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SPECIAL REPORT

Hematopoietic SCT in Europe 2013: recent trends in the use of alternative donors showing more haploidentical donors but fewer cord blood transplants

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A record number of 39 209 HSCT in 34 809 patients (14 950 allogeneic (43%) and 19 859 autologous (57%)) were reported by 658 centers in 48 countries to the 2013 survey. Trends include: more growth in allogeneic than in autologous HSCT, increasing use of sibling and unrelated donors and a pronounced increase in haploidentical family donors when compared with cord blood donors for those patients without a matched related or unrelated donor. Main indications were leukemias, 11 190 (32%; 96% allogeneic); lymphoid neoplasias, 19 958 (57%; 11% allogeneic); solid tumors, 1543 (4%; 4% allogeneic); and nonmalignant disorders, 1975 (6%; 91% allogeneic). In patients without a matched sibling or unrelated donor, alternative donors are used. Since 2010 there has been a marked increase of 96% in the number of transplants performed from haploidentical relatives (802 in 2010 to 1571 in 2013), whereas the number of unrelated cord blood transplants has slightly decreased (789 in 2010 to 666 in 2013). The use of donor type varies greatly throughout Europe.

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INTRODUCTION

Hematopoietic SCT (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.[5–10] 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.[11] This coincides with the recent interest of the WHO (www.who.org) in cell and tissue transplants and further stresses the need for adequate and timely information.[12] The analysis of the survey data spanning over 20 years has shown a continued and constant increase in the annual numbers of HSCT and transplant rates (number of HSCT per 10 million inhabitants) for both allogeneic and autologous HSCT.

This report is based on the 2013 survey data. In addition to transplant rates and indications, this report focuses on the use of donors other than HLA-identical siblings and matched unrelated donors for allogeneic HSCT.

PATIENTS AND METHODS

Data collection and validation

Participating teams were invited to report data for 2013 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 DLIs, reduced intensity HSCT and the numbers of pediatric HSCT is also collected. 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, cross-checking with the National Registries.

Teams

Six hundred and eighty-seven centers from 48 countries were contacted for the 2013 survey (39 European and 9 affiliated countries); of which 658 teams reported. This corresponds to a 96% return rate and includes 551 active EBMT member teams. Twenty nine teams failed to report in 2013.

Contacted teams are listed in the Supplementary appendix in alphabetical order by country, city, EBMT centre code, with their reported numbers of first and total HSCT, and of first allogeneic and autologous HSCT. The WHO regional office definitions (www.who.org) were used to

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Table 1. Numbers of hematopoietic SCTs in Europe 2013 by indication, donor type and stem cell source

	Allogeneic													*Autologous*			*Total*		
	Family								*Total family*	*Unrelated*			*Total unrelated*						
	HLA identical			*Non-identical*			*Twin*							*BM*	*BM+*				
	BM	*PB*	*Cord*	*BM*	*PB*	*Cord*	*BM*	*PB*		*BM*	*PB*	*cord*		*only*	*PB*	*cord*	*Allo*	*Auto*	*Total*
Leukemias	725	3140	15	332	557	2	5	24	4800	795	4675	420	5890	10	489	1	10 690	500	11 190
AML	309	1599	5	169	271	1	2	9	2365	315	2337	211	2863	7	373	0	5228	380	5608
1st CR	232	1123	2	88	118	1	1	9	1574	209	1340	114	1663	6	313	0	3237	319	3556
Not 1st CR	77	476	3	81	153	0	1	0	791	106	997	97	1200	1	60	0	1991	61	2052
Acute lymphatic leukemia	276	688	9	86	185	1	2	8	1255	271	767	112	1150	3	72	0	2405	75	2480
1st CR	148	486	3	41	77	1	1	6	763	141	477	60	678	0	57	0	1441	57	1498
Not 1st CR	128	202	6	45	108	0	1	2	492	130	290	52	472	3	15	0	964	18	982
CML	31	107	0	18	20	0	0	0	176	36	173	13	222	0	3	0	398	3	401
Chronic phase	20	51	0	6	6	0	0	0	83	21	65	5	91	0	0	0	174	0	174
Not 1st chronic phase	11	56	0	12	14	0	0	0	93	15	108	8	131	0	3	0	224	3	227
MDS, MDS/MPN overlap	93	476	1	42	69	0	1	6	688	134	882	58	1074	0	11	1	1762	12	1774
MPN	11	129	0	9	8	0	0	0	157	22	257	16	295	0	5	0	452	5	457
CLL	5	141	0	8	4	0	0	1	159	17	259	10	286	0	25	0	445	25	470
Lymphoproliferative disorders	94	721	0	80	111	0	1	17	1024	108	1097	55	1260	51	17 623	0	2284	17 674	19 958
Plasma cell disorders—MM	18	220	0	6	16	0	1	10	271	29	283	3	315	4	9532	0	586	9536	10 122
Plasma cell disorders—other	1	6	0	0	0	0	0	0	7	0	12	1	13	2	256	0	20	258	278
Hodgkin's lymphoma	14	102	0	34	55	0	0	1	206	20	161	23	204	21	1859	0	410	1880	2290
Non-Hodgkin lymphoma	61	393	0	40	40	0	0	6	540	59	641	28	728	24	5976	0	1268	6000	7268
Solid tumors	2	5	0	4	34	0	0	0	45	7	8	0	15	54	1428	1	60	1483	1543
Neuroblastoma	0	2	0	2	26	0	0	0	30	2	5	0	7	22	464	1	37	487	524
Soft tissue sarcoma	0	0	0	0	3	0	0	0	3	1	0	0	1	5	19	0	4	24	28
Germinal tumors	0	0	0	0	0	0	0	0	0	0	0	0	0	2	353	0	0	355	355
Breast cancer	0	1	0	0	0	0	0	0	1	0	0	0	0	0	42	0	1	42	43
Ewing	1	0	0	1	2	0	0	0	4	1	1	0	2	15	200	0	6	215	221
Other solid tumors	1	2	0	1	3	0	0	0	7	3	2	0	5	10	350	0	12	360	372
Non malignant disorders	601	227	47	86	111	1	1	3	1077	355	245	119	719	4	175	0	1796	179	1975
BM failure—SAA	165	124	4	13	20	0	1	3	330	117	84	19	220	0	0	0	550	0	550
BM failure—other	72	17	8	17	9	1	0	0	124	51	37	10	98	0	1	0	222	1	223
Hemoglobinopathies—thalassemia	161	55	17	19	8	0	0	0	260	27	13	1	41	0	1	0	301	1	302
Hemoglobinopathies—other	55	7	5	5	3	0	0	0	75	7	1	0	8	0	0	0	83	0	83
Primary Immune deficiencies	120	18	10	28	56	0	0	0	232	118	89	57	264	2	2	0	496	4	500
Inherited disorders of metabolism	25	6	1	3	11	0	0	0	46	28	16	31	75	1	1	0	121	2	123
Auto immune disease	3	0	2	1	4	0	0	0	10	7	5	1	13	1	170	0	23	171	194
Others	23	20	0	5	7	0	0	0	55	27	26	12	65	0	23	0	120	23	143
Total patients	1445	4113	62	507	820	3	7	44	7001	1292	6051	606	7949	119	19 738	2	14 950	19 859	34 809
Retransplants	73	265	2	54	165	2	1	5	567	69	468	58	595	5	1543		1162	1548	2710
Additional transplants	11	25		13	7				56		41	2	43	5	1586		99	1591	1690
Total ALL transplants	1529	4403	64	574	992	5	8	49	7624	1361	6560	666	8587	129	22 867	2	16 211	22 998	39 209
Pediatric transplants	878	241	62	166	292	1	2	6	1648	728	475	254	1457	65	1064	2	3105	1131	4236

Abbreviations: MDS = myelodysplastic; MPN = myeloproliferative neoplasm; PBSC = peripheral blood; SAA = severe aplastic anemia.

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classify countries as European or Non-European. Nine non-European countries participated in the 2013 EBMT survey: Algeria, Iran, Israel, Jordan, Lebanon, Nigeria, Saudi Arabia, South Africa and Tunisia. Their data from 26 actively transplanting teams make up 6.2% of the total data set and is included in all analyses.

Definitions

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 PB and bone marrow as a stem cell source but not cord blood HSCT, these are shown as cord blood HSCT in Figures 3–5. Mismatched family donors are termed 'haploidentical' for the purpose of this analysis but this category includes also mismatched related donors that are mismatched to a lesser degree than a full haplotype. As the haplotype mismatched donors are the vast majority in this category, the term 'haploidentical' is used for the entire group.

Multiple 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.

Information on additional cellular therapies was subdivided into: HSC for non-hematopoietic use; non-hematopoietic stem cell therapies; MSC therapies for rejection or GVHD prevention/treatment; and DLIs. Collection of information was validated by cross-checking with a similar more detailed survey carried out by TERMIS-EU (Tissue Engineering and Regenerative Medicine International Society; www.termis.org), EULAR (European League against Rheumatism; www.eular.org), ICRS-EU (International Cartilage Repair Society; www.cartilage.org) and ISCT (International Society of Cellular Therapy; www.celltherapysociety.org).[11]

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 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, absolute numbers of transplanted patients, transplants or transplant rates are shown for specific countries, indications or transplant techniques.

RESULTS

2013 data

Participating teams in 2013. Of the 658 teams, 406 (62%) performed both allogeneic and autologous transplants; 225 (34%) restricted their activity to autologous HSCT only, and 17 teams (3%) to allogeneic transplants only. Ten teams (1%) reported having performed no transplants in 2013 owing to renovation or temporary closure of the transplant unit. Of the 648 active centers, 120 (19%) centers performed transplants on both adult and pediatric patients. An additional 105 (16%) centers were dedicated pediatric transplant centers, and 423 (65%) centers performed transplants on adults only.

Numbers of patients and transplants. A total of 34 809 patients received their first transplant in 2013. Of these, 14 950 (43%) were allogeneic and 19 859 (57%) autologous. When compared with 2012, the total number of patients transplanted increased by 3.4% (5.5% allogeneic HSCT and 1.8% autologous HSCT).[10] Furthermore, there were 2710 retransplants (1162 allogeneic and 1548 autologous) and 1690 multiple transplants (99 allogeneic and 1591 autologous), bringing the total to 39 209 HSCT procedures, 16 211 allogeneic (41%) and 22 998 autologous (59%) performed in 2013, which is an increase of 26% compared with 5 years and 88% compared with 15 years previously.

Indications for HSCT in 2013 are listed in detail in Table 1. The main indications were leukemias; 11 190 (32% of total; 96% of which were allogeneic); lymphoid neoplasias including Non-Hodgkin lymphoma, Hodgkin lymphoma and plasma cell disorders, 19 958 (57%; 11% allogeneic); solid tumors, 1543 (4%; 4% allogeneic); and nonmalignant disorders, 1975 (6%; 91%

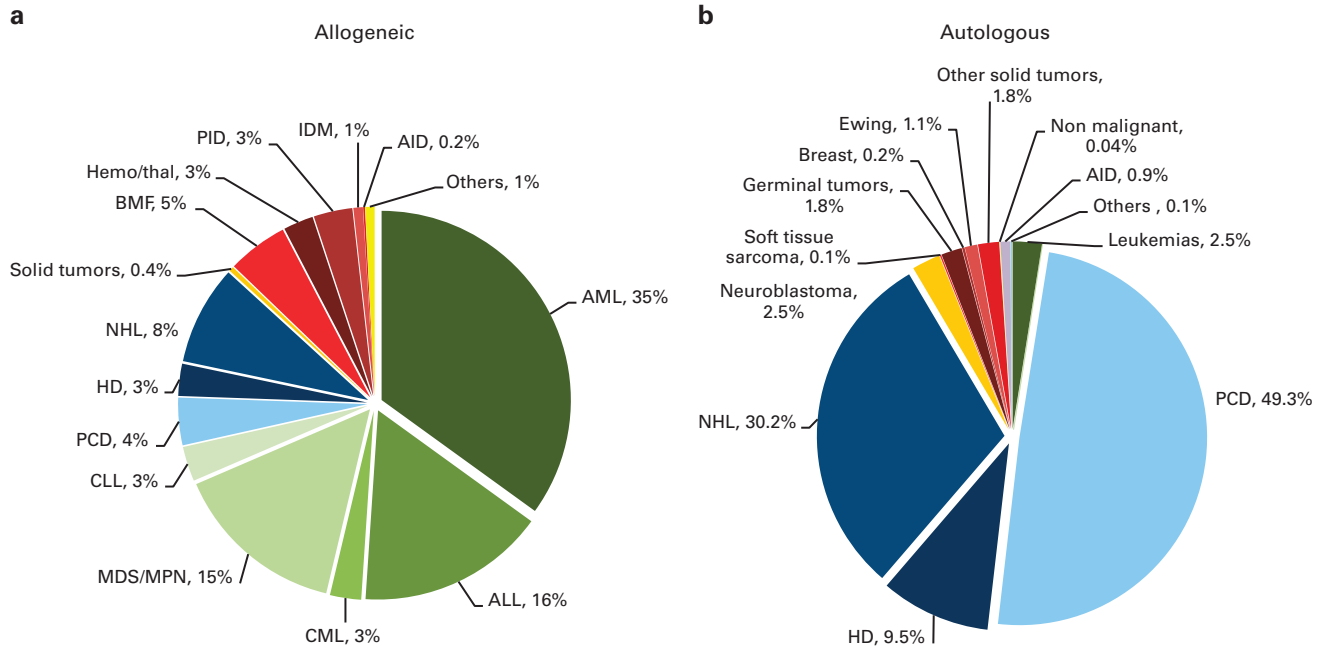

Figure 1. Relative proportions of indications for an HSCT in Europe in 2013. (**a**) Proportions of disease indications for an allogeneic HSCT in Europe in 2013. (**b**) Proportions of disease indications for an autologous HSCT in Europe in 2013.

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allogeneic). As seen in previous years, the majority of HSCT for lymphoid malignancies were autologous, whereas most transplants for leukemia were performed using stem cells from allogeneic donors. Autologous HSCT for nonmalignant disorders predominantly include patients with autoimmune disorders.

Distributions of indications for HSCT are shown in Figures 1a and b for allogeneic and autologous HSCT, respectively. Compared with 2012, there were increases in allogeneic HSCT for AML in CR1 (10.7%), MPN (11.1%) and NHL (12.5%). For autologous HSCT, there was a decrease in activity for AML

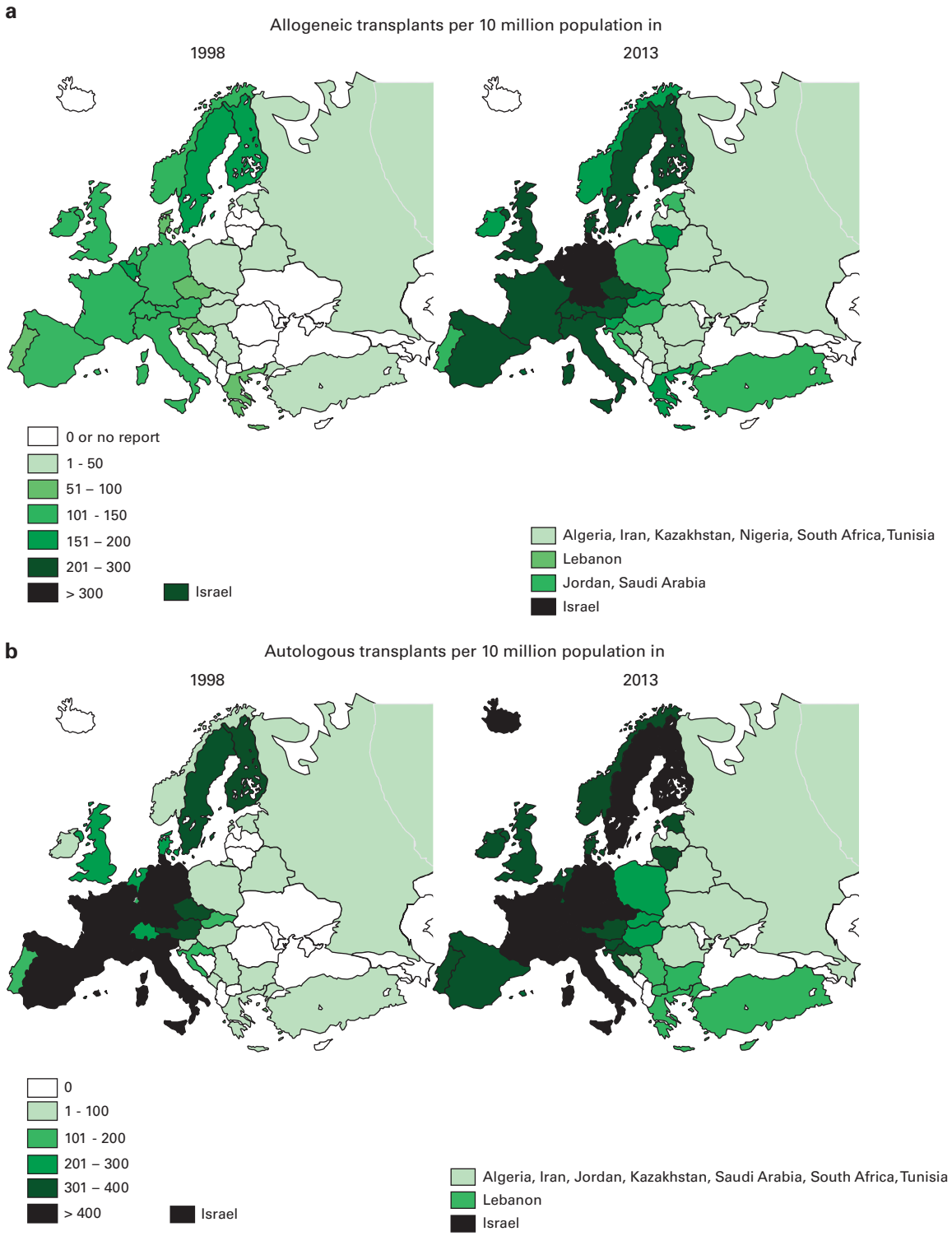

Figure 2. Transplant rates in Europe (= total number of HSCT per 10 million inhabitants) by participating country, showing 15-year trends 1998–2013. (**a**) Allogeneic transplant rates per 10 million population in 1998–2013 (**b**) Autologous transplant rates per 10 million population in 1998–2013.

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(18%) and HD (10%) but an increase for plasma cell disorders by 6.1%.

DLIs. 2513 patients received treatment with DLIs, a 12% increase since 2012.

Reduced intensity conditioning. 6534 of the total allogeneic HSCT were performed using non myeloablative conditioning. This is an increase of 11.4% since 2012 and is 40% of all allogeneic HSCT.

Fifteen year trends

Figures 2a and b show transplant rates by country for allogeneic and autologous HSCT comparing rates in 2013 to rates 15 years ago, to 1998. Median transplant rates per 10 million inhabitants were 124 (range, 0.1–493) for allogeneic HSCT and 233 (range, 1.0–538) for autologous HSCT in 2013 as compared with 89 and 164 in 1998.

Figure 3a shows the 15-year trends for allogeneic and autologous HSCT showing some narrowing in the difference between autologous and allogeneic HSCT performed.

Figure 3b shows trends for allogeneic HSCT over the past 15 years for sibling donor and unrelated donor transplantation, with more unrelated donor HSCT since 2007 as compared with sibling donor HSCT, unrelated donor HSCT accounting for (53% of all allogeneic HSCT)% in 2013.[13] Figure 3c shows trends in the use of alternative donor transplantation, separately for cord blood and for haploidentical family donor HSCT. It is obvious that the use of cord blood has stabilized in 2011 and is going down slightly; the number of haploidentical HSCT has more than doubled since 2010. For haploidentical HSCT, marrow is used in 37% and PB in 63% as a stem cell source[14,15] in 2013.

Figures 4a–d depict the indications for allogeneic HSCT separately for sibling donor, unrelated donor, cord blood donor and haploidentical donor HSCT in 2013. When comparing leukemias, lymphoid neoplasias and nonmalignant disorders, distributions of indications do not differ greatly; except for nonmalignant disorders receiving more commonly cord blood transplants, reflecting the younger age of these patients and the preference for cord blood in children.

Figure 5 shows transplant rates for the 15 countries with the highest rates of allogeneic HSCT in Europe ordered by decreasing rate of unrelated donor HSCT. This figure shows considerable heterogeneity in the use of HSCT technology among countries.

Additional cellular therapies

Seventeen teams from 11 countries reported having treated 130 patients with hematopoietic stem cells for non-hematopoietic use in 2013. All therapies were performed using autologous HSC's. The main indications were cardiovascular, 75; neurological, 32; tissue repair, 20; and epithelial, 3. In addition, 405 patients in 86 teams and 21 countries received mesenchymal stromal cells for prevention/treatment of GVHD (344), prevention/treatment of graft failure (34) and for unspecified reasons (27).[11]

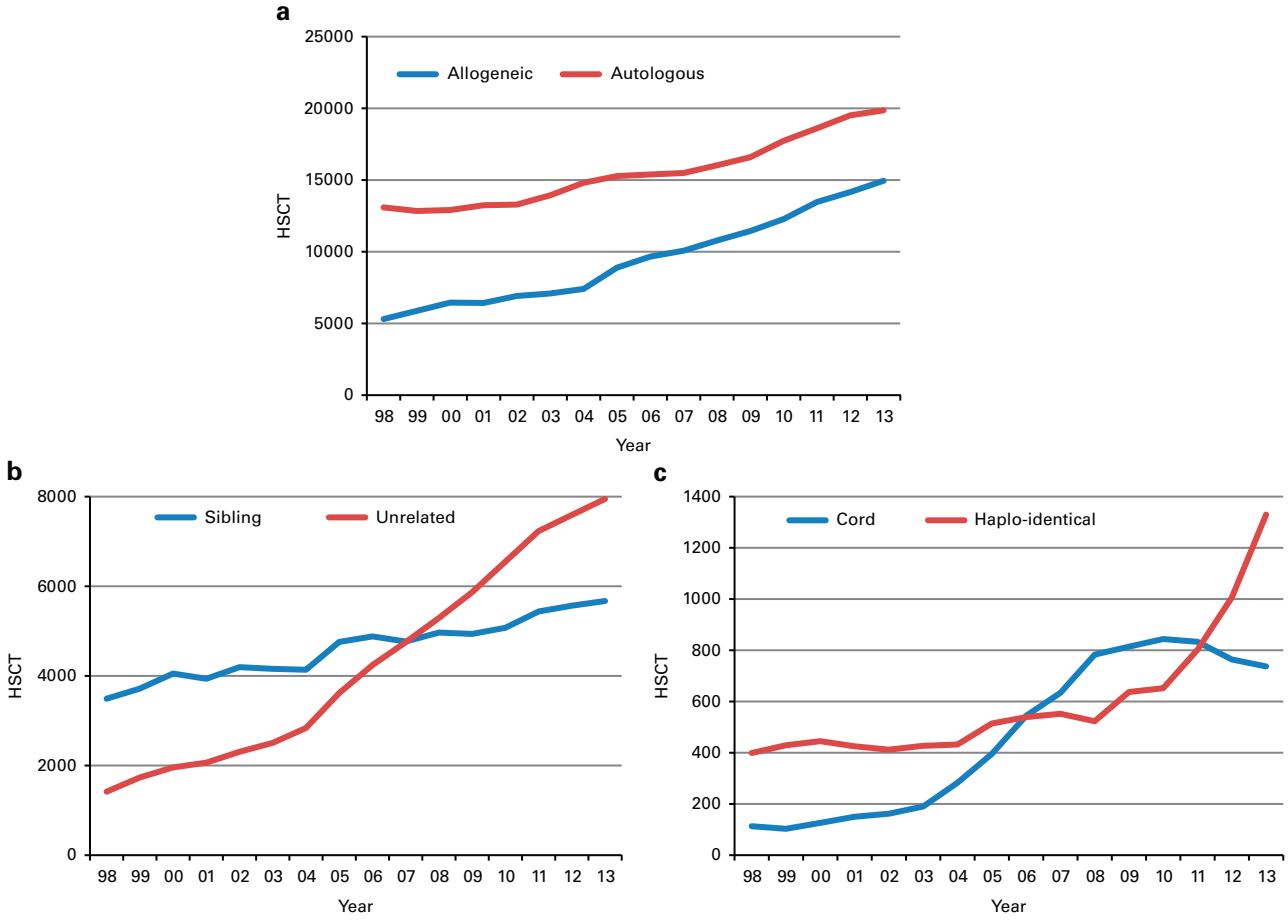

Figure 3. Absolute numbers by transplant and donor type 1998–2013. (**a**) Absolute numbers of allogeneic and autologous HSCT in Europe in 1998–2013. (**b**) Absolute numbers of sibling donor and unrelated donor HSCT in Europe 1998–2013. (**c**) Absolute numbers of haploidentical and cord blood HSCT in Europe 1998–2013.

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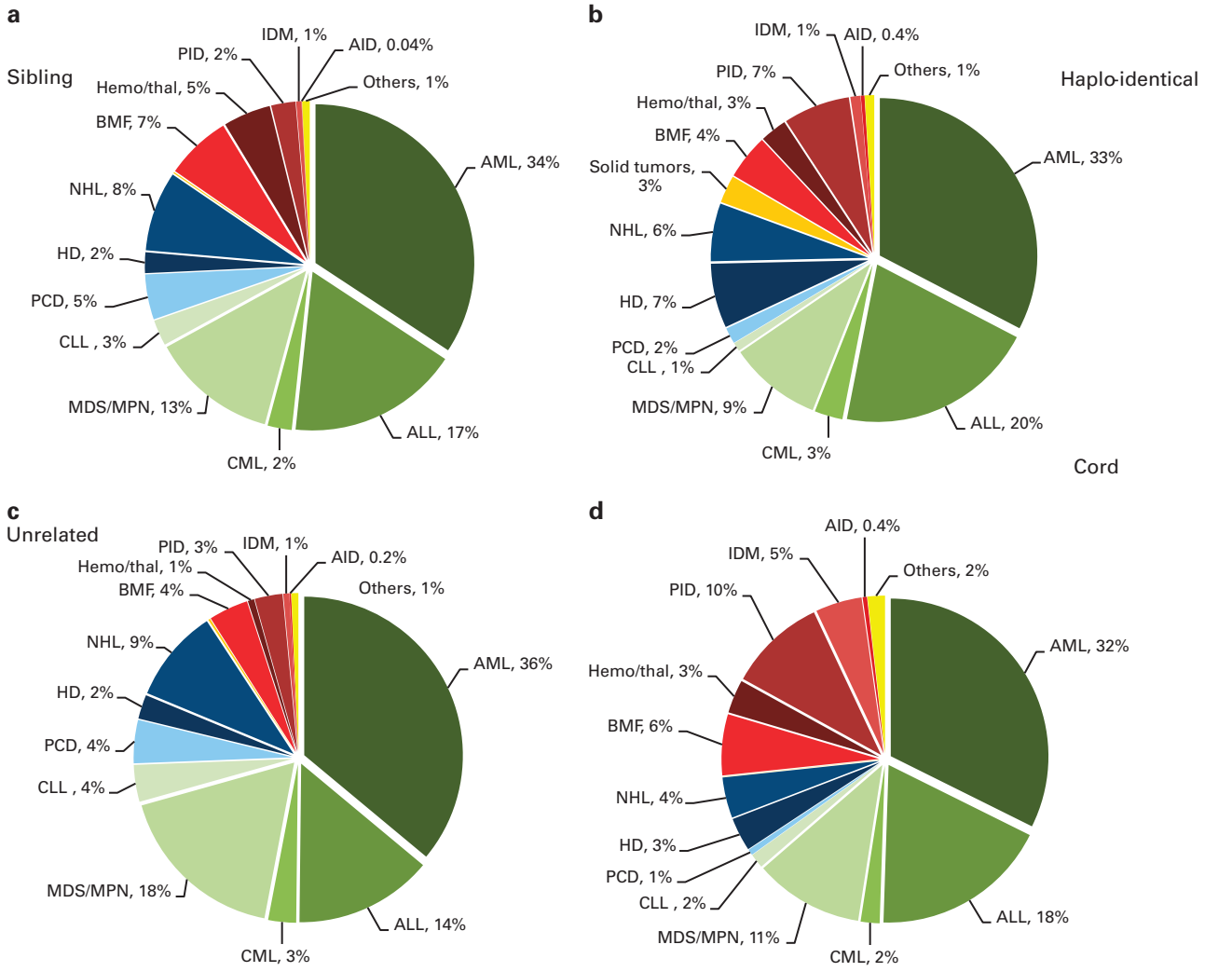

Figure 4. Disease indications by donor type in 2013. (**a**) Proportions of disease indications in 2013 for sibling donor HSCT. (**b**) Proportions of disease indications in 2013 for haplo-identical donor HSCT. (**c**) Proportions of disease indications in 2013 for unrelated donor HSCT. (**d**) Proportions of disease indications in 2013 for cord blood HSCT.

DISCUSSION

The EBMT activity survey has been conducted annually since 1990.[6] The 2010 survey reported for the first time in more than 30 000 patients transplanted in a given year.[16] This trend continues with an additional increase by 3.6% in 2013, suggesting that HSCT remains an increasingly important treatment modality in the era of targeted antibody and molecular therapy. The present 2013 report focuses on allogeneic transplants using different types of donors.

HSCT for some indications continues to increase but not for others. Of interest is growth of allogeneic HSCT for AML in CR1, MPN and lymphoma. For autologous HSCT, the number of transplants for myeloma continues to increase. In autologous HSCT, the numbers of procedures for AML in CR1 and for Hodgkin's lymphoma dropped slightly. The decrease in autologous HSCT for Hodgkins Lymphoma of 10% may be related to the availability of monoclonal antibodies in this disease.

Notable in this year's survey is the increase in the use of allogeneic HSCT more than autologous HSCT and the increasing use of alternative donor transplants, where an impressive trend for more haploidentical HSCT has been observed. The category of haploidentical HSCT as used for this analysis includes haploidentical HSCTs as well as mismatched family donor HSCTs, where the mismatch does not include a full haplotype, for example, 1 or 2 allele mismatched relatives. Unfortunately we do not have the data to separate these categories but we think it is unlikely that the increase observed could be explained by one allele mismatched siblings. The increase in haploidentical HSCT coincides with the publications of the post-transplant CY GVHD prophylaxis in haploidentical HSCT.[14] Again we do not have the data within this survey to separate haploidentical HSCTs using this strategy from other ways to perform haploidentical HSCT.

This is accompanied by a slight decrease in HSCT using cord blood pointing to the fact that mismatched unrelated cord blood and haploidentical donors are in competition for patients in whom no sibling or matched unrelated donor has been identified.[14,5,17]

When comparing the use of donors for allogeneic HSCT in countries with high transplant rates, it is obvious that there are important differences. Some may be explained by availability of sibling donors as there are differences in family size across Europe. There are, however, threefold differences in transplant rates for sibling and unrelated donor HSCT among countries and even larger differences in the use of unrelated cord blood and haploidentical donors probably reflecting availability, financial

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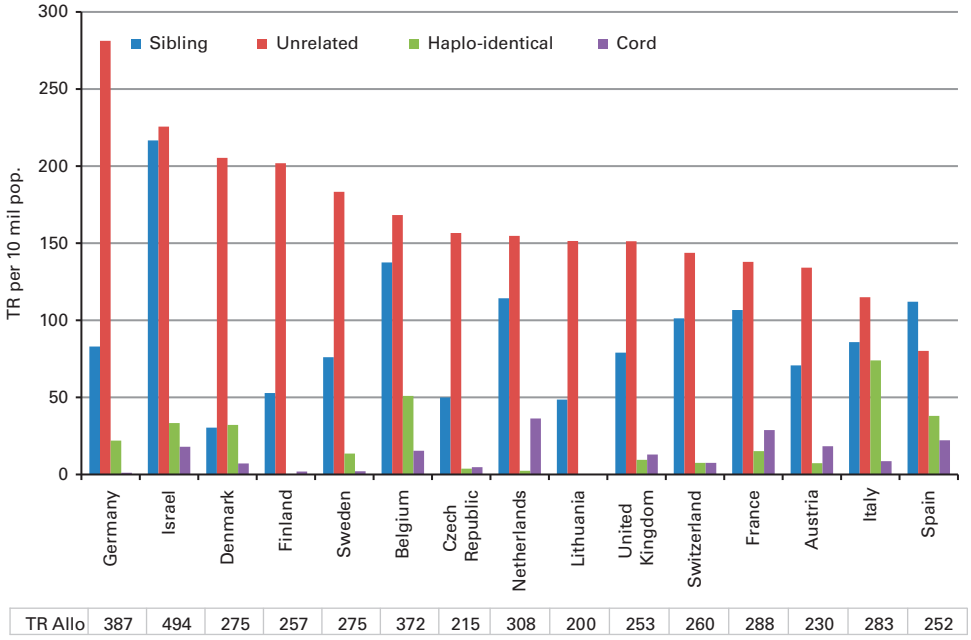

TR Allo	387	494	275	257	275	372	215	308	200	253	260	288	230	283	252

Figure 5. Transplant rates for sibling donor, unrelated donor, haploidentical donor and cord blood HSCT in Europe in 2013 for the 15 countries with the highest transplant rates.

issues as well as differences in the interpretation of results of recent studies and local experience.

Overall, this paper reflects current practice, and results may be useful to health care planning and health policy makers.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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