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Improved outcome of patients with graft-*versus*-host disease after allogeneic hematopoietic cell transplantation for hematologic malignancies over time: an EBMT mega-file study

Hildegard T. Greinix,[1] Dirk-Jan Eikema,[2] Linda Koster,[3] Olaf Penack,[4] Ibrahim Yakoub-Agha,[5] Silvia Montoto,[6] Christian Chabannon,[7] Jan Styczynski,[8] Arnon Nagler,[9] Marie Robin,[10] Stephen Robinson,[11] Yves Chalandon,[12] Malgorzata Mikulska,[13] Stefan Schönland,[14] Zinaida Peric,[15] Annalisa Ruggeri,[16] Francesco Lanza,[17] Liesbeth C. de Wreede,[18] Mohamad Mohty,[19] Grzegorz W. Basak[20] and Nicolaus Kröger[21]

[1]Department of Medicine, Division of Haematology, Medical University of Graz, Graz, Austria; [2]EBMT Statistical Unit, Leiden, the Netherlands; [3]EBMT Data Office Leiden, Leiden, the Netherlands; [4]Medical Department of Hematology, Oncology and Tumor Immunology, Charité Universitaetsmedizin Berlin, Berlin, Germany; [5]Department of Haematology, CHU de Lille, University Lille, INSERM U1286, Infinite, Lille, France; [6]St. Bartholomew`s hospital, Barts Health NHS Trust, London, UK; [7]Institut Paoli Calmettes, Marseille, France; [8]Collegium Medicum, Nicolaus Copernicus University Torun, Bydgoszcz, Poland; [9]Hematology and BMT Division, Chaim Sheba Medical Center, Tel-Hashomer, Tel-Aviv University, Ramat-Gan, Israel; [10]Hematology / Transplantation, Hôpital Saint-Louis, Paris Cedex 10, France; [11]Bristol Oncology Centre, Bristol, UK; [12]Département d'Oncologie, Service d'Hématologie, Hôpitaux Universitaires de Genève and Faculty of Medicine, University of Geneva, Geneva, Switzerland; [13]Division of Infectious Diseases, University of Genova, Ospedale Policlinico San Martino, Genova, Italy; [14]University Hospital of Heidelberg, Heidelberg, Germany; [15]University Hospital Center Rebro, Zagreb, Croatia; [16]Hematology and Bone Marrow Transplant Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy; [17]Ravenna Hospital, Ravenna, Italy; [18]Department of Biomedical Data Sciences, LUMC Leiden, Leiden, the Netherlands; [19]Hopital Saint Antoine, Paris Cedex 12, Paris, France; [20]Department of Hematology, Oncology and Internal Medicine, Medical University of Warsaw, Warsaw, Poland and [21]University Hospital Eppendorf, Hamburg, Germany

ABSTRACT

Acute graft-*versus*-host disease (aGvHD) remains a major threat to successful outcome following allogeneic hematopoietic cell transplantation though advances in prophylaxis and supportive care have been made. The aim of this study is to test whether the incidence and mortality of aGvHD have decreased over time. 102,557 patients with a median age of 47.6 years and with malignancies after first allogeneic sibling or unrelated donor (URD) transplant were studied in the following periods: 1990-1995, 1996-2000, 2001-2005, 2006-2010 and 2011-2015. Findings: 100-day incidences of aGvHD grades II-IV decreased from 40% to 38%, 32%, 29% and 28%, respectively, over calendar time (P<0.001). In multivariate analysis URD, not in complete remission (CR) at transplant or untreated, and female donor for male recipient were factors associated with increased risk whereas the use of ATG/alemtuzumab decreased aGvHD incidence. Median follow-up was 214, 169, 127, 81 and 30 months, respectively, for the periods analyzed. Three-year-survival after aGvHD grades II-IV increased significantly from 38% to 40%, 43%, 44%, and 45%, respectively. In multivariate analysis URD, not in CR at transplant, peripheral blood as stem cell source, female donor for male recipient, and the use of ATG/alemtuzumab were associated with increased mortality whereas reduced-intensity conditioning was linked to lower mortality. Mortality increased with increasing patient age but decreased in the recent cohorts. Our analysis demonstrates that aGvHD has decreased over recent decades and also that the survival rates of patients affected with aGvHD has improved.

Correspondence:

HILDEGARD GREINIX
hildegard.greinix@medunigraz.at

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Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) has been increasingly used to cure malignant and benign hematologic diseases.[1] Transplanted T-cells from the donor can recognize and eradicate hematologic malignancies through the immunologic graft-*versus*-leukemia effect. Unfortunately, donor conventional T-cells recognize normal recipient tissues and attack them, causing graft-*versus*-host disease (GvHD); this is the major cause of non-relapse mortality (NRM) following HSCT: GvHD is commonly reported in 40-60% of patients following HSCT.[2,3] Despite advances in GvHD prophylaxis, current pharmacological approaches fail to completely prevent acute GvHD (aGvHD).[4-6] Corticosteroids remain the established first-line therapy, however only around 50% of patients with aGvHD achieve complete responses[7] and prognosis of steroid-refractory patients is dismal.[8] Therefore, aGvHD and its associated infectious complications and organ toxicities contribute substantially to morbidity and early mortality following HSCT.

Over recent decades, transplant practices have changed markedly with recipient age increasing, the use of unrelated and mismatched donors, reduced-intensity conditioning (RIC) and peripheral blood stem cells (PBSCs) as the predominant graft source.[9,10] Furthermore, improvements in supportive care measures such as novel antimicrobial agents and diagnostic procedures have also had an impact on HSCT outcome over time.

Retrospective analyses have revealed an improvement in the survival of more recent transplant recipients.[9,11] Gooley *et al*., observed reduced incidences of aGvHD grades III-IV, less major organ injury and a reduction in life-threatening infections in the early stages following HSCT in recently-transplanted HSCT patients.[11] Khoury *et al*. reported improved survival over time for transplant recipients after myeloablative conditioning with aGvHD given tacrolimus-based GvHD prophylaxis. This was most evident for patients with grade II aGvHD.[12]

To date, analyses on changes in survival outcome over time in an aGvHD-affected patient cohort given various conditioning regimen intensities are lacking. Therefore, we conducted a large registry study to assess whether outcome of HSCT patients experiencing severe aGvHD has improved over time.

Methods

Data collection

This was a multicenter, retrospective study performed by the Transplant Complications and Chronic Malignancies Working Parties of the European Society for Blood and Marrow Transplantation (EBMT). Data on transplantations were obtained from the EBMT registry. A total of 590 transplant centers contributed patients. The study was approved by the scientific board of both EBMT working parties.

Patient selection

Patients were 18 to 80 years of age with hematological malignant disease and received a first allograft between 1990 and 2015 from a HLA-identical sibling or matched or mismatched unrelated donor. Both myeloablative and RIC regimens, and any disease stage at HSCT, were included. Recipients of in-vitro T-cell depleted grafts, haplo-identical transplants and cord-blood transplants were excluded. The maximal severity of aGvHD for each patient was used in all analyses.[13]

Study endpoints

The primary endpoints were aGvHD grades II-IV following HSCT and overall survival (OS) after aGvHD grades II-IV, with events defined as death from any cause after experiencing aGvHD grades II-IV. Secondary endpoints were incidence of aGvHD grades III-IV following HSCT; OS after aGvHD grades III-IV; NRM after aGvHD grades II-IV, defined as death occurring before signs of progression or relapse; relapse and progression after aGvHD II-IV, defined as recurrence and continuation of the original disease, respectively, following aGvHD II-IV and disease-free survival (DFS) after aGvHD II-IV, and defined as survival after aGvHD II-IV in the absence of signs of progression or relapse. For outcomes following aGvHD, only the subset of patients experiencing aGvHD were analyzed. In this subset, the starting point was the date of aGvHD onset. A clock-back approach was used, i.e., the timescale starts from the date of aGvHD onset rather than the date of HSCT.

Statistical analysis

The primary comparison concerned outcomes in transplantation periods 1990-1995, 1996-2000, 2001-2005, 2006-2010, and 2011-2015. Cumulative incidence estimates were calculated for aGvHD, relapse and NRM, in a competing risks framework. NRM was a competing risk in the estimation of malignancy relapse, and relapse was a competing risk for estimation of NRM. For aGvHD, only mortality was considered a competing event. Baseline characteristics were compared across these transplant periods and tested by means of χ^2 tests for categorical variables and Kruskal-Wallis tests for continuous variables. Univariate analyses compared the outcomes OS, DFS, NRM, and relapse incidence between the five time cohorts. The probabilities of OS and DFS for all patients were calculated using the Kaplan Meier estimator. Group differences were tested by means of log rank test and Gray's test. The median follow-up was estimated by reverse Kaplan-Meier estimator. Multivariable analyses were performed using Cox proportional hazards regression models for OS and RFS. Cause-specific hazards models were applied in the analysis of aGvHD, relapse and NRM. Each of the outcomes was analyzed using the same covariate structure. Covariates included were age at transplant (continuous in decades), transplantation year (in decades), conditioning intensity (reduced vs myeloablative), donor type (unrelated vs HLA identical), graft source (bone marrow (BM) vs PBSC), patient-donor gender match (male/female, female/male, and female/female vs male/male), antithymocyte globulin (ATG) and alemtuzumab. Models were stratified by malignant disease (Acute Lymphocytic Leukemia (ALL), Acute Myeloid Leukemia (AML), Myelodysplastic Syndrome (MDS), Multiple Myeloma (MM), Myeloproliferative Disorder (MPE) and Other. Hazard ratios including 95% confidence intervals and *P*-values are provided. Analyses were done in R, version 3.6.0, using *survival, prodlim* and *cmprsk* packages.

Results

Patients

Between 1990 and 2015, 102,557 patients with a median age (range) of 47.6 (18-83.8) years with malignant disease received a first allogeneic HSCT. Conditioning was myeloablative in 55.8% and RIC in 44.2% of patients. Of note is that 50.6% of patients had an HLA-identical sibling and 49.4% a matched or mismatched unrelated donor. The stem cell source in 79.2% of patients was PBSC and BM in 20.8% of patients. Cyclosporine-based GvHD prophylaxis was given in 77.2% of patients; of these patients,

57.9% also were given methotrexate (MTX) while 25.3% received mycophenolate mofetil (MMF). Donor, recipient and transplant characteristics are summarized in Table 1. The median follow-up for all patients was 214 (207.4-220.3) months, 169.3 (166.5.7-172.1) months, 127.7 (125.9-129.4) months, 81 (80.3-81.8) months and 29.7 (29.2-30.2) months for 1990-1995, 1996-2000, 2001-2005, 2006-2010, and 2011-2015, respectively.

Characteristics of aGvHD

Incidences (95% CI) of aGvHD grades II-IV by 100 days significantly (p<0.001) decreased from 40% (38-42%), to 38% (37-39%), 32% (31-33%), 29% (28-29%), and 28% (27-28%) for the periods 1990-1995, 1996-2000, 2001-2005, 2006-2010, and 2011-2015, respectively (Figure 1A). Of the patients who developed aGvHD grades II-IV, the median days to aGvHD (interquartile range, IQR) was 20 (14-31), 22 (15-35), 25 (16-39), 25 (16-40), and 25 (16-40) in the periods 1990-1995, 1996-2000, 2001-2005, 2006-2010, and 2011-2015, respectively. Involvement of the gastrointestinal (GI) tract was observed in 50.3%, 54.3%, 55.1%, 59% and 66.3% of all patients experiencing aGvHD, respectively. First-line therapy consisted of corticosteroids in 55.5%, 87.1%, 78.7%, 79.1%, and 72.3% of patients, respectively.

In multivariate analysis (Table 2) URD (HR 1.61 (1.54-1.67); *P*<0.001), not in CR at HSCT (HR 1.25 (1.2-1.3); *P*<0.001) or untreated (HR 1.11 (1.02-1.2); *P*=0.02), BM stem cell source (HR 1.2 (1.15-1.25); *P*<0.001), and a female donor for a male recipient (HR 1.16; 1.11-1.21; *P*<0.001) were all associated with increased risk for aGvHD grades II-IV whereas the use of ATG or alemtuzumab (HR 0.79 (0.74-0.84); *P*<0.001) was associated

Table 1. Transplant characteristics.

		1990-1995 N (%)	1996-2000 N (%)	2001-2005 N (%)	2006-2010 N (%)	2011-2015 N (%)	*P*
Number of patients		3512 (100)	9521 (100)	19865 (100)	30194 (100)	39465 (100)	
Age, median (range)		35.4 (18-75.8)	39.4 (18-71.7)	44.5 (18-77.3)	48.9 (18-83.8)	52.4 (18-79.7)	<0.001
Patient sex	Male	2074 (59.1)	5598 (58.8)	11555 (58.2)	17633 (58.4)	23481 (59.5)	0.01
	Female	1438 (40.9)	3923 (41.2)	8310 (41.8)	12561 (41.6)	15984 (40.5)	
Diagnosis	MM	154 (4.4 %)	460 (4.8)	1912 (9.6)	2111 (7)	2382 (6)	<0.001
	MPE	1006 (28.6)	3140 (33)	3071 (15.5)	2768 (9.2)	3306 (8.4)	
	MDS	280 (8)	797 (8.4)	1935 (9.7)	3800 (12.6)	6258 (15.9)	
	AML	1109 (31.6)	2437 (25.6)	5754 (29)	10358 (34.3)	13799 (35)	
	ALL	422 (12)	1106 (11.6)	2320 (11.7)	3726 (12.3)	4550 (11.5)	
	Other	541 (15.4)	1581 (16.6)	4873 (24.5)	7431 (24.6)	9170 (23.2)	
Disease status at HSCT	CR	2399 (69.6)	5928 (64)	11022 (57.3)	17573 (60)	24068 (62.7)	<0.001
	noCR	940 (27.3)	3004 (32.4)	7178 (37.3)	10071 (34.4)	12274 (32)	
	Untreated	107 (3.1)	333 (3.6 %)	1042 (5.4)	1668 (5.7)	2016 (5.3)	
Donor/recipient relationship	Related	2954 (84.1)	6776 (71.2)	12406 (62.5)	14486 (48)	15262 (38.7)	<0.001
	Unrelated	558 (15.9)	2745 (28.8)	7459 (37.5)	15708 (52)	24203 (61.3)	
Donor/recipient sex match	MM	1195 (34.3)	3389 (36.2)	7184 (36.8)	11413 (38.5)	15851 (41)	<0.001
	MF	862 (24.7)	2117 (22.6)	4178 (21.4)	5887 (19.9)	7176 (18.6)	
	FM	765 (21.9)	2040 (21.8)	4511 (23.1)	7020 (23.7)	9227 (23.9)	
	FF	664 (19)	1803 (19.3)	3657 (18.7)	5303 (17.9)	6424 (16.6)	
Time from diagnosis to HSCT, median (range)		8.6 (0-237.2)	9.8 (0-238.2)	10.6 (0.1-239.8)	10.2 (0-238.3)	9 (0-239.9)	<0.001
Conditioning intensity	standard	3335 (100)	6187 (83)	11324 (58.6)	15610 (52.1)	18806 (48.3)	<0.001
	reduced		1263 (17)	8009 (41.4)	14324 (47.9)	20123 (51.7)	
Stem cell source	BM	3369 (95.9)	5411 (56.8)	4685 (23.6 %)	4094 (13.6)	3816 (9.7)	<0.001
	PB	143 (4.1)	4110 (43.2)	15180 (76.4)	26100 (86.4)	35649 (90.3)	
GvHD prophylaxis	CsA alone	276 (9)	811 (12.4)	1808 (15.6)	3627 (13.5)	4682 (12.1)	<0.001
	CsA + MTX	2340 (76.3)	4244 (64.6)	5703 (49.1)	11574 (43.1)	14962 (38.6)	
	CsA + MMF		167 (2.5)	1805 (15.5)	6009 (22.4)	9053 (23.4)	
	Tacrolimus + MTX			26 (0.2)	301 (1.1)	659 (1.7)	
	Tacrolimus + MMF		1 (0 .0)	59 (0.5)	782 (2.9)	1327 (3.4)	
	Other	451 (14.7)	1342 (20.4)	2207 (19)	4581 (17)	8062 (20.8)	
ATG/Campath	no	2821 (89.5)	5150 (74.1)	7680 (59.8)	13531 (48.8)	15420 (39.2)	<0.001
	yes	331 (10.5)	1798 (25.9)	5169 (40.2)	14194 (51.2)	23956 (60.8)	

AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; MDS: myelodysplastic syndrome; MPE: myeloproliferative disease; MM: myeloma; HSCT: hematopoietic stem cell transplantation; CR: complete remission; URD: unrelated donor; BM: bone marrow; PBSC: peripheral blood stem cells; CsA: cyclosporine A; MTX: methotrexate; MMF: mycophenolate mofetil; ATG: antithymocyte globulin.

with a lower incidence. Of note is that aGvHD grades II-IV decreased with increasing transplant year (HR 0.57 (0.55-0.59); *P*<0.001), even in patients treated without ATG or alemtuzumab. The increased risk of aGvHD due to an increase in age was minimally reduced in more recent transplant years (per year: HR = 0.99 (0.99-1.0), *P*=0.05).

Incidences of aGvHD grades III-IV by 100 days significantly decreased from 19% (18-20%), to 16% (16-17%), 13% (13-14%), 11% (11-12%), and 11% (11-11%) for the periods 1990-1995, 1996-2000, 2001-2005, 2006-2010, and 2011-2015, respectively (Figure 1B).

In multivariate analysis, URD (HR 1.52 (1.43-1.62); *P*<0.001), not in CR at HSCT (HR 1.5 (1.41-1.6); *P*<0.001) or untreated (HR 1.29 (1.13-1.46); *P*<0.001), use of BM instead of PBSC as stem cell source (HR 1.08; 1.01-1.16;

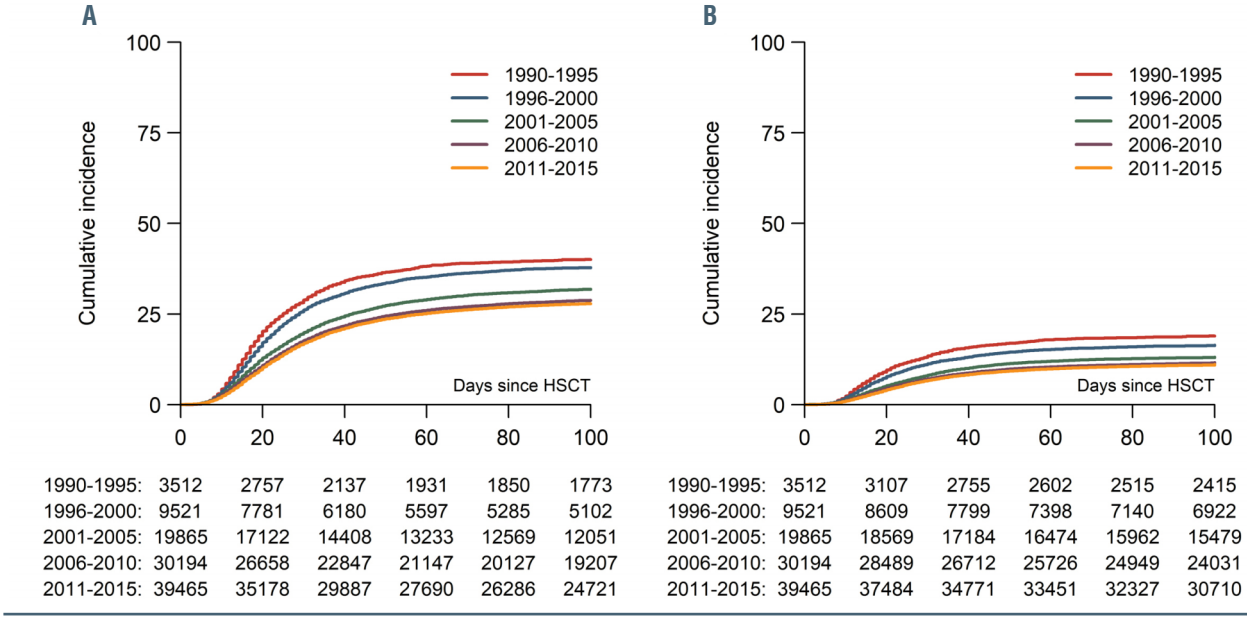


Figure 1. Incidences of aGvHD grades II-IV and grades III-IV over time. (A) Incidences of aGvHD grades II-IV over time. Cumulative incidence estimates were calculated for aGvHD grades II-IV with mortality considered as a competing event. The endpoint aGvHD grades II-IV was estimated from the date of first transplantation. Data are shown according to transplantation periods 1990-1995, 1996-2000, 2001-2005, 2006-2010 and 2011-2015. (B) Incidences of aGvHD grades III-IV over time. Cumulative incidence estimates were calculated for aGvHD grades III-IV with mortality considered as a competing event. The endpoint aGvHD grades III-IV was estimated from the date of first transplantation. Data are shown according to transplantation periods 1990-1995, 1996-2000, 2001-2005, 2006-2010 and 2011-2015.

Table 2. Multivariable Cox regression analysis regarding acute GvHD grades II-IV.

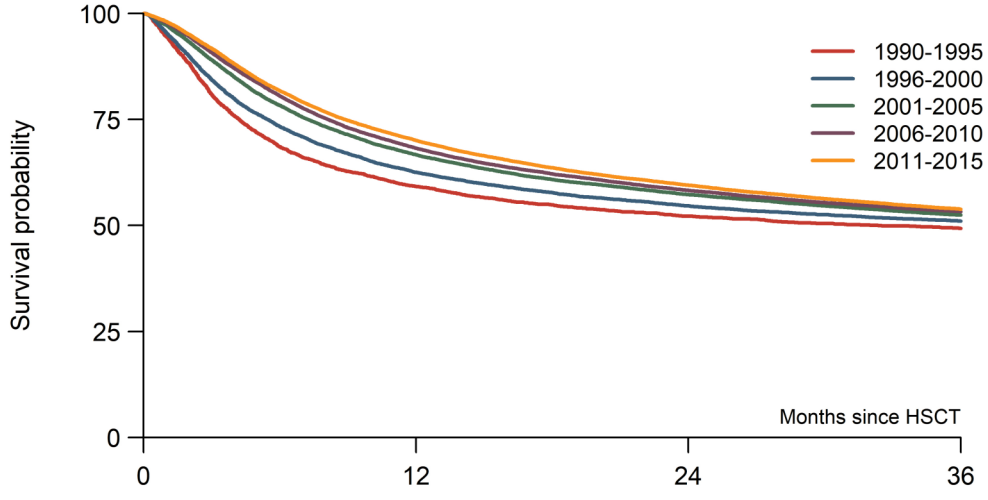
		aGvHD II-IV		aGvHD III-IV	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Age at HSCT (dec)		1.02 (1-1.03)	0.022	1.02 (1-1.04)	0.11
Conditioning intensity	Standard				
	Reduced	0.93 (0.9-0.97)	0.001	0.88 (0.83-0.94)	<0.001
Donor/recipient relationship	Related				
	Unrelated	1.61 (1.54-1.67)	<0.001	1.52 (1.43-1.62)	<0.001
Disease status at HSCT	CR				
	noCR	1.25 (1.2-1.3)	<0.001	1.5 (1.41-1.6)	<0.001
	untreated	1.11 (1.02-1.2)	0.02	1.29 (1.13-1.46)	<0.001
Stem cell source	PB				
	BM	1.2 (1.15-1.25)	<0.001	1.08 (1.01-1.16)	0.029
Recipient/donor sex match	MM				
	MF	1.16 (1.11-1.21)	<0.001	1.2 (1.12-1.29)	<0.001
	FM	0.93 (0.89-0.98)	0.002	0.87 (0.81-0.94)	<0.001
	FF	1.03 (0.98-1.08)	0.3	0.89 (0.82-0.96)	0.004
ATG/Alemtuzumab	No				
	Yes	0.79 (0.74-0.84)	<0.001	1.03 (0.95-1.12)	0.5
HSCT year (dec)		0.57 (0.55-0.59)	<0.001	0.56 (0.53-0.6)	<0.001
ATG/Alemtuzumab x HSCT year (dec)		0.97 (0.92-1.03)	0.4	0.73 (0.67-0.8)	<0.001

OS: overall survival; DFS: disease-free survival; NRM: non-relapse mortality; CR: complete remission; BM: bone marrow; PBSC: peripheral blood stem cells; ATG: antithymocyte globulin; HSCT: hematopoietic stem cell transplantation.

P<0.001), and a female donor for a male recipient (HR 1.2; 1.12-1.28; *P*<0.001) were all associated with increased risk for aGvHD grades III-IV whereas RIC (HR 0.88 (0.83-0.94); *P*<0.001), male donor (HR 0.87 (0.81-0.94); *P*<0.001) or female donor for a female recipient (HR 0.89 (0.82-0.96); *P*=0.004) were associated with a lower incidence, respectively. Use of ATG/alemtuzumab reduced risk for aGvHD grades III-IV per decade (HR 0.73 (0.67-0.8), *P*<0.001). Of note is that aGvHD grades III-IV also decreased per decade in patients treated without ATG or alemtuzumab (HR 0.56 (0.53-0.6); *P*<0.001).

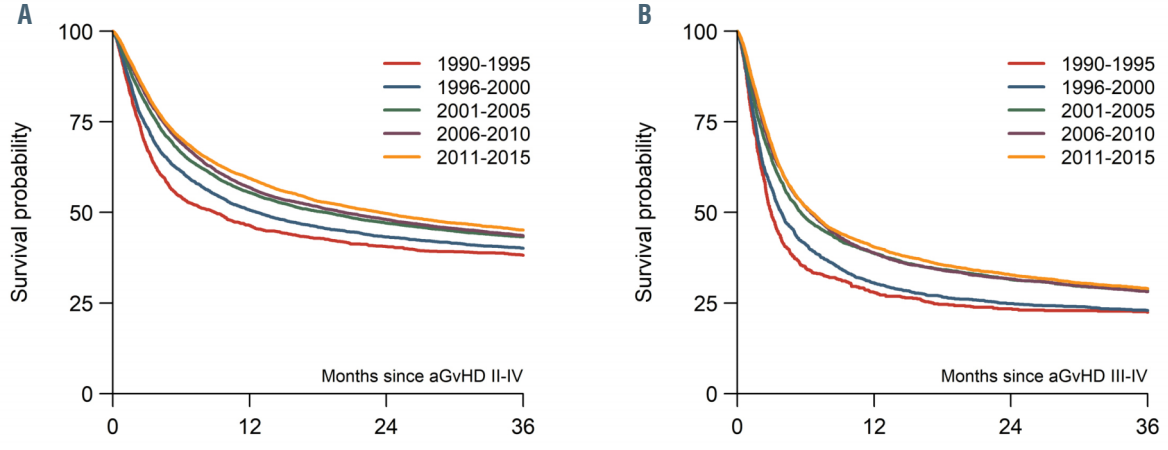
Outcomes

For the total study population (n=102,557), three-year OS significantly increased from 49% (48-51%), to 51% (50-52%), 52% (52-53%), 53% (53-54%), and 54% (53-54%) for the periods 1990-1995, 1996-2000, 2001-2005, 2006-2010, and 2011-2015, respectively (Figure 2).



1990-1995:	3512	2066	1805	1692
1996-2000:	9521	5824	4941	4477
2001-2005:	19865	12521	10455	9286
2006-2010:	30194	18551	14821	12725
2011-2015:	39465	21385	13912	8889

Figure 2. Three-year overall survival over time for the whole patient cohort. The probability of OS for all patients was calculated using the Kaplan Meier estimator. Data are shown according to transplantation periods 1990-1995, 1996-2000, 2001-2005, 2006-2010 and 2011-2015.



1990-1995:	1407	647	561	526
1996-2000:	3597	1777	1465	1322
2001-2005:	6318	3319	2739	2441
2006-2010:	8670	4343	3448	2915
2011-2015:	10902	4842	3063	1909

1990-1995:	666	184	152	145
1996-2000:	1559	468	364	328
2001-2005:	2601	968	769	680
2006-2010:	3503	1210	919	752
2011-2015:	4343	1304	808	474

Figure 3. Three-year overall survival over time. (A) Three-year overall survival after aGvHD grades II-IV over time. The probability of OS for patients experiencing aGvHD grades II-IV was calculated using the Kaplan Meier estimator. Data are shown according to transplantation periods 1990-1995, 1996-2000, 2001-2005, 2006-2010 and 2011-2015. (B) Three-year overall survival after aGvHD grades III-IV over time. The probability of OS for patients experiencing aGvHD grades III-IV was calculated using the Kaplan Meier estimator. Data are shown according to transplantation periods 1990-1995, 1996-2000, 2001-2005, 2006-2010 and 2011-2015.

Outcomes after aGvHD grades II-IV

Survival at 36 months after aGvHD grades II-IV increased significantly (P<0.001) from 38% (36-41%) to 40% (38-42%), 43% (42-45%), 44% (43-45%), and 45% (44-46%), respectively, for the times periods studied (Figure 3A). Causes of death are shown in *Online Supplementary Table 2*: though GvHD- and infection-associated deaths decreased over time, mortality due to relapse/progression of underlying malignant disease increased.

Results of multivariate analysis are shown in Table 3. In multivariate analysis, URD (HR 1.14; 1.09-1.2; P<0.001), not in CR at HSCT (HR 1.47; 1.4-1.55; P<0.001), PBSC as stem cell source (HR 1.09 (1.03-1.15); P=0.004), a female donor for a male recipient (HR 1.11; 1.05-1.18; P<0.001), and use of ATG/alemtuzumab (HR 1.27 (1.18-1.36); P<0.001) were all associated with increased mortality after aGvHD grades II-IV whereas RIC (HR 0.92; 0.87-0.97; P=0.004) was associated with lower mortality, respectively. Patients transplanted more recently and given BM had improved outcomes after experiencing aGvHD: in earlier HSCT periods, BM as stem cell source had no significant impact on mortality (HR 0.95 (0.89-1.02); P=0.2) per decade but, in later periods, BM was associated with significantly reduced mortality after aGvHD (HR 0.89 (0.82-0.96); P=0.003). Of note is mortality increasing with increasing patient age (HR 1.15 per decade; 1.13-1.18; P<0.001) e.g., three-year OS was 60% (57-63%) in patients aged 20 years and 40% (37-44%) in patients aged 70 years, respectively. Mortality decreased in the more recent transplant years (HR 0.73; 0.7-0.78; P<0.001).

Three-year NRM after experiencing aGvHD grades II-IV significantly (P<0.001) decreased from 47% (45-50%), to 42% (40-44%), 35% (34-37%), 37% (36-38%), and 36% (35-37%) for the periods 1990-1995, 1996-2000, 2001-2005, 2006-2010, and 2011-2015, respectively (Figure 4).

In multivariate analysis (Table 3), age (HR 1.22 (1.18-1.25); P<0.001), URD (HR 1.23 (1.15-1.31); P<0.001), not in CR at HSCT (HR 1.21 (1.13-1.29); P<0.001), and female donor for a male recipient (HR 1.22; 1.14-1.31; P<0.001) were associated with increased NRM whereas more recent HSCT year (HR 0.72 (0.67-0.77); p<0.001) and RIC (HR 0.89 (0.83-0.95); P<0.001) were associated with decreased NRM.

Three-year DFS after aGvHD grades II-IV significantly (P<0.001) increased from 34% (32-37%), to 35% (33-36%), 38% (36-39%), 39% (38-40%), and 40% (38-41%), respectively.

In multivariate analysis, use of RIC (HR 0.95 (0.9-1); P=0.04) was associated with improved DFS after experiencing aGvHD grades II-IV whereas URD (HR 1.09 (1.04-1.14); P<0.001) and not in CR at HSCT (HR 1.48 (1.42-1.56); P<0.001) had reduced DFS, respectively. Of note is that DFS reduced with increasing patient age (HR 1.12; 1.09-1.14; P<0.001), but improved in more recent transplants in patients not treated with ATG/alemtuzumab (HR 0.8 (0.76-0.84); P<0.001) and in patients treated with ATG/alemtuzumab (HR 0.79 (0.74-0.85); P<0.001).

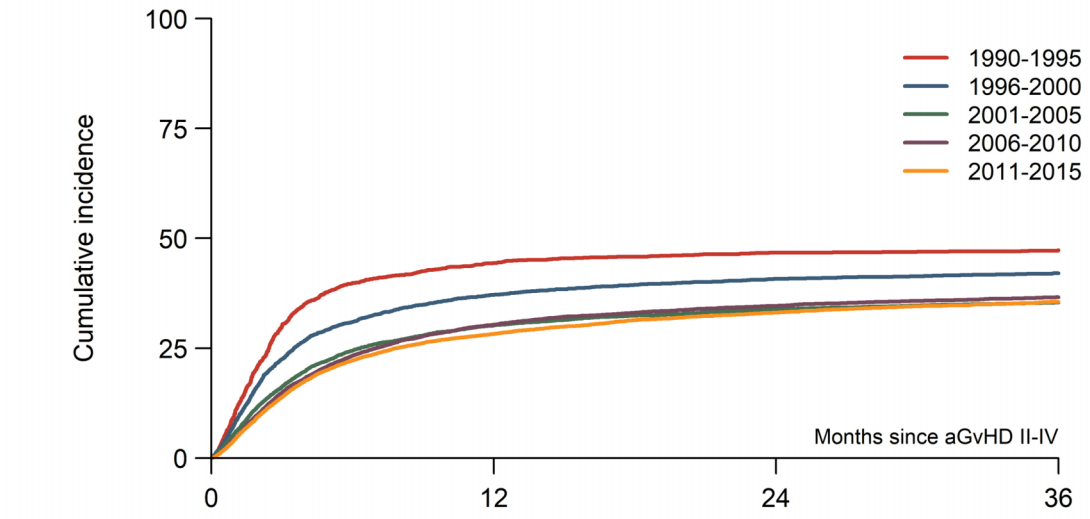
Three-year relapse incidence after aGvHD grades II-IV significantly (P<0.001) increased from 19% (17-21%), to 23% (22-24%), 27% (26-28%), 25% (24-26%), and 25% (24-26%), respectively (Figure 5).

In multivariate analysis, use of URD (HR 0.9; 0.84-0.98; P=0.01) and female donor for a male recipient (HR 0.83 (0.76-0.9); P<0.001) and use of BM as stem cell source (HR 0.87 (0.8-0.95); P=0.002) were associated with reduced relapse incidence whereas not being in CR at HSCT (HR 2.02 (1.87-2.18); P<0.001), and use of PBSC as stem cell source (HR 1.15; 1.05-1.25; P=0.002) were associated with increased relapse risk. Although conditioning intensity

Table 3. Multivariable Cox regression analysis regarding outcome after aGvHD grades II-IV.

		OS		DFS		Relapse		NRM	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age at HSCT (dec)		1.16 (1.13-1.18)	<0.001	1.12 (1.09-1.14)	<0.001	0.99 (0.96-1.02)	0.7	1.22 (1.18-1.25)	<0.001
Conditioning intensity	standard								
	reduced	0.92 (0.87-0.97)	0.004	0.95 (0.9-1)	0.041	1.03 (0.95-1.13)	0.4	0.89 (0.83-0.95)	<0.001
Donor/recipient relationship	related								
	unrelated	1.14 (1.09-1.2)	<0.001	1.09 (1.04-1.14)	<0.001	0.9 (0.84-0.98)	0.011	1.23 (1.15-1.31)	<0.001
Disease status at HSCT	CR								
	noCR	1.47 (1.4-1.55)	<0.001	1.48 (1.42-1.56)	<0.001	2.02 (1.87-2.18)	<0.001	1.21 (1.13-1.29)	<0.001
	untreated	1.05 (0.94-1.17)	0.4	1.04 (0.93-1.16)	0.5	0.94 (0.77-1.15)	0.5	1.07 (0.94-1.22)	0.3
Stem cell source	PB								
	BM	0.92 (0.87-0.97)	0.004	0.92 (0.87-0.97)	0.002	0.87 (0.8-0.95)	0.002	0.94 (0.88-1.01)	0.12
Recipient/donor sex match	MM								
	MF	1.11 (1.05-1.18)	<0.001	1.05 (1-1.11)	0.07	0.83 (0.76-0.9)	<0.001	1.22 (1.14-1.31)	<0.001
	FM	0.96 (0.91-1.02)	0.2	0.96 (0.91-1.01)	0.14	0.92 (0.84-1)	0.05	0.99 (0.92-1.07)	0.8
	FF	0.95 (0.89-1.01)	0.08	0.94 (0.89-1)	0.047	0.93 (0.85-1.02)	0.11	0.95 (0.88-1.03)	0.2
ATG/Alemtuzumab	no								
	yes	1.27 (1.18-1.36)	<0.001	1.34 (1.25-1.43)	<0.001	1.3 (1.16-1.45)	<0.001	1.34 (1.23-1.45)	<0.001
HSCT year (dec)		0.76 (0.72-0.8)	<0.001	0.8 (0.76-0.84)	<0.001	0.93 (0.86-1)	0.06	0.72 (0.67-0.77)	<0.001
ATG/Alemtuzumab x HSCT year (dec)		0.81 (0.75-0.87)	<0.001	0.79 (0.74-0.85)	<0.001	0.88 (0.78-0.99)	0.03	0.75 (0.69-0.82)	<0.001

OS: overall survival; DFS: disease-free survival; NRM: non-relapse mortality; CR: complete remission; BM: bone marrow; PBSC: peripheral blood stem cells; ATG: antithymocyte globulin; HSCT: hematopoietic stem cell transplantation.



1990-1995:	1398	590	504	471
1996-2000:	3555	1581	1288	1150
2001-2005:	6245	2940	2373	2136
2006-2010:	8597	3866	3046	2585
2011-2015:	10797	4314	2685	1655

Figure 4. Three-year non-relapse mortality after aGvHD grades II-IV over time. Cumulative incidence estimates were calculated for NRM in a competing risks framework with relapse as a competing risk for estimation of NRM. Data are shown according to transplantation periods 1990-1995, 1996-2000, 2001-2005, 2006-2010 and 2011-2015.

had no significant impact on relapse incidence for the cohort as a whole, patients with AML (HR 1.22 (1.08-1.37); P<0.001) and ALL (HR 1.53 (1.21-1.94), P<0.001) given RIC had a significant increased relapse risk while this was not the case in patients with MDS, respectively.

Outcomes after aGvHD grades III-IV

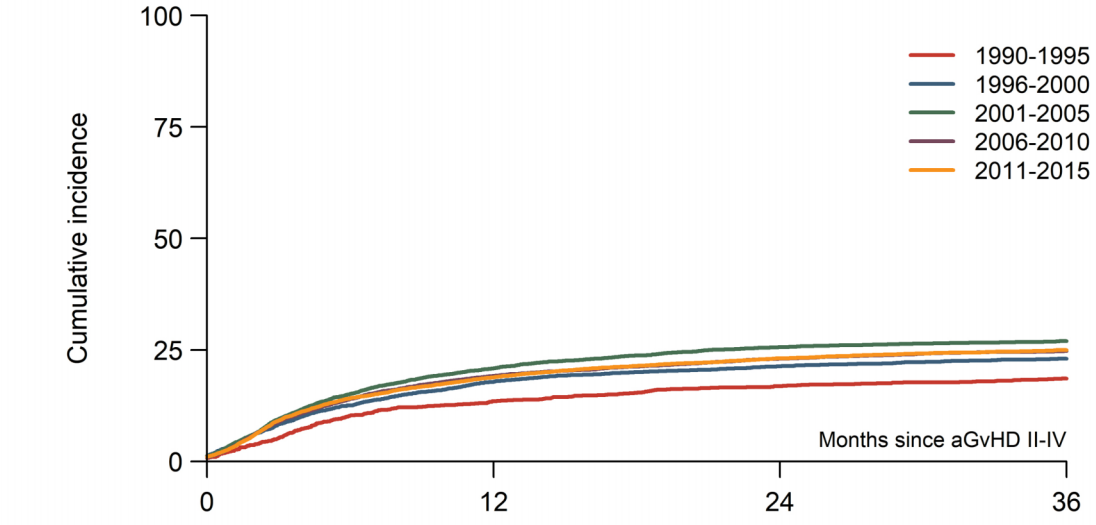
Survival at 36 months after aGvHD grades III-IV increased significantly (P<0.001) from 22% (19-25%) to 23% (21-25%), 28% (27-30%), 28% (27-30%), and 29% (27-31%) for the periods 1990-1995, 1996-2000, 2001-2005, 2006-2010, and 2011-2015, respectively (Figure 3B).

In multivariate analysis, URD (HR 1.18 (1.1-1.27); P<0.001), not in CR at HSCT (HR 1.25 (1.17-1.34); P<0.001) and use of ATG/alemtuzumab (HR 1.28 (1.17-1.4); P<0.001) were all associated with increased mortality after aGvHD grades III-IV. Of note is that mortality decreased in the more recent transplant cohorts treated without ATG/Alemtuzumab (HR 0.74 (0.69-0.8); P<0.001) and treated with ATG/Alemtuzumab (HR 0.86 (0.78-0.95); P=0.002).

Discussion

In retrospective analyses, improvement over time in survival outcome for patients given allogeneic HSCT has been reported in parallel with changes of transplant practices. These include a spectrum of diseases treated with allografting, more frequent use of PBSC rather than BM, administration of more unrelated instead of related donor grafts, and older patient and donor age.[11] Whether outcome improvement over time is also found in patients experiencing severe aGvHD is less well known. Therefore, we analyzed the outcome of patients experiencing severe aGvHD over time in a large patient cohort reported to the EBMT. We observed a significant decrease of aGvHD grades II to IV and grades III to IV over time that was most pronounced in the more recent transplant cohort. Since having an URD compared to a related donor significantly increased the risk for aGvHD in multivariate analysis of our patient cohort, improvements in HLA typing in the more recent transplant years could have an impact on this finding. Over recent years and based on the outcome of numerous studies, the identity of ten alleles in five HLA loci, namely HLA-A, -B, -C, -DRB1, and -DQB1, and using high-resolution typing instead of serologic typing has become the gold standard of URD matching. Several studies have shown an association between allelic mismatches in HLA-A, -B, -C and -DRB1 and higher rates of aGvHD.[14-16] Recent developments in clinical diagnosis, improved understanding of pathophysiological features, the use of both standard and experimental options for prevention, and the use of biomarkers to tailor treatment to individual patients could lead to a further reduction in aGvHD rates in the future.

After adjusting for significant patient-, disease-, and transplant-related variables, patients with aGvHD grades II-IV, in the more recent cohort, had significantly lower NRM and better DFS and OS compared with those in the earlier years. Three-year survival of patients experiencing aGvHD grades II-IV improved significantly over time, reaching 45% for patients given HSCT between 2011 and 2015. Whereas Khoury *et al.*, observed significant improvements in OS over time that was limited to patients treated with tacrolimus-based GvHD prophylaxis, and mostly in those with overall grade II aGvHD, GvHD prophylaxis had no significant impact on OS in our cohorts, in multivariate analysis.[12] Of note is that three-



1990-1995:	1398	590	504	471
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Figure 5. Three-year relapse incidence after aGvHD grades II-IV over time. Cumulative incidence estimates were calculated for relapse in a competing risks framework with NRM as a competing risk in the estimation of malignancy relapse.

year OS also increased over time in patients experiencing aGvHD grades III-IV, reaching 29% in the most recent HSCT cohort, independent of GvHD prophylaxis.

Previous studies reported an overall long-term survival of 10% to 25% in patients with severe aGvHD, defined as overall grades III to IV.[17-20] Our survival rates compare favorably to Khoury *et al*. as well as El-Jawahri *et al*., who reported that longer time to aGvHD onset and younger recipient age were associated with improved OS,[12,21] respectively. In our study, recipients of URD, patients not in CR at HSCT, and use of a female donor for a male patient were associated with increased mortality after aGvHD grades III-IV whereas recipients of RIC had a significantly lower mortality.

The significant improvement in outcome of patients over the past 25 years can also be seen in the decrease of three-year NRM from 47% in 1990-1995 to 36% in 2011-2015 in patients experiencing aGvHD grades II-IV. The reduction in NRM over time is even more impressive when considering the significant changes in patient characteristics over recent decades, with an increase of median recipient age from 35.4 to 52.3 years, more frequent use of URD (from 15.8% to 61.3%) and an increase in patients not in CR at HSCT from 27.3% to 32%, respectively. The reasons behind these impressive improvements are likely multifactorial, including improved prevention and treatment of infectious complications that are a main cause of morbidity and mortality of GvHD patients under long-lasting immunosuppressive treatment and improved supportive care practices.[22] Of note is that infectious death in our study declined from 30.1% to 23.4% over time. McDonald *et al*., recently reported a significant reduction of NRM in a patient cohort undergoing HSCT between 2013 and 2017, compared to previous years.[23] No change in overall cytomegalovirus (CMV) infection, but a substantial reduction in higher level CMV DNAemia and in gram-negative bacteremia and invasive mold infections was observed. This supports the notion that the use of less intensive conditioning regimens and the availability and use of improved antifungal drugs as prophylaxis for high-risk patients may have contributed to this reduction. Of note, in our study, RIC administration was also significantly associated with a lower risk for NRM. In recent years, clinicians have applied lower steroid doses for front-line therapy of aGvHD compared to the 1990s[23,24] due to an increased awareness of steroid toxicity and increased NRM without improved response rates resulting from high-dose steroid treatment.[25,26] Preclinical studies have revealed major pathophysiological pathways driving aGvHD and including tissue damage due to the administration of conditioning regimens or infection, alloreactivity seen as the body's recognition of foreign major and minor histocompatibility antigens, and altered mechanisms of tissue repair and protection, such as microbiome dysregulation with a decline in protective microbial-derived metabolites.[27] In recent years, more therapeutic strategies regarding aGvHD have become available in clinic, including the administration of costimulatory pathway blockade, targeted anti–interleukin-6 monoclonal antibodies, histone deacetylase inhibitors, kinase inhibitors and proteasome inhibitors, the anti-inflammatory protease inhibitor alpha-1-antitrypsin, CTLA-4 antagonism, CCR5 blockade, and adoptive regulatory T cell transfer.[27-34] These and other new strategies that are being developed will have a positive impact not only on response rates of aGvHD but also on the overall outcome of patients afflicted by this serious HSCT complication.

Interestingly, the use of BM as stem cell source was associated with an increased risk for aGvHD grades II-IV and grades III-IV but also with a significantly higher DFS and overall survival. In a phase III, multicenter, randomized study of transplantation of PBSC *versus* BM from URD, the rates of aGvHD were similar in the two groups.[35] However, these incidences were around 50% and, thus, markedly higher than in our cohorts where, in the most recent patient group, incidence was 28%. Further, Anasetti *et al*., did not observe survival differences between their study cohorts. In a retrospective analysis including 2463 recipients of PBSC and 1713 of BM from URD, no significant differences in the three-year probabilities of TRM, relapse, leukemia-free survival, and OS between the groups were observed in patients with leukemia and MDS.[36] In a long-term follow-up report of the randomized study, recipients of URD BM had better psychological well-being, less burdensome cGvHD symptoms, and were more likely to return to work than recipients of PBSC at five years after HSCT.[37]

In our study, three-year relapse incidence after aGvHD grades II-IV significantly increased from 19% to 25% over time and was associated with a lack of CR at HSCT. It is important to acknowledge that more patients with MDS have been given HSCT in recent years and, of these, it is probable that patients were either not in CR or were untreated due to the fact that it still controversial as to whether pretreatment of MDS patients prior to HSCT is of clinical benefit and thus, should be recommended.[38] Furthermore, in recent years, AML patients referred to HSCT in first CR have intermediate and adverse risk disease, as defined by the European Leukemia Net criteria[39] and, especially, the later patient category is known to have a higher relapse risk after HSCT.[39] Three-year relapse incidence in our cohort was also significantly increased after the use of RIC in patients with AML and MM. In line with our findings, substantially higher relapse rates after RIC compared to myeloablative conditioning have been reported in patients with AML and MDS.[40,41]

The strength of our study is the large sample size and long time period for comparison of HSCT outcome, as well as the participation of many transplant centers reporting consecutive patients to the EBMT registry and thus, providing real world data for detailed analysis over time. We would like to acknowledge the following limitations to this analysis. First, we cannot distinguish between mismatched and matched unrelated donors (10/10). Second, limitations in data on antimicrobial agents and other supportive care measures do not allow an analysis of changes in these practices over time as a potential factor for improved outcome. Thirdly, insufficient data on steroid dose, and type/duration of salvage immunosuppressive therapy do not allow detailed analyses of treatment intensity on outcome. In addition, detailed aGvHD treatment response data are not available, therefore we cannot characterize the burden of steroid-refractory aGvHD across cohorts.

In conclusion, our findings demonstrate that the advances and changes in allogeneic HSCT practices over the past 2.5 decades have led to significantly improved outcomes in patients experiencing severe aGvHD. Although incidences of aGvHD have significantly declined and the OS of patients experiencing aGvHD has improved, there is still a need for further progress. Increasing use of posttransplant cyclophosphamide for GvHD prophylaxis, not only after haploidentical but also related and URD transplants, could have an impact on incidences of both acute as well as chronic GvHD, as previously reported.[42,43] The administration of BM rather than PBSC as stem cell source reportedly reduces the incidence of cGvHD and the use of myeloablative conditioning regimens in patients with aggressive malignant disease is another option for improvement of HSCT outcome. More efficient and less toxic front-line immunosuppressive therapies for treatment of aGvHD, including treatments without the administration of corticosteroids, would have the potential to further reduce NRM and improve survival of patients following allogeneic HSCT.

Disclosures

No conflicts of interest to disclose.

Contributions

HTG designed the study and wrote the manuscript; LK prepared the dataset and DJE LK performed statistical analyses; OP, IYA, SM, CC, JS, AN, MR, SR, YC, MM, SS, ZP, AR, FL, MM, GWB, and NK interpreted the data. All authors critically reviewed the manuscript and approved the final version for submission.

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