Africa; SEAR/WPR: South East Asia Pacific Region/West Pacific Region.

tion period. Increased allogeneic HCT activities were observed for almost all indications in all regions. The highest increase was noted for related donors in the SEAR/WPR region (279%; Table 1; Figure 3). The only observed decrease involved solid tumors (44% decrease) in almost all regions except for SEAR/WPR and LPD in North America.

Autologous hematopoietic cell transplantation

The most frequent indication for autologous HCT in 2016 was LPD ($n=39,878$, 84.2% of all autologous HCT; Table 1) and the most frequent single indication PCD and HD/NHL with 59.4% and 40.4%, respectively. HCT for solid tumors ($n=2,853$) accounted for 6.4% of autologous HCT and 844 (1.9%) were performed for leukemias mostly for AML (74.8%) and ALL (18.4%). Autoimmune diseases (AID) (92.2%) were the predominant indication for autologous HCT within non-malignant diseases ($n=691$). Frequencies of autologous HCT increased in almost all indications and regions especially for LPD and non-malignant disorders. Decreases in autologous HCT were observed for leukemia (except SEAR/WPR) and for solid tumors in Europe. The highest increase in autologous HCT was observed in Latin America for non-malignant disorders. The frequency of autologous HCT increased by 68.9% predominantly in non-malignant disorders (258%), primarily AID (246.2%) in PCD (122%) and in lymphoma (46.7%; *Online Supplementary Figure 4B*; Table 1). Decreased activity of autologous HCT was reported for all leukemias (-51.1%; Figure 3).

Trends in donor type and stem cell source

Autologous HCT (range, 0-11,655) were reported from 85 participating countries, while allogeneic HCT (range, 0-7,850) were reported from 76 countries, including procedures from unrelated donors and from CB in 55 and in 41 countries, respectively. Overall, related HCT has become

more frequent than unrelated HCT starting in 2014 (*Online Supplementary Figure S5*). The increase in related HCT was mainly due to the use of non-identical related donors (39.5% of related HCT), which increased significantly over the last 4 years, while unrelated CB showed a moderate decline. A detailed analysis of identical and non-identical related HCT according to indication and in comparison to unrelated HCT is given in Table 2. Highest increases were observed for severe aplastic anemia and hemoglobinopathies (Delta 2007-2016 >1,000%) and for leukemia (Delta 2007-2016 >550%; especially AML CR1, ALL CR1, CML first CP with maximum 2,456%, data not shown), but also in LPD (especially in HD and NHL max Delta 2007-2016 =711%). In comparison, HCT from related identical donors showed Delta 2007-2016 of maximum 189% for ALL CR1 and from unrelated for AML CR1 of 430%.

Amongst allogeneic HCT, the proportion of unrelated donor HCT ranged from 4.4% to 78.3% (median 20%), with 30 countries performing more unrelated than related donor HCT. Absolute unrelated HCT numbers ranged from 0 to 4,311 and those of CB ranged from 0 to 1,233 in individual countries. It is not surprising that more related HCT were performed in regions without an unrelated donor registry (Latin America, EMR, AFR and SEAR/WPR). Related haploidentical HCT ($n=8,131$) were evenly distributed in 62 countries; with absolute numbers ranging from 0 to 2,554 and proportions of all allogeneic HCT ranging between 1.5% to 77% (median 8%). TR for haploidentical HCT was highest in North America ($n=38$), 25 in Europe, eight in Latin America and ≤ 4 in Asia Pacific, AFR and EMR (Figure 1). However, TR as % of allogeneic HCT reached 34% in SEAR/WPR and 26% in Latin America, while it was only 14% in Europe and EMR.

Peripheral blood (PB) was the predominant graft source in both autologous (99.7%) and allogeneic (72.8%) HCT, while CB as a source has declined (in 2016 13.9% of all

Table 2. Trend of global hematopoietic cell transplantation activity according to disease indication and donor type.

	Related identical			Related non-identical			Related total			Unrelated		
	2007	2016	Δ%(07-16)	2007	2016	Δ%(07-16)	2007	2016	Δ%(07-16)	2007	2016	Δ%(07-16)
Leukemias	6,858	8,906	29.9	1,101	6,056	450.1	8,018	14,992	87.0	7,868	13,727	74.5
AML	3,249	4,453	37.1	472	3,064	549.2	3,749	7,531	100.9	3,610	6,803	88.5
ALL	1,635	2,256	38.0	376	1,702	352.7	2,023	3,965	96.0	2,015	2,930	45.4
CML	601	388	-35.4	56	236	321.4	663	624	-5.9	479	484	1.0
MDS/MD/MPN	1,044	1,559	49.3	156	905	480.1	1,211	2,472	104.1	1,358	3,144	131.5
CLL	279	166	-40.5	17	53	211.8	298	220	-26.2	316	240	-24.1
Other leukemias	50	84	68.0	24	96	300.0	74	180	143.2	90	126	40.0
LPD	1,677	1,238	-26.2	163	758	365.0	1,877	2,023	7.8	1,338	1,949	45.7
Plasma cell disorders	542	234	-56.8	23	64	178.3	583	312	-46.5	245	348	42.0
Multiple myelomas	341	211	-38.1	8	54	575.0	356	279	-21.6	192	316	64.6
Others	9	23	155.6	1	10	900.0	11	33	200.0	7	32	357.1
Lymphoma	1,135	979	-13.7	140	681	386.4	1,294	1,673	29.3	1,093	1,573	43.9
Hodgkin disease	186	205	10.2	29	170	486.2	222	377	69.8	175	181	3.4
Non-Hodgkin lymphoma	796	774	-2.8	63	511	711.1	871	1,296	48.8	683	1,392	103.8
Solid tumors	47	4	-91.5	32	42	31.3	84	47	-44.1	35	37	5.7
Non-malignant disorders	1,354	2,185	61.4	196	1,232	528.57	1,559	3,423	119.56	984	2,004	103.66
Bone marrow failure	789	1,136	44.0	65	633	873.9	862	1,775	105.9	448	909	102.9
Severe aplastic anemia	644	964	49.7	48	553	1,052.1	700	1,523	117.6	320	743	132.2
Other	145	172	18.6	17	80	370.6	162	252	55.6	128	166	29.7
Hemoglobinopathies	338	711	110.4	21	251	1,095.2	359	962	168.0	66	301	356.1
Immune deficiencies	140	234	67.1	84	238	183.3	224	472	110.7	255	500	96.1
Inherited diseases of metabolism	44	54	22.7	19	57	200.0	63	111	76.2	98	182	85.7
Autoimmune disorders	12	10	-16.7	1	9	800.0	13	19	46.2	8	22	175.0
Other non malignant disorders	31	40	29.0	6	44	633.3	38	84	121.1	109	90	-17.4
Other	61	66	8.2	12	43	258.3	73	109	49.3	68	114	67.7
TOTAL	9,997	12,399	24.0	1,504	8,131	440.6	11,611	20,594	77.4	10,293	17,831	73.2

unrelated and 6.7% of all allogeneic HCT). Of the 38,425 allogeneic HCT, 7,868 (20%) were bone marrow (BM)-derived, 27,963 (73%) were from PB and 2,594 (7%) from cord blood (CB). Of the 44,293 autologous HCT, 99.7% were from PB, 0.3% from BM and only three single HCT were from CB.

Discussion

The analysis of global HCT activity based on data from 2006-2016 on 700,000 HCT over the last 10 years gathered by the WBMT gives important insights into the global trends in the field of HCT.

As per previous reports,⁸⁻¹³ HCT activities continue to increase worldwide without plateau and exceeded 80,000 procedures annually for the first time in 2016 and are expected to exceed 90,000 in 2018 to reach a total of 1.5 million by 2019. Although allogeneic HCT has increased more than autologous in recent years, the later remains the predominant transplant type and LPD the leading disease indication. Leukemia is the second most frequent HCT indication and 94.9% of these use allogeneic donors. While HCT on patients with acute leukemias (predominantly in CR1, but not in non-CR1) and MDS/MPN increase, a decrease of frequencies in chronic leukemias (CLL and CML) was observed. Non-malignant disorders now account for 7.3%

of all HCT (89.2% of which are allogeneic) with BM failures as the most frequent group of disease indications (47.5%, mostly severe aplastic anemia). Hemoglobinopathies were the second most frequent indication (22.4%) with an increase of 222.3%. Finally, solid tumors were the indication in 3.6% of all HCT and were almost exclusively transplanted with autologous grafts (97%). Striking is the pronounced increase in haploidentical HCT in hemoglobinopathies, severe aplastic anemia, leukemia and LPD (especially MM and NHL) in developing countries. Findings are partly in agreement on a larger scale with the development in Europe and US, but also diverge especially on the use of haploidentical HCT for non-malignant diseases, in the use of autologous HCT in autoimmune disease (LABMT) and in leukemias (SEAR/WPR) and in the use of allogeneic HCT in autoimmune diseases in SEAR/WPR.

There was substantial divergence in the rate of growth of HCT between different regions, with increases of more than 129% in SEAR/WPR and Latin-America over the last decade contributing strongly to the continuous global upward trend in activity. Both regions reported their major increases in non-malignant disorders, in the SEAR/WPR with allogeneic and in Latin America with autologous HCT. AFR/EMR had a remarkable growth of 80% in comparison to 65% in North America and 54% in Europe. Despite the differential increase, TR still vary by more than 10-fold from region to region. A deeper analysis of the number of HCT teams in

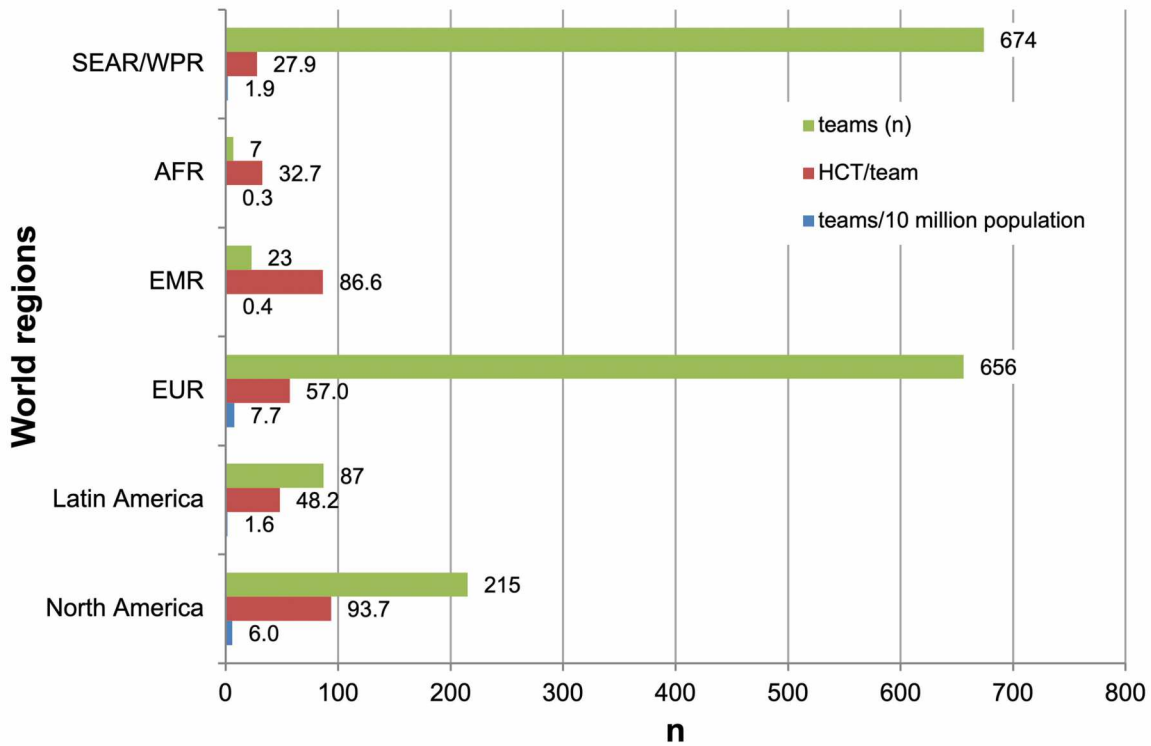


Figure 2. Number of hematopoietic cell transplant (HCT) teams, HCT team density and HCT per team according to world regions. EUR: Europe; EMR: East Mediterranean Region; AFR: Africa; SEAR/WPR: South East Asia Region/Western Pacific Region; TD: team density.

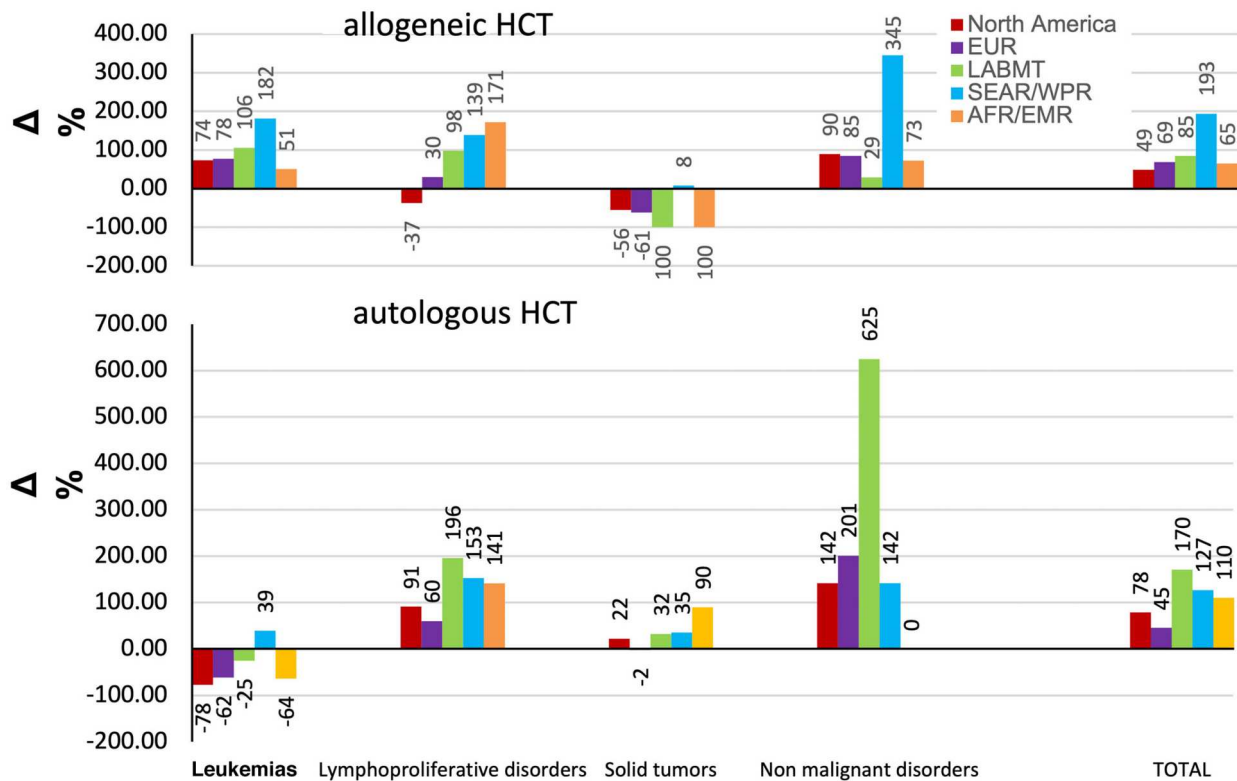


Figure 3. Change in activity in percent from 2006 and 2016 according to disease indication and world region. HCT: hematopoietic cell transplantation; EUR: Europe; LABMT: Latin American Blood and Marrow Transplantation Group; TAFR/EMR: Africa/East Mediterranean Region; SEAR/WPR: South East Asia Region/Western Pacific Region.

the different regions showed three patterns: high (>500 teams; SEAR/WPR and EUR), intermediate (100-500 teams; North America) and low (<100 teams; AFR, EMR, Latin America). TD was similar in North America and Europe (6.0 and 7.7 respectively), between 1-2 in SEAR/WPR and Latin America and <1 in all other regions. While North America and EMR had most HCT per HCT team (93.7 and 86.6, respectively), Europe and Latin America had intermediate (57.0 and 48.2, respectively), SEAR/WPR and AFR had the lowest (27.9 and 32.7, respectively) HCT per team. It is encouraging that HCT and TR in developing regions are increasing steadily, although there are differences in indications and diseases, and are closing the HCT access gap. However, the disparities in access between regions remains substantial.

Although the WBMT has established a global coverage of international transplant societies with an estimated >90% reporting, at least one very large country had incomplete reporting and lacked a national registry. With the aim of establishing such a registry, the WBMT organized a successful workshop to highlight the importance of coordinated reporting. Increased numbers of teams and activities in that country are now expected starting in 2016 (Xu L-P, Lu P-H, Wu D-P *et al.* Hematopoietic stem cell transplantation activity in China 2019: a report from the Chinese Blood and Marrow Transplantation Registry Group. Bone marrow transplantation; 2021 [in press]). Therefore, the data presented here are certainly an underestimate but are expected to increase further with greater completeness of reporting.¹⁴

The considerable increase seen in the SEAR/WPR and Latin American region in non-malignant disorders, hemoglobinopathies (allogeneic HCT) and AID (autologous HCT, predominantly in multiple sclerosis), is of special interest. It is reassuring to see a worldwide trend of more patients to be transplanted in CR1 rather than later in their disease course. This phenomenon is much more evident in AML and remains constant in ALL. Lymphoma accounts for less of the increase in autologous HCT than do PCD. The indications for CML decreased only slightly in the 10 year period following the availability of successive tyrosine kinase inhibitor pharmaceuticals. However, it should be noted here that more patients were transplanted beyond chronic phase CML, and not in line with ELN recommendations.¹⁵ The changes in donor type and graft source confirm trends previously described. Frequencies of haploidentical HCT increased considerably to reach >10% of all allogeneic HCT throughout all regions. As a consequence, more related (matched and haploidentical) HCT were performed than were unrelated HCT, and the later appears to have reached a plateau. The increase of haploidentical related donors might have several reasons including lack of donors for Latin-American patients in international registries, lack of local national donor registries and economic. The availability of new technologies like the post-cyclophosphamid protocol and the so called 'Beijing Protocol' using G-CSF/anti-thymocyte globulin and multiple stem cell sources (BM and PB stem cells)^{14,16} may have contributed to this development. Overall, CB HCT decreased consistent with the pattern seen in Europe.

There are a few limitations in this analysis. The first one relates to the reporting lag of the analysis. Logistics in obtaining data from 1,660 transplant centers worldwide are the main cause for this delay. While some of the regions are reporting in real time, emerging regions have not a central national or regional reporting system. In these regions, WBMT collected the information from individual transplant

centers returning the results to the regional societies for completeness checking. An internet-based reporting system was developed by the WBMT and is expected to gradually bring up the survey reports to real time. An additional limitation of this analysis is the inability to provide information on utilization of HCT for specific illnesses and on information restricted to first HCT. Utilization is currently being analyzed worldwide for myeloma and AML by the WBMT, but should be extended to major indications. Furthermore, information on second or third HCT is not currently available, although these account for approximately 10% of HCT in developed countries, but will be implemented with the new reporting system.

One of the challenges that the WBMT faces, is how to go beyond calculations of global HCT activity and accelerate global equity of access to HCT. The most efficient method may be to increase HCT activity/team. In fact, transplant teams have already increased their annual HCT/team by a median of 14 HCT/team since 2006. As shown in this study, 50 HCT/team are feasible even in developing countries and almost 100 HCT/team are currently being performed in North America.

Increasing team numbers might be more difficult. This is due in part to the funds allocated to local health expenditure, but also due to limitations in the infrastructure required including blood banks, intensive care units, multidisciplinary teams and microbiology expertise. Shortages and unavailability of medicines and lack of trained biomechanical/biotechnical technicians have also hindered HCT activities in developing countries. The WBMT has the capacity to review and analyze global HCT activity data and apply this data to support HCT activities globally. Global activity survey data has been instrumental in informing and shaping HCT support workshops in the different regions, which have been successful in fostering collaboration amongst international societies and supportive expert HCT networks globally. The WBMT, on its site, has already prepared a variety of documents to facilitate the establishment of new transplant programs (requirements for establishing a program, list of essential medicines, use of biosimilars to reduce costs and establishing unrelated donor registries).¹⁷⁻²¹ In addition, supervisory telemedicine is an evolving and potentially powerful tool to overcome lack of experience with collateral benefits for conventional hematology, blood banking, microbiology and virology. Devoted physicians and willing health authorities are essential for the application of such technologies and successful collaborations accompanied by demonstration of compliance with international standards to provide reassurance to internal and external stakeholders.²²

The achievements obtained in the last decade should be an incentive to continue and even increase the common efforts to improve access and close the gap worldwide faster. This is a common effort of professional organizations, WHO, politicians and Health Authorities. The role of the WHO is essential in coordinating this process among their member states.

Disclosures

No conflicts of interest to disclose.

Contributions

DN, HB, MA, KB, KF, and FRA designed the study; HB, NB, CB, NC, SC, AE,CF, SG, NH, AAH, SH, AH, MH, MI, GJ, AK, JK, NK, RPL, JWJ, JMR, MP, JP, KP, AS, JAS, AS, JS, DW, NW, MK, MA, HG, YA, WS contributed data

and assured quality of the data given to the analysis; HB, DN, MP, and LF analysed data; DN, HB, WS, and NH drafted the manuscript; DN, HB, NB, CB, NC, SC, AE, CF, SG, NH, AAH, SH, AH, MH, MI, GJ, AK, JK, NK, RPL, JWL, JMR, MP, JP, KP, AS, JAS, AS, JS, DW, NW, MK, MA, HG, YA processed the manuscript. European data were derived from the European Society for Blood and Marrow Transplantation (EBMT) database for the years 1965–89 and from the EBMT annual activity survey office since 1990. Non-european data were initially provided by the Center for International Blood and Marrow Transplant Research (CIBMTR) since 1964. They were supplemented or replaced by the activity surveys of the Asian Pacific Blood and Marrow Transplantation Group (APBMT) since 1974, the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR) since 1992, the Eastern Mediterranean Blood and Marrow Transplantation Group (EMBMT) since 1984, the Cell Therapy Transplant Canada (CTTC) since 2002, the Latin American Bone Marrow Transplantation Group (LABMT) since 2009, and the African Blood and Marrow Transplant Group (AFBMT) since 2010. Unrelated donor and cord blood information were derived from the World Marrow Donor Association (WMDA) and Bone Marrow Donors Worldwide (BMDW).

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