SPECIAL REPORT

Use of Haploidentical Stem Cell Transplantation continues to increase, the 2015 European Society for Blood and Marrow Transplant activity survey report

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ABSTRACT

Hematopoietic stem cell transplantation (HSCT) is an established procedure for many acquired and congenital disorders of the hematopoietic system.

A record number of 42'171 HSCT in 37'626 patients [16'030 allogeneic (43%), 21'596 autologous (57%)] were reported by 655 centers in 48 countries in 2015. Trends include continued growth in transplant activity over the last decade, with the highest percentage increase seen in middle income countries but the highest absolute growth in the very high income countries in Europe. Main indications for HSCT were myeloid malignancies 9'413 (25%; 96 % allogeneic); lymphoid malignancies 24'304 (67%; 20% allogeneic); solid tumors 1'516 (4%; 3% allogeneic); and non-malignant disorders 2'208 (6%; 90% allogeneic). Remarkable is decreasing use of allogeneic HSCT for CLL from 504 patients in 2011 to 255 in 2015, most likely due to new drugs. Use of haploidentical donors for allogeneic HSCT continues to grow: 2'012 in 2015, a 291% increase since 2005. Growth is seen for all diseases. In AML, haploidentical HSCT increases similarly for patients with advanced disease and for those in CR1. Both marrow and peripheral blood is used as stem cell source for haploidentical HSCT with higher numbers reported for the latter.

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is an established procedure for many acquired and congenital disorders of the hematopoietic system, including disorders of the immune system, and as enzyme replacement in metabolic disorders (1-4). The annual activity survey of the European Society of Blood and Marrow Transplantation (EBMT), describing the status of HSCT in Europe and affiliated countries, has become an instrument used to observe trends and to monitor changes in technology use (5-12). The survey captures the numbers of HSCT performed in the preceding year from each participating team, divided by indication, donor type and stem cell source. The standardized structure of the survey over many years and the excellent commitment of the participating teams allow us to observe changes over time and to evaluate factors associated with these changes. More recently, the survey has included additional information on novel cell therapies with hematopoietic stem cells for non-hematopoietic use, as well as on the use of non-hematopoietic stem and progenitor cells. This coincides with the recent interest of the World Health Organization WHO (www.who.org) in cell and tissue transplants and further stresses the need for adequate and timely information (13). The analysis of the survey data spanning over 25 years and amassing data on more than 600'000 transplants in over 550’000 patients, has shown a continued and constant increase in the annual numbers of HSCT and transplant rates (number of HSCT/10 million inhabitants) for both allogeneic and autologous HSCT. This report is based on the 2015 survey data. In addition to transplant rates and indications, this report focuses on the use of haploidentical donors for transplantation including disease entities and stem cell source.

PATIENTS AND METHODS

Data collection and validation

Participating teams were invited to report data for 2015 by indication, stem cell source and donor type as listed in table 1. The survey allows the possibility to report additional information on the numbers of subsequent transplants performed as a result of relapse,

rejection or those that are part of a planned sequential transplant protocol. Supplementary information on the numbers of donor lymphocyte infusions, reduced intensity HSCT and the numbers of pediatric HSCT is also collected. New in this year's survey is the more detailed report on cellular therapies (table 2). Quality control measures included several independent systems: confirmation of validity of the entered data by the reporting team, selective comparison of the survey data with MED-A data sets in the EBMT Registry database and cross-checking with the National Registries.

Teams

687 centers from 48 countries were contacted for the 2015 survey (39 European and 9 affiliated countries); of which 655 teams reported. This corresponds to a 95% return rate and includes 552 active EBMT member teams. 32 active teams failed to report in 2015. Contacted teams are listed in the online appendix in alphabetical order by country, city and EBMT centre code, with their reported numbers of first and total HSCT, and of first allogeneic and autologous HSCT as supplementary material. The WHO regional office definitions (www.who.org) were used to classify countries as European or Non-European. Nine non-European countries participated in the 2015 EBMT survey: Algeria, Iran, Israel, Jordan, Lebanon, Nigeria, Saudi Arabia, South Africa and Tunisia. Their data (2'776 HSCT in 2'657 patients) from 29 actively transplanting teams makes up 6.6% of the total data set and is included in all analyses (13).

Patient and Transplant numbers

Wherever appropriate, patient numbers corresponding to the number of patients receiving a first transplant and transplant numbers reflecting the total number of transplants performed are listed.

The term sibling donor includes HLA identical siblings and twins but not siblings with HLA mismatches. Unrelated donor transplants includes HSCT from unrelated donors with peripheral blood and marrow as a stem cell source but not cord blood HSCT, In the 2015

survey we collected separately the numbers of haplo-identical and other family member HSCT. Haplo-identical being described as any family member with 2 or more loci mismatch within the loci HLA-A,-B,-C,-DRB1 and -DQB1 in GvH and/or HvG direction. Other family member donors are those related donors that are mismatched to a lesser degree than a full haplotype. Additional non first transplants may include multiple transplants defined as subsequent transplants within a planned double or triple autologous or allogeneic transplant protocol, and retransplants (autologous or allogeneic) defined as unplanned HSCT for rejection or relapse after a previous HSCT.

Transplant rates

Transplant rates, defined as the total number of HSCT per 10 million inhabitants, were computed for each country without adjustments for patients who crossed borders and received their HSCT in a foreign country. Population numbers were obtained from Eurostats for 2015 for the European countries, (http://epp.eurostat.ec.europa.eu/portal/page/portal/statistics/search_database) and the US census bureau database for the non-European countries (http://www.census.gov/population/international/data/idb/rank.php).

Analysis

Wherever appropriate the absolute numbers of transplanted patients, transplants or transplant rates are shown for specific countries, indications or transplant techniques. Myeloid malignancies include acute myeloid leukemia (AML), myelodysplastic or myelodysplastic/myeloproliferative neoplasm (MDS/MPN), myeloproliferative neoplasm (MPN) and chronic myeloid leukemia (CML). Lymphoid malignancies include acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), Hodgkin's disease (HD), Non-Hodgkin lymphoma (NHL) and plasma cell disorders (PCD).The non-malignant disorders include bone marrow failure (BMF), thalassemia, sickle cell disease, primary immune disease (PID), inherited disease of metabolism (IDM) and auto immune disease

AID. Others include histiocytosis and other rare disorders not included in the above.

RESULTS

2015 Data

Participating teams in 2015

Of the 655 teams, 412 (62%) performed both allogeneic and autologous transplants; 227 (35%) restricted their activity to autologous HSCT, and 11 teams (2%) to allogeneic transplants only. Five teams (1%) reported having performed no transplants in 2015 due to renovation or temporary closure of the transplant unit. Of the 655 active centers, 131 (20%) centers performed transplants on both adult and pediatric patients. An additional 106 (16%) centers were dedicated pediatric transplant centers and 417 (64%) centers performed transplants on adults only.

Numbers of patients and transplants

In 2015 42'171 transplants were reported in 37'626 patients (first transplant); of these, 17'302 HSCT (41%) were allogeneic and 24'869 (59%) autologous (Table 1). When compared with 2014 the total number of transplants increased by 3.3% (2.1% allogeneic HSCT and 4.1% autologous HSCT) (12). Furthermore, there were 4'545 second or subsequent transplants, 1'272 allogeneic and 3'273 autologous. The total number of patients transplanted under the age of 18 in both dedicated and joint adult-pediatric units was 4'490 (3'338 allogeneic and 1'152 autologous HSCT). Of these, 3'015 patients (67%, 2'570 allogeneic and 896 autologous) reporting a total of 3'466 transplants were performed in dedicated pediatric centers. 4'545 transplants were second or multiple transplants. Among these 3'273 were autologous, the majority of which were probably part of multiple transplant programs e.g. as for plasma cell disorders. 1'272 were allogeneic HSCTs mainly to treat relapse or graft failure. In addition, 794 HSCTs were reported as allogeneic HSCT after a previous autologous HSCT and were mainly for lymphoma or plasma cell disorders.

Indications

Indications for HSCT in 2015 are listed in detail in table 1. Main indications were myeloid malignancies (AML, CML, MDS/MPN and MPN): 9'413 (25% of total; 96% of which were allogeneic); lymphoid malignancies (ALL, CLL, HD, NHL and PCD): 24'340 (65%; 20% allogeneic); solid tumors: 1'516 (4%; 3% allogeneic); non-malignant disorders: 2'208 (6%; 90% allogeneic) and others: 149 (0.4%). As seen in previous years, the majority of HSCT for lymphoid malignancies were autologous, while most transplants for leukemia were performed using stem cells from allogeneic donors. Autologous HSCT for non-malignant disorders predominantly include patients with autoimmune disorders.

Figures 1a and 1b show as a pie graph the distribution of disease indications for allogeneic (figure 1a) and autologous (figure 1b) respectively. Of interest, we show that for allogeneic HSCT AML is the most frequent indication (39%), of these 21% were for patients in CR1, 12% for patients with more advanced disease and 6% for patients with transformed AML, either therapy related or from MDS/MPN. Compared to 2014, there were increases in allogeneic HSCT for AML by 7.9% and MPN 3.5% and a major decrease by 28% was seen in allogeneic HSCT use for CLL (figure 2), dropping from 504 patients in 2011 to 255 in 2015. Among allogeneic HSCT 6'933 were performed using non myeloablative conditioning. This is an increase of 1% since in 2014 and is 40% of all allogeneic HSCT. For autologous HSCT there was an increase in myeloma by 8.1%, and Hodgkin lymphoma by 2.1%, proportions for most other diseases remained stable.

Important trends in 2015 include continued increase in patients treated with allogeneic and autologous HSCT use as shown in supplementary figure 1, and increasing use among allogeneic HSCT recipients of unrelated donor transplantation (14) although it might appear that the growth rate is slowing down (supplementary figure 2). Figure 3a shows the continued use of alternative donor transplantation and among these an impressive increase of the use of haploidentical donors to 2'012 patients in 2015 across Europe; an increase of 291% since

2005. The highest growth is seen in myeloid malignancies 1'008, with lymphoid malignancies 636, nonmalignant disorders 316 and 52 others. Figure 3b shows that the growth of haploidentical donor HSCT is seen more in patients with myeloid malignancy, but also in lymphoid malignancy and nonmalignant disorders although to a lesser degree. Among myeloid malignancies the majority (n=735) are patients with AML. Of note, there are equal proportions of patients with AML receiving haploidentical donor HSCT transplanted in CR1 and with more advanced disease (Figure 3c). Stem cell source for haploidentical donor HSCT is shown in Figure 3d, peripheral blood is used more frequently than marrow. Figure 3e as well as Figure 3a shows in contrast to haploidentical donor HSCT the decreasing use of unrelated cord blood as a donor source. As shown in Figure 3e this decrease pertains to myeloid and lymphoid malignancies but not to nonmalignant disorders where the use of unrelated cord blood is stable over time.

Transplant rates

Supplementary figures 3a and 3b show transplant rates by country for allogeneic and autologous HSCT comparing rates in 2015 on maps of Europe. Median transplant rates per 10 million inhabitants were 153.1 (range, 4.4 – 460.9) for allogeneic HSCT and 251.8 (range, 1.0 – 759.9) for autologous HSCT in 2015. For the purpose of this analysis we have grouped countries according to World Bank income group GNI per capita in USD in 2015, (http://data.worldbank.org/data-catalog/world-development-indicators). All European countries fall within the group of either middle income or high income category, so we created a third group to split furthermore the high income countries into very wealthy countries defined as >40'000 USD per capita GNI. Median transplant rates in 2015 for the 3 groups are: 266, 178, 41 for very high, high and medium income countries (allogeneic HSCT, transplants per 10 million inhabitants) and 941,525, 178 for autologous HSCT respectively. Figure 4 shows growth rates in allogeneic and autologous HSCT use by income category as relative growth i.e. % increase from 2005 to 2015 or as absolute increase in transplant rates from 2005 to 2015 normalized for size of the population. Figure 4a and 4b shows that %

increase is highest for middle income countries (GNI < 12500 USD per capita) for both allogeneic and autologous HSCT and lowest for the very high income countries. The higher income countries had already achieved a high level of transplant rates in 2005. To the contrary the absolute growth i.e. increase in access of patients to transplant centers is highest in the very high income countries in the period of 2005-2015 again for both allogeneic and autologous HSCT.

Additional cellular therapies (Table 2)

A total of 35 countries (330 teams) reported having performed 3'882 cellular therapies in 2015. Of these, 2'940 patients received donor lymphocyte infusions. Indications were graft enhancement: 803 (27%); residual disease: 410 (14%); relapsed disease: 1'285 (44%) and per protocol 442 (15%).

Other cellular therapies were given either within the context of a HSCT or not. The majority were MSCs given for GvHD treatment (396) of for graft enhancement (45). 74 patients received MSCs for various other indications. The largest additional group of cellular therapies were selected or expanded T cells given to treat infectious complications (119 patients) or for anti-malignant effects (37). Other cellular therapies including NK cells (14), TREGs (35), genetically modified T-cells (14), dendritic cells (25) and expanded or genetically modified hematopoietic stem cells (36) were reported more rarely. 121 patients received cellular products for purposes of regenerative medicine (15,16).

DISCUSSION

The EBMT activity survey has been conducted annually since 1990 (6). The 2010 survey reported for the first time more than 30'000 patients transplanted in a given year (17), and more than >40'000 transplants in 2014. Again transplant numbers continue to increase unabated across Europe.

HSCT for some indications continues to increase but not for others. Of interest is decreasing use of allogeneic HSCT for CLL and a growth in allogeneic HSCT using haploidentical

donors, an increase over 200% in the last 5 years. The drop in allogeneic HSCT for CLL is remarkable and reminds us of the drop seen in CML transplants once kinase inhibitors became available (18,19). Whether this drop is going to be permanent or whether this is temporary will depend on the long-term results of kinase inhibitors and possibly bcl2 inhibitors developed to treat CLL.

The continuing use of haploidentical donors is impressive, and it becomes apparent that haploidentical donor HSCT is not only used for advance disease stages but also for early disease stages as exemplified by AML (figure 3c). The use of peripheral blood as a stem cell source has surpassed the use of marrow (figure 3d) although the original studies describing haploidentical donor HSCT with post-transplant cyclophosphamide as GvHD prophylaxis have been using mainly marrow (20). The use of unrelated cord blood, a competitor for alternative donor HSCT when identical siblings and well matched unrelated donors are not available continues to decrease but only for malignant disorders (21). Cord blood transplant rates for nonmalignant diseases remains stable, reflecting the practice mainly in pediatric centers.

We looked at development of transplant technology in countries in Europe by economic strength of the societies and for this purpose show growth of allogeneic and autologous HSCT as relative and as absolute growth for countries in the middle, high and very high income category. We here confirm that the relative growth is more significant in middle income countries but that the highest absolute growth over the last decade is seen in the category of very high income countries. This exemplifies that autologous and allogeneic HSCT remains an expensive technology broadly available in wealthy societies.

We have added data on the use of cellular therapies, most of which is donor lymphocyte infusions given to treat relapse or residual disease in over 2’900 patients. Other cellular therapies have been given to over 900 patients, the largest group of which is mesenchymal stromal cells to treat GvHD. Although we have established confidence in the reported transplant numbers we cannot exclude a certain degree of underreporting, particularly in the most advanced fields of cellular therapies of patients included in studies across Europe.

In conclusion, this year's activity survey shows continued increase in the use of HSCT across Europe. Some trends are visible and are discussed here. The paper reflects current practice and results may be useful to health care planning and health policy makers.

Abbreviations:

AML; acute myeloid leukemia, ALL; acute lymphoblastic leukemia, CML; chronic myeloid leukemia, MDS/MPN; myelodysplastic or myelodysplastic/myeloproliferative neoplasm, MPN; myeloproliferative neoplasm, CLL; chronic lymphocytic leukemia, PCD; plasma cell disorders, HD; Hodgkin’s disease, NHL; Non-Hodgkin lymphoma; BMF; bone marrow failure, Thal/sickle; thalassemia/sickle cell disease, PID; primary immune disease, IDM; inherited disease of metabolism, AID; auto immune disease. CR1: first complete remission. DLI; donor lymphocyte infusions, MSC; mesenchymal stem cells, NK; natural killer cells, selected/expanded T cells or CIK; cytokine induced killer cells, TREGS; regulatory T cells.

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Conflicts of Interest:

There are no conflicts of interest to declare.

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Legend to the tables

Table 1

Numbers of hematopoietic stem cell transplants in Europe 2015 by indication, donor type and stem cell source.

Table 2

Numbers of cellular therapies in Europe 2015 by indication, donor type and cell source.

Legend to the Figures

Figure 1: Relative proportion of indications for HSCT in Europe in 2015.

Fig 1a: Proportions of disease indications for allogeneic HSCT in Europe in 2015.

Fig 1b: Proportions of disease indications for autologous HSCT in Europe in 2015.

Figure 2: The rise and fall in absolute numbers of allogeneic HSCT for CLL in Europe 1990-2015

Figure 3: Change in the absolute numbers of haploidentical and cord blood HSCT in Europe 1990 - 2015

Fig 3a: Change in donor selection from cord blood HSCT to haploidentical HSCT

Fig 3b: Increase in the use of haploidentical donors by main indication group.

Fig 3c: Haploidentical HSCT by AML early disease and advanced disease.

Fig 3d: Haploidentical HSCT by cell source; bone marrow versus peripheral blood.

Fig 3e: Trend in the use of unrelated cord blood HSCT by main indication group 2006-2015.

Figure 4: Effect of income group on transplant activity and transplant rates in 2015.

Fig 4a: percentage increase in transplant activity for allogeneic HSCT (top left), increase in transplant rates for allogeneic HSCT (bottom left).

Fig 4b: percentage increase in transplant activity for autologous HSCT (top right), increase in transplant rates for autologous HSCT (bottom right).

Supplementary figures

Figure 1: Absolute numbers of HSCT activity by transplant type; allogeneic and autologous in Europe 1990-2015

Figure 2: Change in donor choice in Europe 1990-2015. Absolute numbers of HLA identical sibling, haploidentical family, unrelated and cord blood donors

Figure 3: Transplant rates in Europe (= total number of HSCT per 10 million inhabitants) by participating country in 2015

Fig 3a: Allogeneic Transplant Rates/per10 million population in 2015

Fig 3b: Autologous Transplant Rates/per10 million population in 2015

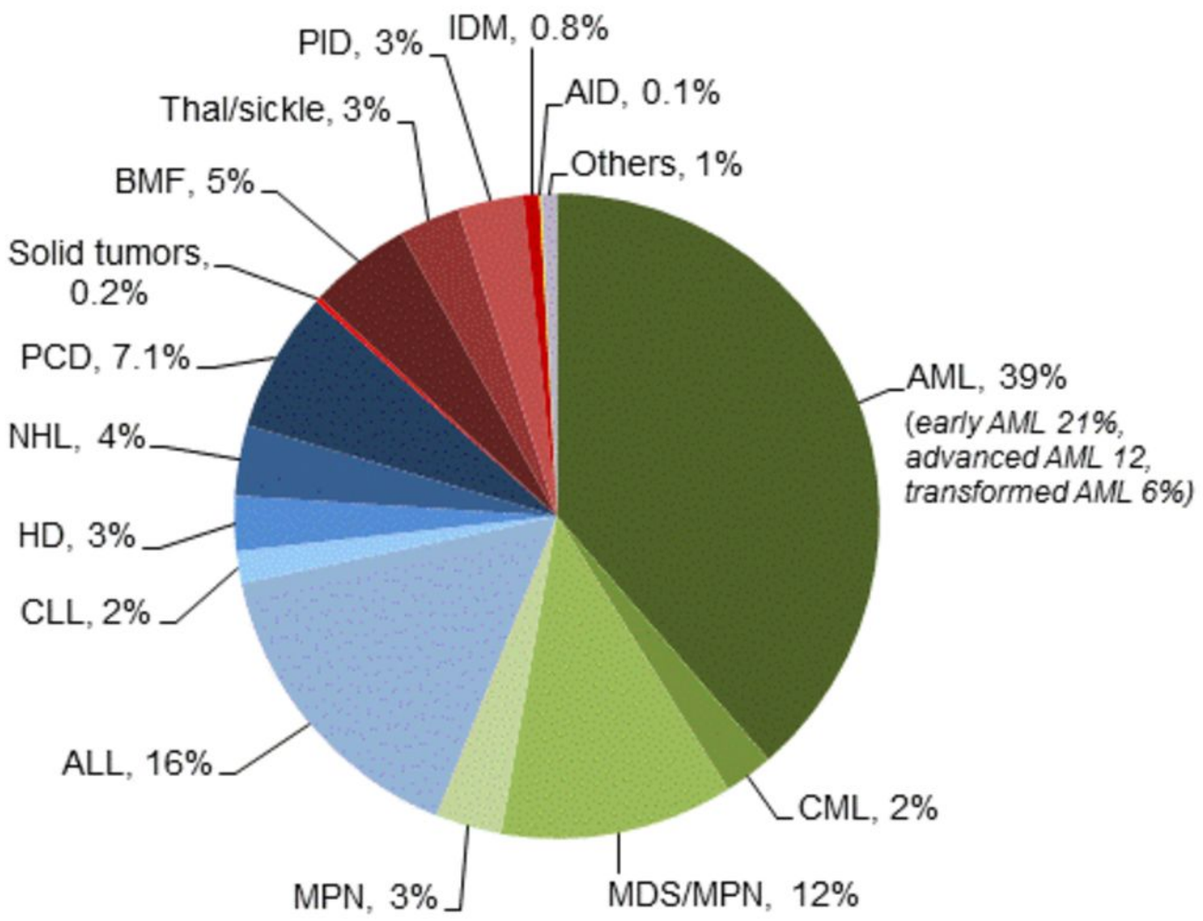
Table 1

	TRANSPLANT ACTIVITY 2015																	
	No. of patients																	
	Allogeneic												Autologous			T o t a l		
	Family									Unrelated								
	HLA-id			Twin	Haplo >=2MM		Other family						BM	BM +				
	BM	PBPC	Cord	all	BM	PBSC	BM	PBPC	Cord	BM	PBPC	cord	only	PBPC	cord	Allo	Auto	
Myeloid malignancies	**412**	**2439**	**5**	**9**	**310**	**603**	**28**	**68**	**0**	**525**	**4425**	**170**	**9**	**410**	**0**	**8994**	**419**	**9413**
Acute myeloid leukemia	290	1750	5	6	208	460	15	52	0	330	2940	133	9	404	0	6189	413	6602
1st complete remission	201	1077	5	3	100	196	10	29	0	203	1537	79	6	349	0	3440	355	3795
not 1st complete remission	64	485	0	3	81	199	4	21	0	90	864	37	3	50	0	1848	53	1901
AML therapy related	11	57	0	0	4	18	0	1	0	9	115	6	0	2	0	221	2	223
AML from MDS/MPN	14	131	0	0	23	47	1	1	0	28	424	11	0	3	0	680	3	683
Chronic myeloid leukemia	26	115	0	0	14	12	0	2	0	27	196	6	0	3	0	398	3	401
chronic phase	14	48	0	0	2	5	0	1	0	14	78	1	0	1	0	163	1	164
not 1st chronic phase	12	67	0	0	12	7	0	1	0	13	118	5	0	2	0	235	2	237
MDS or MD/MPN	87	442	0	3	68	108	12	9	0	146	971	28	0	3	0	1874	3	1877
MPN	9	132	0	0	20	23	1	5	0	22	318	3	0	0	0	533	0	533
Lymphoid malignancies	**338**	**1410**	**5**	**11**	**222**	**356**	**16**	**41**	**1**	**392**	**1984**	**114**	**26**	**19424**	**0**	**4890**	**19450**	**24340**
Acute lymphatic leukemia	264	641	5	2	101	185	15	27	1	309	851	93	3	81	0	2494	84	2578
1st complete remission	164	457	0	2	49	92	9	12	1	146	556	43	1	65	0	1531	66	1597
not 1st complete remission	100	184	5	0	52	93	6	15	0	163	295	50	2	16	0	963	18	981
Chronic lymphocytic leukemia	9	83	0	0	7	13	0	3	0	7	131	2	0	36	0	255	36	291
Plasma cell disorders - MM	6	194	0	2	13	14	0	1	0	20	285	3	5	10856	0	538	10861	11399
Plasma cell disorders - other	0	15	0	2	0	1	0	0	0	2	9	0	0	326	0	29	326	355
Hodgkin's lymphoma	12	130	0	2	55	61	1	2	0	9	166	4	8	2062	0	442	2070	2512
Non Hodgkin lymphoma	47	347	0	3	46	82	0	8	0	45	542	12	10	6063	0	1132	6073	7205
Solid tumors	**5**	**2**	**1**	**1**	**2**	**19**	**0**	**1**	**0**	**2**	**4**	**1**	**47**	**1430**	**1**	**38**	**1478**	**1516**
Neuroblastoma	3	1	1	0	2	12	0	0	0	0	1	1	27	459	1	21	487	508
Soft tissue sarcoma/Ewing	0	0	0	0	0	5	0	1	0	0	2	0	10	205	0	8	215	223
Germinal tumors	0	0	0	0	0	0	0	0	0	0	0	0	1	350	0	0	351	351
Breast cancer	0	0	0	0	0	0	0	0	0	0	0	0	0	29	0	0	29	29
Other solid tumors	2	1	0	1	0	2	0	0	0	2	1	0	9	387	0	9	396	405
Non malignant disorders	**648**	**241**	**28**	**4**	**64**	**131**	**72**	**49**	**4**	**419**	**227**	**98**	**9**	**214**	**0**	**1985**	**223**	**2208**
Bone marrow failure - SAA	185	105	5	3	16	22	11	3	1	124	79	12	0	0	0	566	0	566
Bone marrow failure - other	68	24	4	0	8	20	9	12	1	73	31	11	0	0	0	261	0	261
Thalassemia	148	66	9	1	5	12	17	7	1	55	19	1	1	3	0	341	4	345
Sickle cell disease	92	11	6	0	10	4	3	1	0	14	5	0	0	0	0	146	0	146
Primary Immune deficiencies	130	26	3	0	19	65	27	22	1	120	77	37	2	6	0	527	8	535
Inh. disorders of Metabolism	23	5	1	0	6	7	5	3	0	30	14	35	4	0	0	129	4	133
Auto immune disease	2	4	0	0	0	1	0	1	0	3	2	2	2	205	0	15	207	222
Others	31	10	1	0	8	16	5	1	0	17	27	7	0	26	0	123	26	149
TOTAL PATIENTS	**1434**	**4102**	**40**	**25**	**606**	**1125**	**121**	**160**	**5**	**1355**	**6667**	**390**	**91**	**21504**	**1**	**16030**	**21596**	**37626**
Re/additional transplants	55	257	0	2	96	257	4	12	0	71	497	21	7	3266	0	1272	3273	4545
TOTAL TRANSPLANTS	**1489**	**4359**	**40**	**27**	**702**	**1382**	**125**	**172**	**5**	**1426**	**7164**	**411**	**98**	**24770**	**1**	**17302**	**24869**	**42171**

Table 2

Number of patients	DLI	MSC		NK cells		selected/expanded T cells or CIK		Regulatory T cells (TREGS)		Genetically modified T cells		Dendritic cells		Expanded CD34+ cells		Genetically modified CD34+ cells		Other	
		Allo	Auto	Allo	Auto	Allo	Auto	Allo	Auto	Allo	Auto	Allo	Auto	Allo	Auto	Allo	Auto	Allo	Auto
GvHD		396				3		29		1				3					
Graft enhancement	803	44	1	2		14								5				24	
Autoimmune dis.		4	40																
Genetic disease		2									1						8		
Infection		4				119												6	
Malignancy		1		11	1	32	5	1	5	8	4	5	20			19			3
DLI for residual disease	410																		
DLI for relapse	1285																		
DLI per protocol	442																		
Regenerative medicine		16	7											1				3	94
Total	**2940**	**467**	**48**	**13**	**1**	**168**	**5**	**30**	**5**	**9**	**5**	**5**	**20**	**9**	**0**	**19**	**8**	**33**	**97**

Figure 1a, b


PID, 3%
IDM, 0.8%
AID, 0.1%
Thal/sickle, 3%
Others, 1%
BMF, 5%
Solid tumors, 0.2%
PCD, 7.1%
AML, 39%
(early AML 21%, advanced AML 12, transformed AML 6%)
NHL, 4%
HD, 3%
CLL, 2%
ALL, 16%
CML, 2%
MPN, 3%
MDS/MPN, 12%

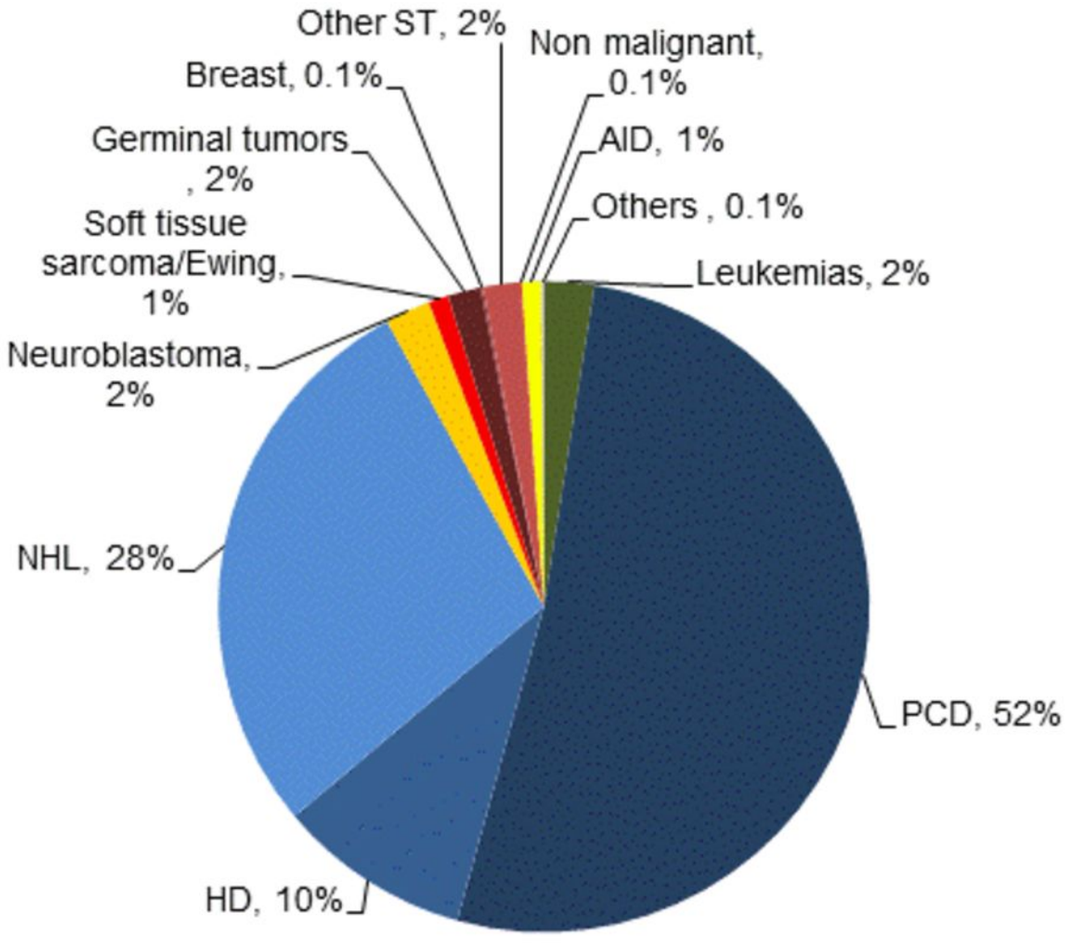

Other ST, 2%
Non malignant, 0.1%
Breast, 0.1%
AID, 1%
Germinal tumors, 2%
Others , 0.1%
Soft tissue sarcoma/Ewing, 1%
Leukemias, 2%
Neuroblastoma, 2%
NHL, 28%
PCD, 52%
HD, 10%

Figure 2

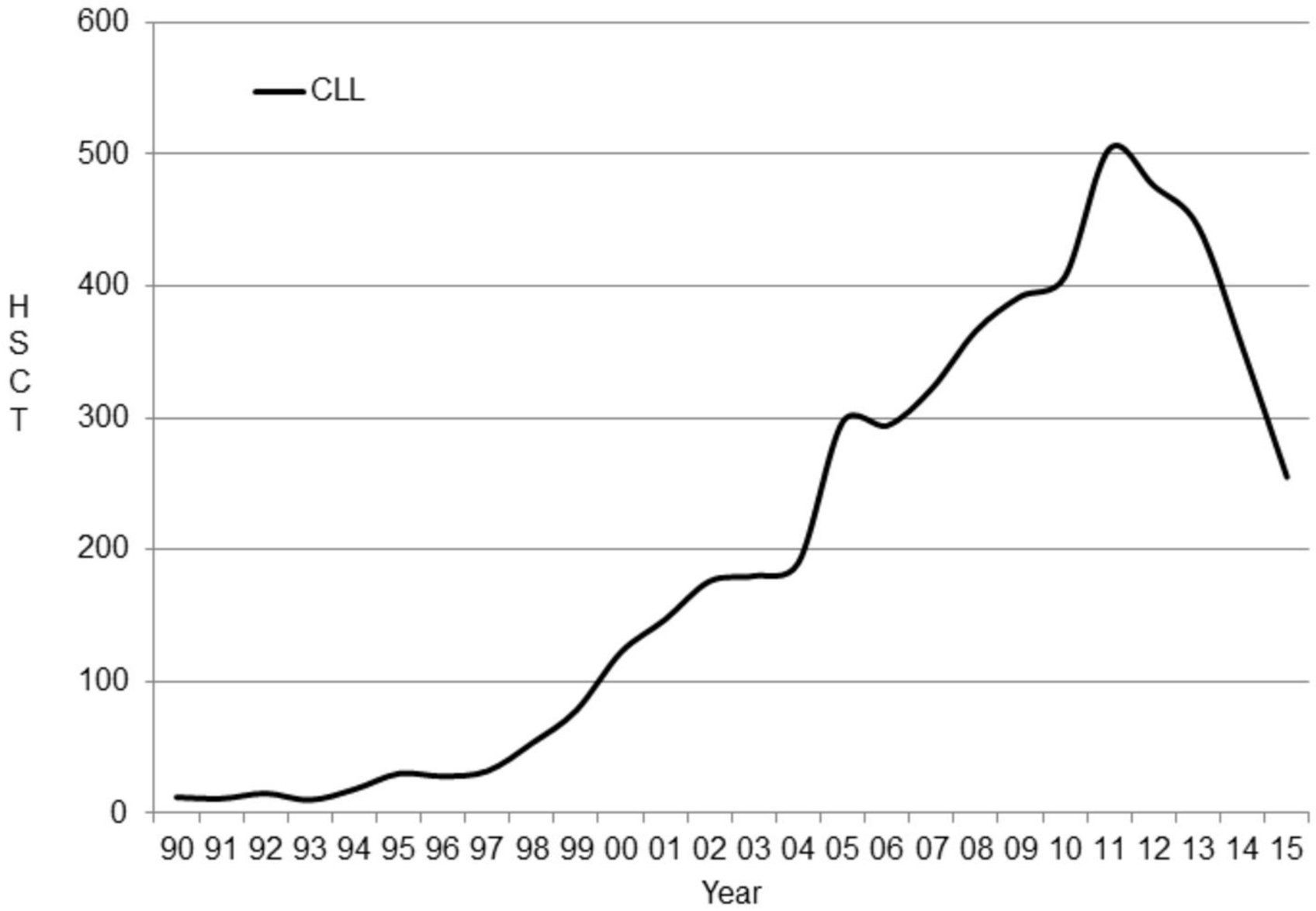

600
500
400
300
200
100
0
HSCT
CLL
90 91 92 93 94 95 96 97 98 99 00 01 02 03 04 05 06 07 08 09 10 11 12 13 14 15
Year

Figure 3a

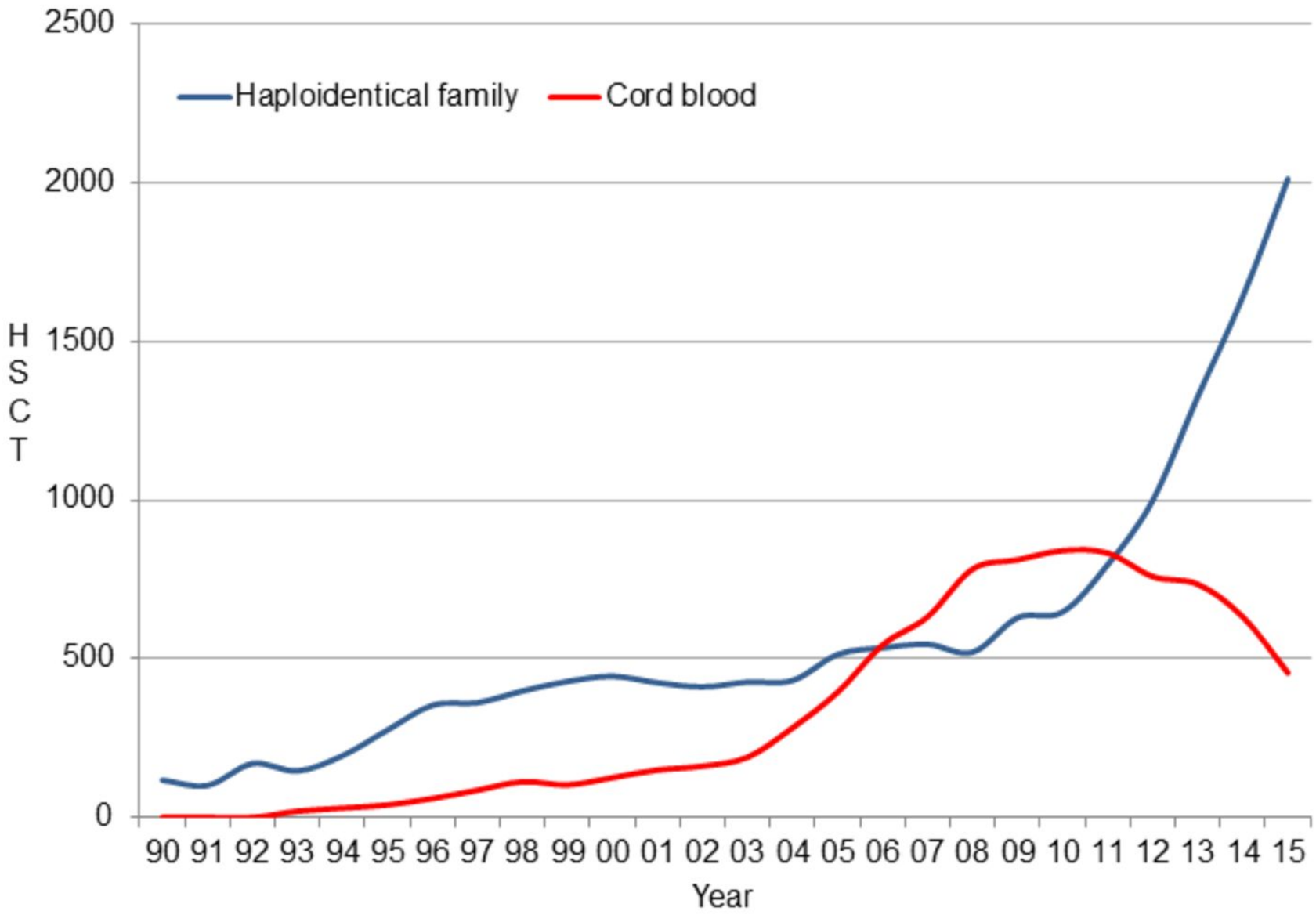

2500
2000
1500
1000
500
0
HSCT
Haploidentical family
Cord blood
90 91 92 93 94 95 96 97 98 99 00 01 02 03 04 05 06 07 08 09 10 11 12 13 14 15
Year

Figure 3b

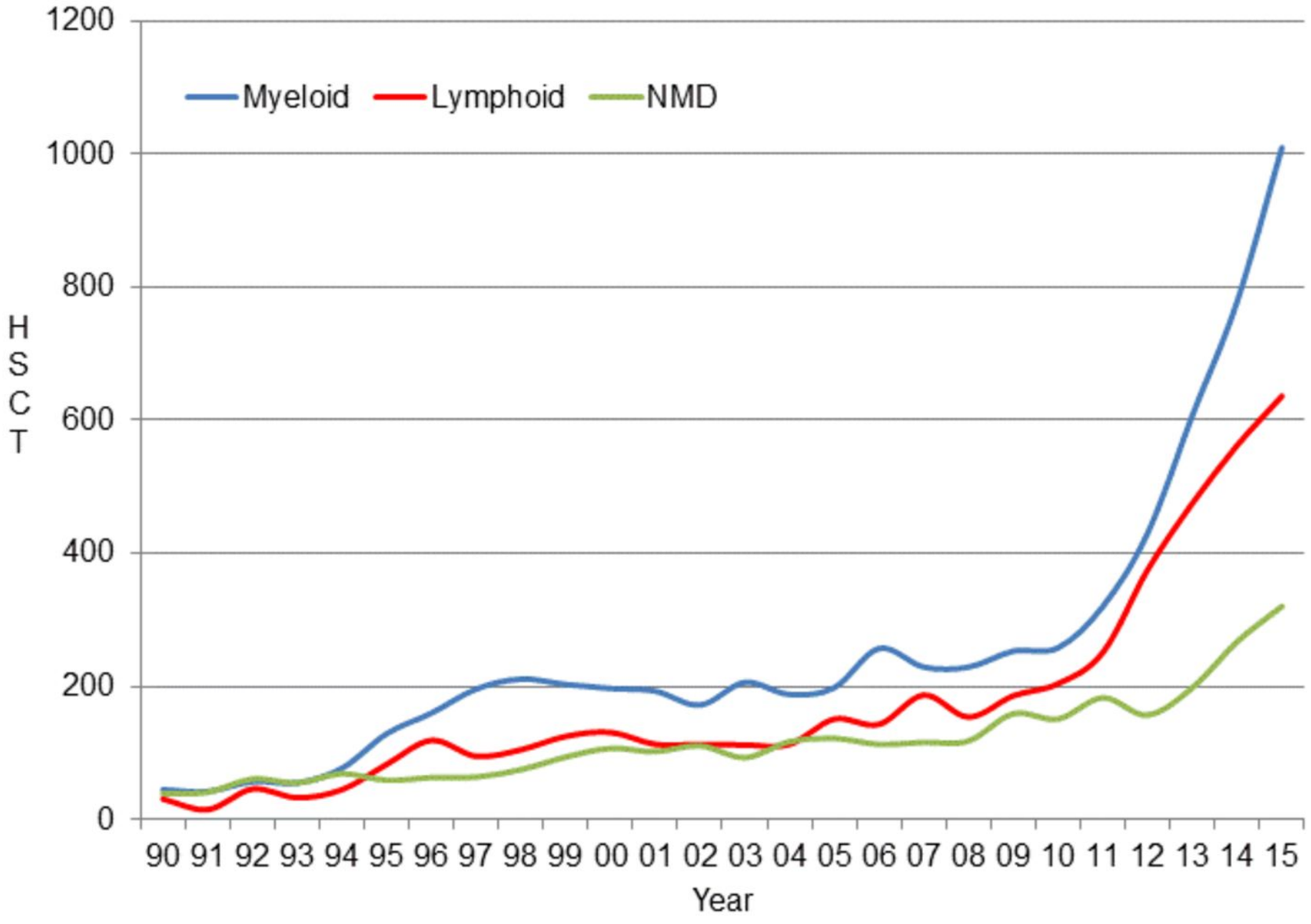

1200
1000
800
600
400
200
0
HSCT
Myeloid
Lymphoid
NMD
90 91 92 93 94 95 96 97 98 99 00 01 02 03 04 05 06 07 08 09 10 11 12 13 14 15
Year

Figure 3c

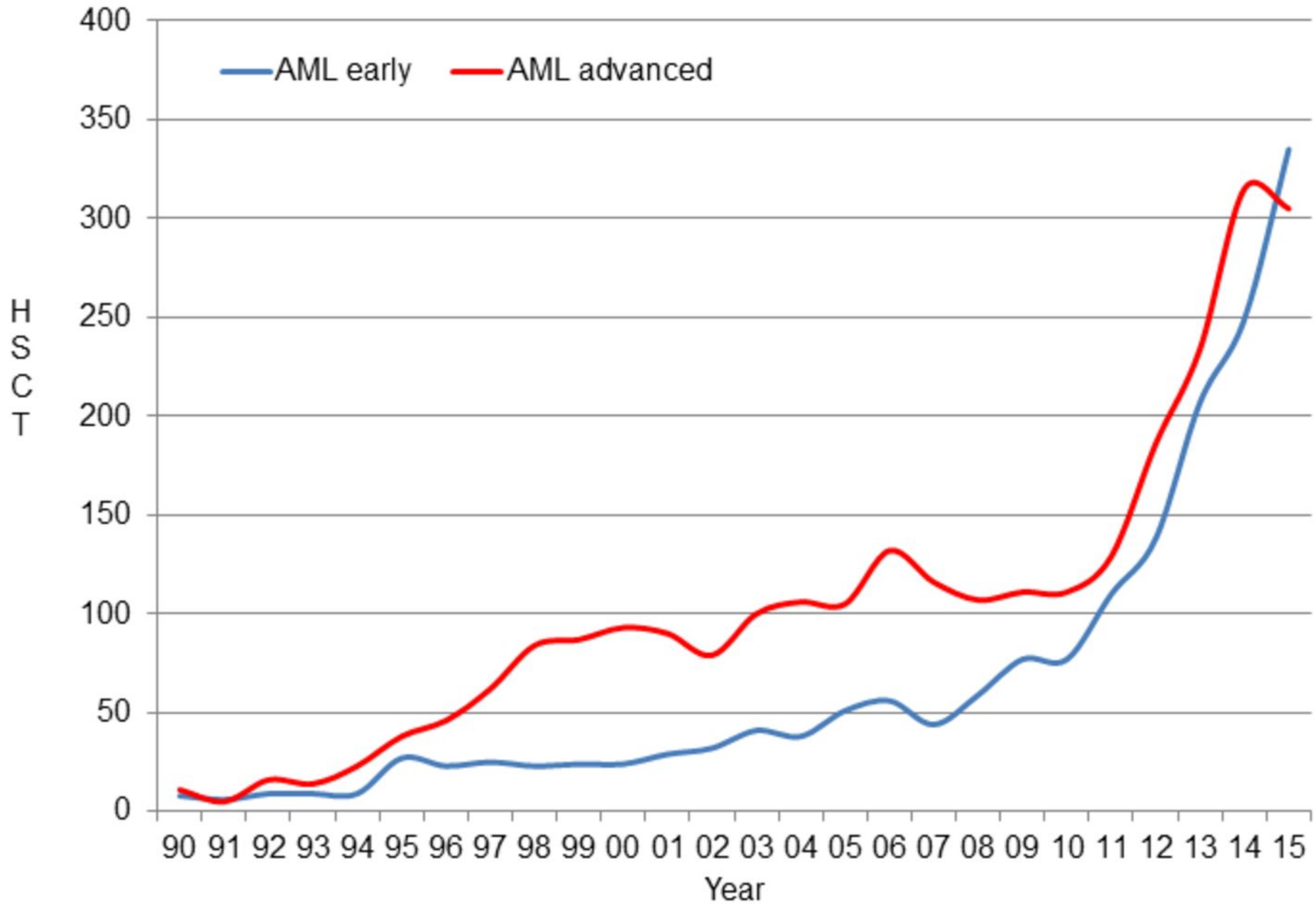

AML early
AML advanced
400
350
300
250
200
150
100
50
0
HSCT
90 91 92 93 94 95 96 97 98 99 00 01 02 03 04 05 06 07 08 09 10 11 12 13 14 15
Year

Figure 3d

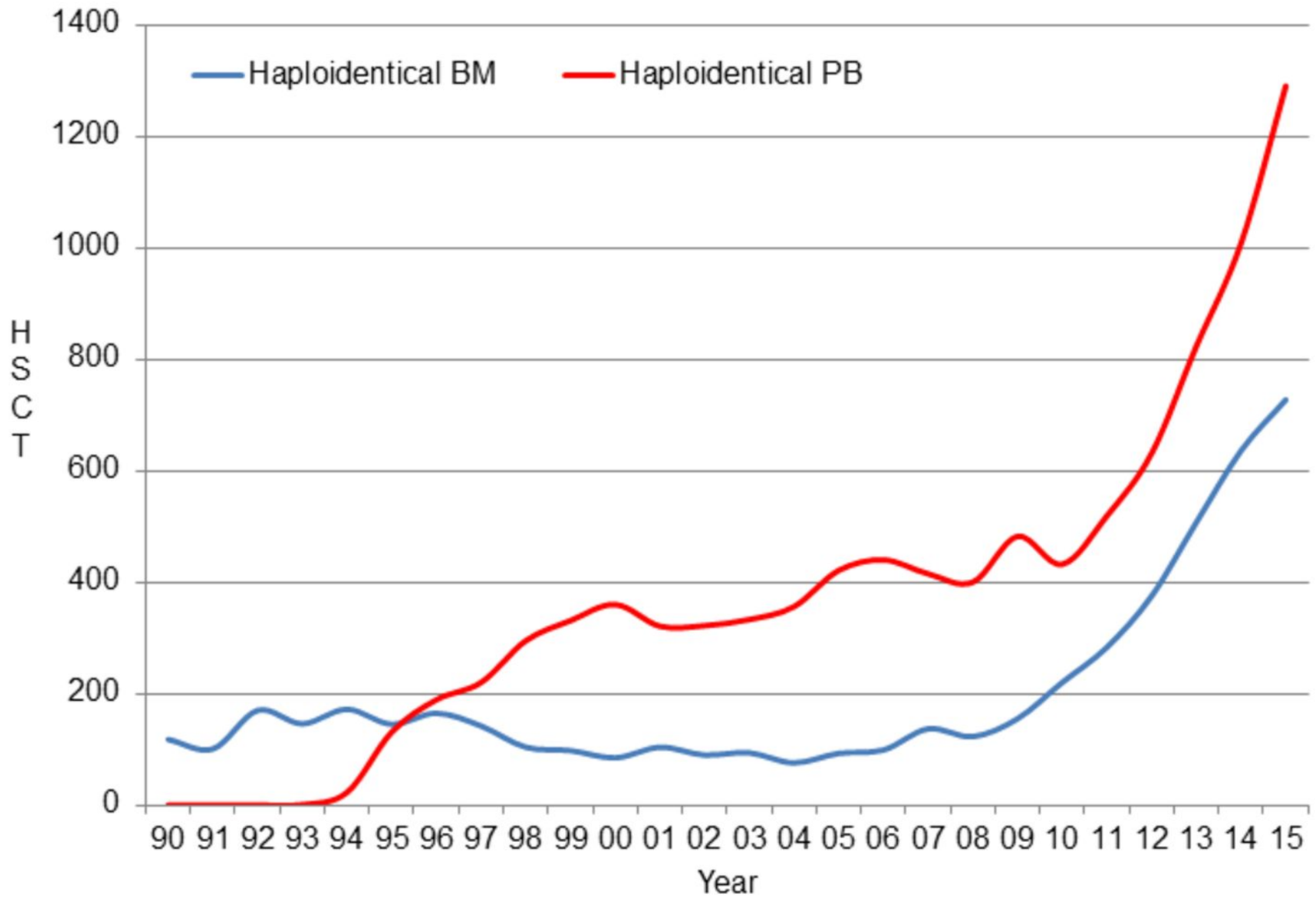

Haploidentical BM
Haploidentical PB
HSCT
1400
1200
1000
800
600
400
200
0
90 91 92 93 94 95 96 97 98 99 00 01 02 03 04 05 06 07 08 09 10 11 12 13 14 15
Year

Figure 3e

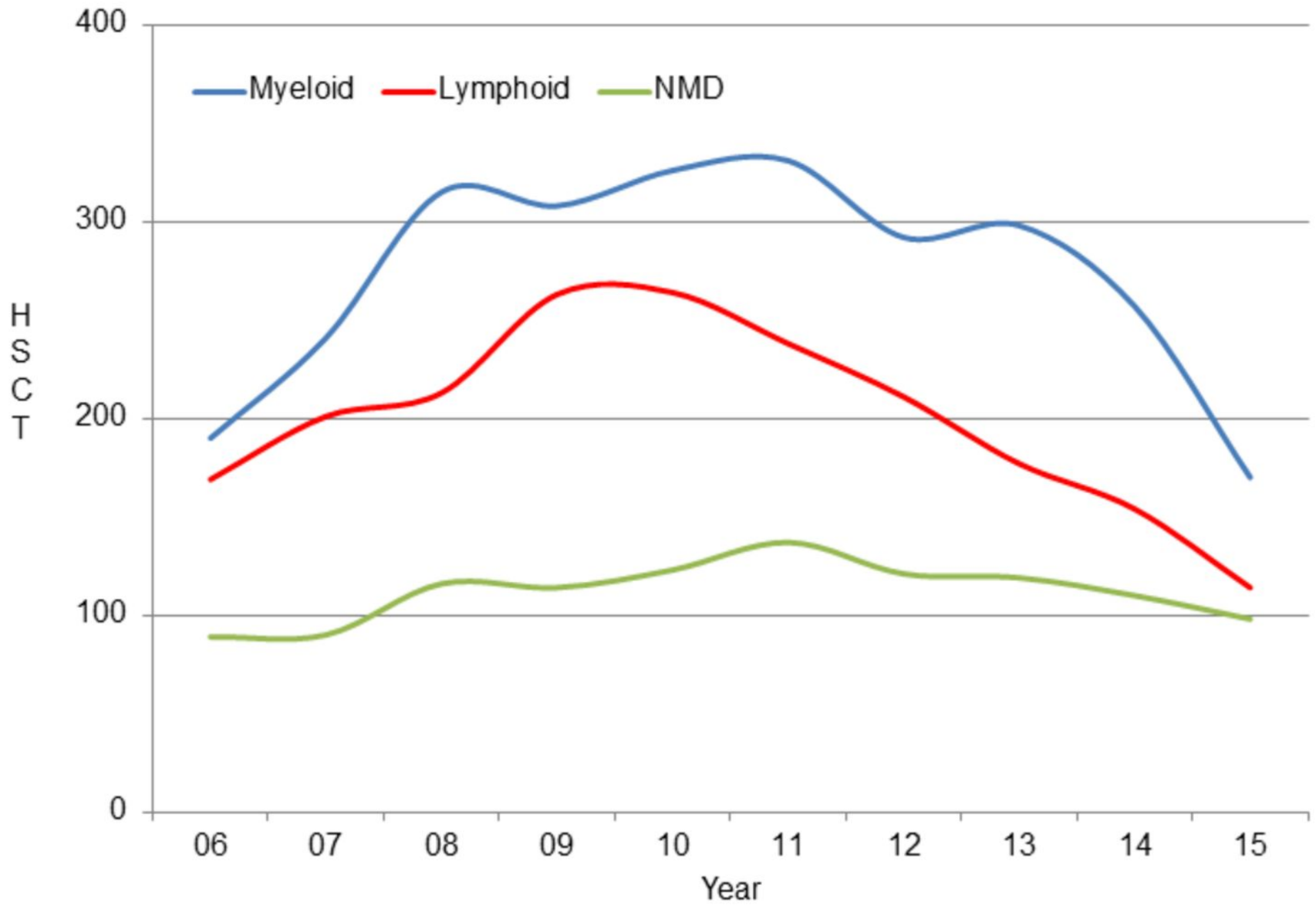
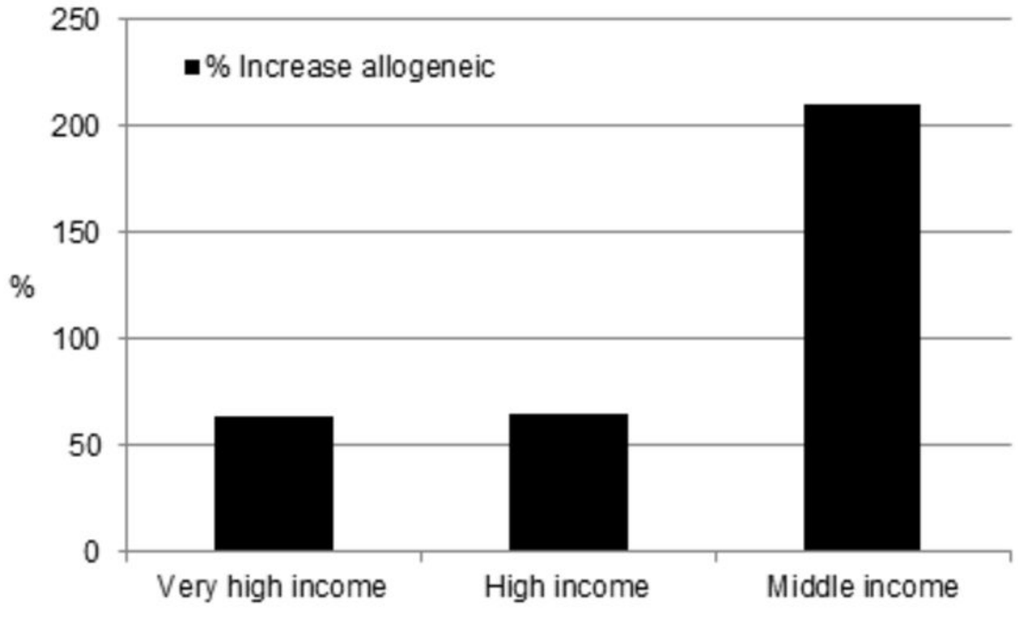
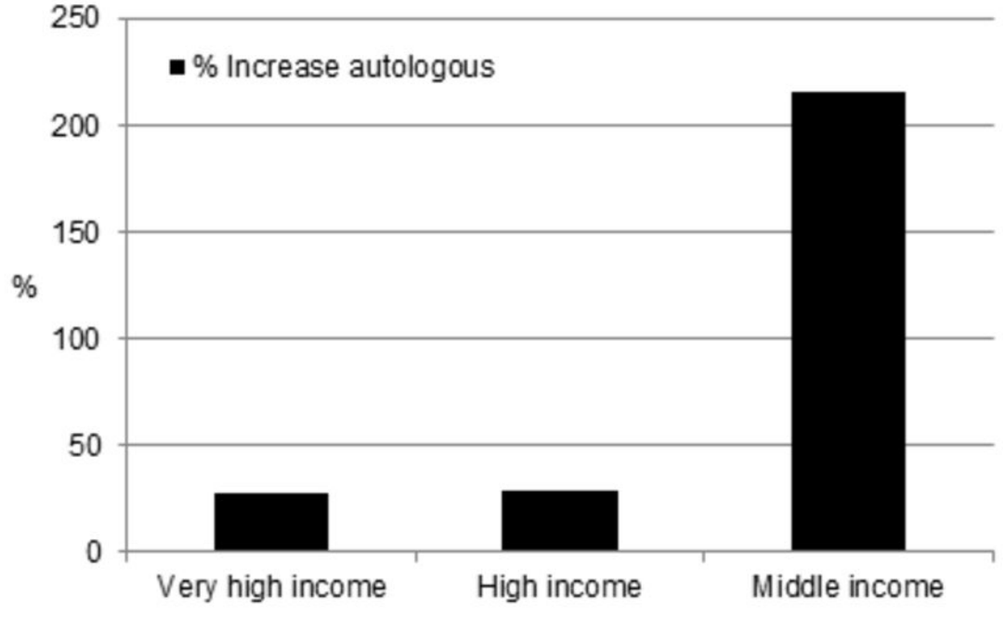
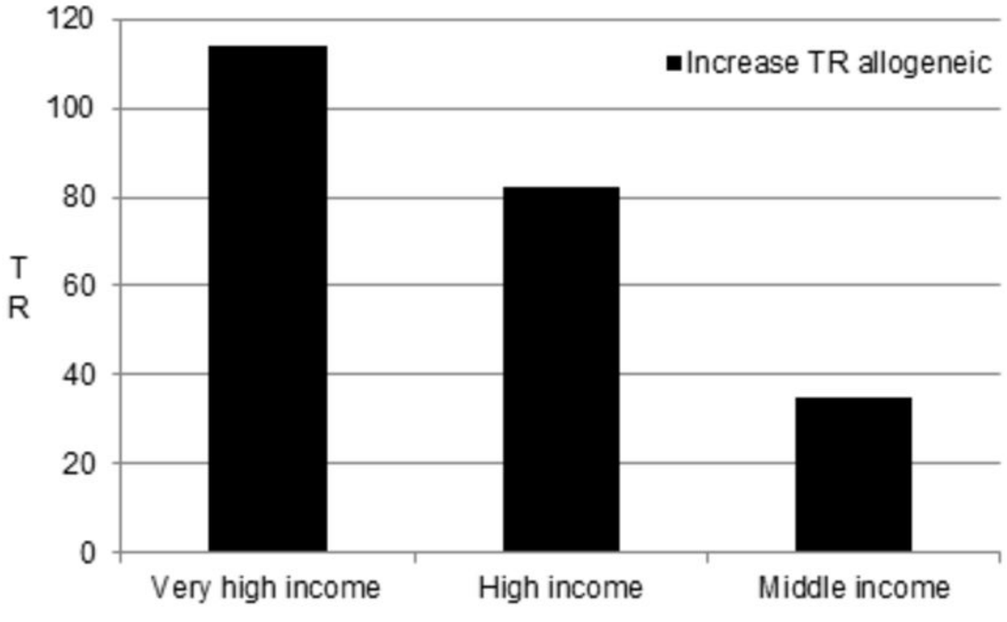
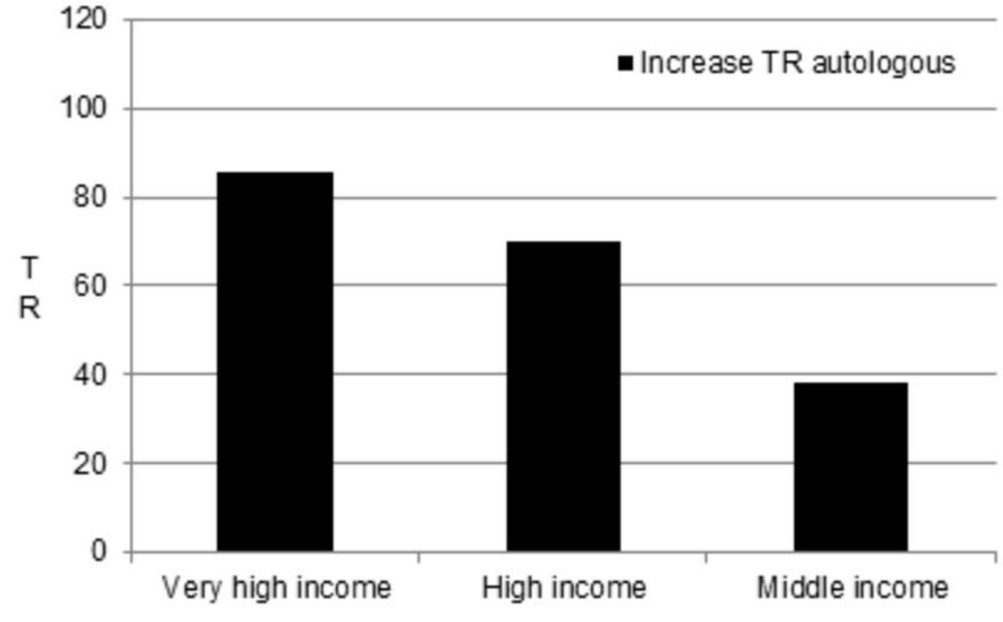

400
300
200
100
0
HSCT
Myeloid
Lymphoid
NMD
06
07
08
09
10
11
12
13
14
15
Year

Figure 4 a,b


250
200
150
100
50
0
%
% Increase allogeneic
Very high income
High income
Middle income


250
200
150
100
50
0
%
% Increase autologous
Very high income
High income
Middle income


120
100
80
60
40
20
0
T
R
Increase TR allogeneic
Very high income
High income
Middle income


120
100
80
60
40
20
0
T
R
Increase TR autologous
Very high income
High income
Middle income