Trends in allogeneic transplantation for favorable risk acute myeloid leukemia in first remission: a longitudinal study of >15 years from the ALWP of the EBMT

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ARTICLE

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Trends in allogeneic transplantation for favorable risk acute myeloid leukemia in first remission: a longitudinal study of >15 years from the ALWP of the EBMT

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We assessed outcomes of allogeneic transplantation (HSCT) in favorable risk AML in CR1 over 3 time periods. 1850 patients were included, 2005 to 2009- 222, 2010 to 2014 -392, and 2015 to 2021-1236; 526 with t (8:21), 625 with inv (16), and 699 with NPM1^{mut}FLT3^{WT}. Patients transplanted in 2015–2021 were older ($p < 0.0001$) with more patients ≥60 years of age ($p < 0.0001$). The most frequent diagnosis in 2015–2021 was NPM1^{mut}FLT3^{WT} *vs*. t (8:21) in the 2 earlier periods, ($p < 0001$). Haploidentical transplants (Haplo) increased from 5.9% to 14.5% ($p < 0.0001$). Graft-versus-host disease (GVHD) prophylaxis with post-transplant cyclophosphamide (PTCy) was more frequent in 2015–2021 *vs*. the other 2 periods ($p < 0.0001$). On multivariate analysis, incidence of total chronic GVHD was reduced in HSCTs performed ≥2015 vs. those performed in 2005–2009, hazard ratio (HR) = 0.74 (95% CI 0.56–0.99, $p = 0.046$) and GVHD-free, relapse-free survival (GRFS) improved for patients transplanted from 2010–2014 *vs*. those transplanted in 2005–2009, HR = 0.74 (95% CI 0.56–0.98, $p = 0.037$). Other HSCT outcomes did not differ with no improvement ≥2015. LFS, OS, and GRFS were inferior in patients with t (8:21) with HR = 1.32 (95% CI 1.03–1.68, $p = 0.026$), HR = 1.38 (95% CI 1.04–1.83, $p = 0.027$) and HR = 01.25 (95% CI 1.02–1.53, $p = 0.035$), respectively. In conclusion, this retrospective analysis of HSCT in patients with favorable risk AML, transplanted over 16 years showed an increased number of transplants in patients ≥60 years, from Haplo donors with PTCy. Most importantly, 3-year GRFS improved ≥2010 and total chronic GVHD reduced ≥2015, with no significant change in other HSCT outcomes.

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is a potential curative mode of therapy for acute myeloid leukemia (AML) as it provides a strong anti-leukemic effect resulting in lower relapse incidence (RI) as compared to other currently available therapeutic options [1–4]. However, the benefit of HSCT may be offset by the transplant-associated rather high rate of morbidity and mortality [3, 4]. Therefore, the prognosis of AML patients is currently based, mainly on cytogenetics and molecular markers on the one hand and transplant-related risk scores, on the other, weighting the expected therapeutic yield versus transplant-related risks [1, 3, 5, 6]. Favorable AML includes the core binding factor (CBF) leukemias that represent up to 12% of all newly diagnosed adult AML comprising two subtypes with typical chromosome markers, t (8;21) (q22; q22.1) and inv(16) (p13.1;q22) and AML with *NPM1* without *FLT3-ITD* (NPM1^{mut}FLT3^{WT}) mutations, without adverse cytogenetics [1, 7, 8]. Although transplantation is usually not indicated in favorable risk AML at first complete remission (CR1) as they are generally considered to have a good prognosis, relapse occurs in 35–40%% of cases, and the long-term survival is only around 50% with chemotherapy alone [1, 9–12]. Relapse incidence is about 20% lower with HSCT, yet the procedure is not usually performed in favorable risk AML at CR1 due to transplant-related mortality

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[13–15]. However, results of HSCT for patients with AML have improved incrementally over the last three decades [16–19] with a substantial reduction in non-relapse mortality (NRM) [20]. Specifically, in transplanted patients, the continuing improvement in outcome has been attained by better treatment of infections (especially invasive fungal and viral), refinement of conditioning regimens, optimization of stem cell harvesting modalities as well as changes in supportive care and the introduction of reduced intensity conditioning (RIC) [21–23]. As a result, the observed improvement in transplantation outcome is mainly due to a significant reduction in transplant-related mortality and less so due to a reduction in post-transplantation relapse [21–23]. Notably, most of these longitudinal studies demonstrating the improvement in transplantation outcomes for AML over time were performed in patients with *intermediate and adverse risk* AML [16–19]. The current study aimed to assess outcomes of HSCT in favorable risk AML t (8:21), inv (16), and NPM1^{mut}FLT3^{WT} in CR1, comparing outcomes according to the period of transplant during three time periods: 2005–2009, 2010–2014, and 2015–2021 taking advantage of the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT) registry.

PATIENTS AND METHODS

Study design and data collection

This was a retrospective, multicenter analysis using the dataset of the ALWP of the EBMT. The EBMT is a voluntary working group of more than 600 transplant centers that are required to report all consecutive stem cell transplantations and follow-ups once a year. EBMT minimum essential data forms are submitted to the registry by transplant center personnel following written informed consent from patients in accordance with the centers' ethical research guidelines. Accuracy of data is assured by individual transplant centers and by quality control measures such as regular internal and external audits. The results of disease assessments at HSCT were also submitted and form the basis of this report. Eligibility criteria for this analysis included adult patients ≥18 years of age with favorable risk AML defined as AML with t (8;21) (q22; q22.1) or inv(16) (p13.1;q22) and AML with *NPM1* without *FLT3-ITD* (NPM1^{mut}FLT3^{WT}) mutations and with no adverse cytogenetics in CR1 who underwent a first HSCT from matched sibling donors (MSD) or 9-10/10 human leukocyte antigen (HLA) compatible unrelated donors (UD) or haploidentical donors (Haplo) between 2005 and 2021. Stem cell sources were bone marrow (BM) or peripheral blood (PB). Cord blood donors were excluded. Other exclusion criteria were previous history of HSCT, disease status >CR1 before transplantation, and ex vivo manipulation. Data collected included recipient and donor characteristics (age, gender, and cytomegalovirus [CMV] serostatus), recipient Karnofsky performance status (KPS), and hematopoietic cell transplantation - specific comorbidity index (HCT-CI), disease characteristics including pre-HSCT measurable residual disease (MRD) status, year of transplant, type of conditioning regimen, stem cell source, and graft-versus-host disease (GVHD) prophylaxis regimen. The conditioning regimen was defined as myeloablative (MAC) or RIC based on the reports from individual transplant centers as per previously established criteria [24]. The conditioning regimen was defined as MAC when containing total body irradiation (TBI) with a dose >6 Gray or a total dose of busulfan (Bu) > 8 mg/kg or >6.4 mg/kg when administered orally or intravenously, respectively. All other regimens were defined as RIC [24]. Regimens for GVHD prophylaxis were per institutional protocols. Grading of acute (a) GVHD was performed using established criteria [25]. Chronic (c) GVHD was classified as limited or extensive according to published criteria [26]. For this study, all necessary data were collected according to the EBMT guidelines, using the EBMT minimum essential data forms. The list of institutions contributing data to this study is provided in the Supplementary Appendix.

Statistical analysis

Median values and interquartile ranges (IQR) were used for quantitative variables and frequencies and percentages for categorical variables. The study endpoints were overall survival (OS), leukemia-free survival (LFS), relapse incidence (RI), and NRM, neutrophil recovery, aGVHD, cGVHD, and GVHD-free, relapse-free survival (GRFS). All endpoints were measured from the time of transplantation. As the follow-up period differed between the three study groups, all survival events were censored at 3 years. Neutrophil recovery was defined as achieving an absolute neutrophil count (ANC) of $\geq 0.5 \times 10^9$/L for three consecutive days. OS was defined as time to death from any cause. Leukemia-free survival (LFS) was calculated from the day of HSCT until disease recurrence or disease progression, death from any cause, or last follow-up. NRM was defined as death from any cause without previous relapse or progression. We used modified GRFS criteria. GRFS events were defined as the first event among grade III-IV aGVHD, extensive cGVHD, relapse, or death from any other cause [27]. Patient-, disease-, and transplant-related characteristics were compared between the three groups according to the period of transplant, 2005–2009 vs. 2010–2014 vs. 2015–2021, using the Mann–Whitney *U* test for quantitative variables, and the chi-squared or Fisher's exact test for categorical variables. The probabilities of OS, LFS, and GRFS were calculated using the Kaplan–Meier (KM) estimate. Neutrophil recovery, aGVHD, cGVHD, RI, and NRM were calculated using cumulative incidence curves in a competing risk setting, with death in remission being treated as a competing event for relapse. Death was considered a competing event for engraftment. To estimate the cumulative incidence of aGVHD or cGVHD, relapse and death were considered as competing events. Univariate analyses were performed using the log-rank test for LFS and OS, while Gray's test was used for cumulative incidence. Multivariate analyses were performed using the Cox proportional-hazards regression model [28]. All variables differing significantly between the three groups, and potential risk factors were included in the model. Results are expressed as the hazard ratio (HR) with a 95% confidence interval (95% CI). To test for a Center effect, we introduced a random effect or frailty for each Center into the model [29]. We checked that there was no interaction between time period and other covariables on LFS. All *p* values were two-sided with a type 1 error rate fixed at 0.05. Statistical analyses were performed with SPSS 27.0 (SPSS Inc., Chicago, IL, USA) and R 4.2.3 (R Core Team Fifty (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/) [30, 31].

RESULTS

Patient, transplant, and disease characteristics

A total of 1850 patients met the inclusion criteria comprising 526 with t (8:21), 625 with inv (16), and 699 with NPM1^{mut}FLT3^{WT} and normal karyotype. Two hundred and twenty-two were transplanted in 2005–2009, 392 were transplanted in 2010–2014 and, 1236 in 2015–2021. Table 1 shows the baseline demographic and clinical characteristics. Median follow-up was 103.1, interquartile range (IQR, 92.1–114.0), 78.3 (IQR, 69.4–86.3), and 32.0 (IQR, 29.5–34.5) months, for patients transplanted in 2005–2009, 2010–2014, and 2015–2021, respectively ($p < 0.0001$). Patients undergoing HSCT in 2015–2021 were older, with a median age of 50.9 (range 18.2–76.4) vs. 40.4 (range 18.3–67.7) and 42.4 (range 18.4–71) years, in those transplanted in 2005–2009 and 2010–2014, respectively ($p < 0.0001$). More patients ≥50 years of age were transplanted in the latest period with 52.7% vs. the 2 earlier periods 27.9% and 32.1% ($p < 0.0001$) and numbers for ≥60 years were 25.4% vs. 8.1% and 11%, in 2005–2009 and 2010–2014, respectively ($p < 0.0001$). Patient sex distribution was similar across the 3 time periods (Table 1). In 2005–2009 and 2010–2014 the most frequent (44.6% and 41.3%, respectively) diagnosis was t (8:21), while in 2015–2021, it was NPM1^{mut}FLT3^{WT} at 45.6% ($p < 0001$). In 2005–2009 and 2010–2014, the most frequent donors were MSD (63.1% and 54.6%, respectively), while in 2015–2021 they were UD (50.7%). Haplo transplants (HaploHSCT) increased from 5.9% in 2005–2009 and 2010–2014 to 14.5% in 2015–2021 ($p < 0.0001$). The KPS and HCT-CI did not differ between the three groups (Table 1). There were also no differences in patient or donor CMV seropositivity between the three groups (Table 1). Bone marrow grafts decreased from 24.8% in 2005–2009 to 13.2% in 2015–2021, while PB grafts increased from 75.2% to 86.8%, respectively ($p < 0.0001$). MAC decreased from 69.8% to 64.8% and 60.2% with a corresponding increase in RIC from 30.2% to 35.2% and 39.8% in patients transplanted in 2005–2009, 2010–2014, and 2015–2021, respectively ($p = 0.014$).

Table 1. Patient and transplant characteristics.

	2005–2009 ($n = 222$)	2010–2014 ($n = 392$)	2015–2021 ($n = 1236$)	*P*	Overall ($n = 1850$)
Follow-up (months), median [IQR]	103.1 [92–114.0]	78.3 [69.4–86.3]	32.0 [29.5–34.5]	<0.0001	39.1 [36.5-42.2]
Patient age (years), median (min-max) [IQR]	40.4 (18.3–67.7) [30.2–52.3]	42.4 (18.4–71) [32–53.5]	50.9 (18.2–76.4) [39.1–60.2]	<0.0001	48.1 (18.2–76.4) [36.2–58.2]
Classes of age					
age<60 y	204 (91.9%)	349 (89%)	922 (74.6%)	<0.0001	1475 (79.7%)
Age≥60 y	18 (8.1%)	43 (11%)	314 (25.4%)		375 (20.3%)
age<50 y	160 (72.1%)	266 (67.9%)	585 (47.3%)	<0.0001	1011 (54.6%)
age≥50 y	62 (27.9%)	126 (32.1%)	651 (52.7%)		839 (45.4%)
Patient sex					
Male	109 (49.1%)	227 (57.9%)	689 (55.9%)	0.097	1025 (55.5%)
Female	113 (50.9%)	165 (42.1%)	544 (44.1%)		822 (44.5%)
Missing	0	0	3		3
Group					
inv(16)	80 (36%)	137 (34.9%)	309 (25%)	<0.0001	526 (28.4%)
t(8;21)	99 (44.6%)	162 (41.3%)	364 (29.4%)		625 (33.8%)
FLT3-wt NPM1pos	43 (19.4%)	93 (23.7%)	563 (45.6%)		699 (37.8%)
Type of donor, details					
MSD	140 (63.1%)	214 (54.6%)	431 (34.9%)	<0.0001	785 (42.4%)
UD 10/10	50 (22.5%)	128 (32.7%)	505 (40.9%)		683 (36.9%)
UD 9/10	19 (8.6%)	27 (6.9%)	121 (9.8%)		167 (9%)
Haplo	13 (5.9%)	23 (5.9%)	179 (14.5%)		215 (11.6%)
Cell source					
BM	55 (24.8%)	85 (21.7%)	244 (13.2%)	<0.0001	104 (8.4%)
PB	167 (75.2%)	307 (78.3%)	1606 (86.8%)		1132 (91.6%)
HCT-CI					
HCT-CI = 0	42 (63.6%)	112 (66.3%)	700 (58.3%)	0.15	854 (59.5%)
HCT-CI = 1 or 2	15 (22.7%)	38 (22.5%)	280 (23.3%)		333 (23.2%)
HCT-CI > = 3	9 (13.6%)	19 (11.2%)	220 (18.3%)		248 (17.3%)
Missing	156	223	36		415
Karnofsky score					
<90	35 (20.2%)	67 (18.7%)	251 (21.3%)	0.55	353 (20.7%)
>=90	138 (79.8%)	291 (81.3%)	925 (78.7%)		1354 (79.3%)
Missing	49	34	60		143
Donor sex					
Donor male	132 (59.5%)	238 (60.9%)	822 (66.9%)	0.021	1192 (64.7%)
Donor female	90 (40.5%)	153 (39.1%)	407 (33.1%)		650 (35.3%)
Missing	0	1	7		8
Female to male combination					
No F- > M	180 (81.1%)	316 (80.6%)	1021 (83.1%)	0.47	1517 (82.3%)
F- > M	42 (18.9%)	76 (19.4%)	208 (16.9%)		326 (17.7%)
Missing	0	0	7		7
Patient CMV					
Pat. CMV neg.	65 (31.1%)	116 (31.4%)	378 (30.9%)	0.99	559 (31%)
Pat. CMV pos	144 (68.9%)	254 (68.6%)	845 (69.1%)		1243 (69%)
Missing	13	22	13		48
Donor CMV					
Don. CMV neg.	92 (42.6%)	167 (44.3%)	526 (43.2%)	0.91	785 (43.4%)
Don. CMV pos	124 (57.4%)	210 (55.7%)	691 (56.8%)		1025 (56.6%)
Missing	6	15	19		40

Table 1. continued

	2005–2009 ($n = 222$)	2010–2014 ($n = 392$)	2015–2021 ($n = 1236$)	*P*	Overall ($n = 1850$)
Conditioning					
MAC	155 (69.8%)	252 (64.8%)	739 (60.2%)	0.014	1146 (62.4%)
RIC	67 (30.2%)	137 (35.2%)	488 (39.8%)		692 (37.6%)
Missing	0	3	9		12
MRD pre HSCT					
MRD neg	52 (45.2%)	131 (48.7%)	402 (43.8%)	0.37	585 (45%)
MRD pos	63 (54.8%)	138 (51.3%)	515 (56.2%)		716 (55%)
Missing	107	123	319		549
Time diagnosis to HSCT (mo)					
Median (min-max) [IQR]	5.4 (2.1–23) [4.1–7.4]	5.6 (1.6-21.4) [4.4–8]	5.8 (1.7–23.9) [4.4–8]	0.071	5.7 (1.6–23.9) [4.3–7.9]
Missing	2	7	31		40
PTCY					
No PTCy	215 (99.5%)	368 (95.1%)	975 (80.2%)	< 0.0001	1558 (85.7%)
PTCy	1 (0.5%)	19 (4.9%)	240 (19.8%)		260 (14.3%)
Missing	6	5	21		32
In vivo T-cell depletion					
No in vivo TCD	123 (56.2%)	202 (52.1%)	481 (39.3%)	< 0.0001	806 (44%)
In vivo TCD	96 (43.8%)	186 (47.9%)	743 (60.7%)		1025 (56%)
Missing	3	4	12		19

IQR interquartile range, *y* year, *mo* month, *min* minimum, *max* maximum, *CMV* cytomegalovirus, *neg* negative, *pos* positive, *Don.* donor, *Pat.* patient, *BM* bone marrow, *PB* peripheral blood, *MAC* myeloablative conditioning, *RIC* reduced intensity conditioning, *MRD* measurable residual disease, *F* female, *M* male, *HSCT* hematopoietic stem cell transplantation, *UD* unrelated donor, *MSD* matched sibling donor, *Haplo* haploidentical donor, *PTCy* post transplant cyclophosphamide, *HCT-CI* hematopoietic stem cell transplantation-specific comorbidity index, *TCD* T cell depletion, *FLT3* wt - Fms-like tyrosine kinase 3-wild type, *NPM1pos* nucleophosmin positive.

The most frequent conditioning regimen for HSCT in 2005–2009, 2010–2014, and 2015–2021 was Bu/cyclophosphamide (BuCy, 40.3%), BuCy, (34.7%), and Bu/ fludarabine (BuFlu, 36.6%), respectively (Supplementary Table S1). The most frequent anti-GVHD prophylaxis was cyclosporine A (CSA) plus methotrexate in 60.4%, 57.5%, and 39.2%, followed by CSA plus mycophenolate mofetil (MMF) in 16.6%, 18.6% and 26.6% in the 2005–2009, 2010–2014 and 2015–2021 groups, respectively (Supplementary Table S2). GVHD prophylaxis with in vivo T-cell depletion or post-transplant cyclophosphamide (PTCy) was more frequent in 2015–2021 compared to the other two periods ($p < 0.0001$) (Table 1).

Transplantation outcomes

Day 60 incidence of neutrophil recovery (ANC $\geq 0.5 \times 10^9$/L) was 99.1% vs. 98.5% vs. 98.5% for patients transplanted in 2005–2009, 2010–2014, and 2015–2021, respectively ($p = 0.91$) (Supplemental Table S3). Day 180 incidence of aGVHD grade II-IV and III-IV were 18.2%, 21.1%, and 21.6% ($p = 0.68$); and 5.1%, 5.7%, and 7.3% ($p = 0.4$), respectively, while 3-year total cGVHD and 3-year extensive cGVHD were 49.3%, 50.4% and 39.2% ($p = 0.001$) and 22.7%,20.7% and 18.6% ($p = 0.2$), respectively (Table 2). Three-year NRM was similar in patients transplanted in 2005–2009 *vs.* those transplanted in 2010–2024 and 2015–2021, with 7.9% *vs.* 11.7% vs.13% ($p = 0.14$) as was 3-year RI at 25.3% *vs.* 17.7% *vs.*20.3%, respectively ($p = 0.11$). Likewise, LFS, OS, and GRFS were comparable between the three groups; 66.7% *vs.*70.6% vs. 66.2% ($p = 0.42$), 73.7% *vs.*76.4% *vs.* 73.9% ($p = 0.62$) and 50.8% *vs.*57.1% *vs.* 53.6% ($p = 0.29$) for the 2005–2009, 2010–2014 and 2015–2021 periods, respectively (Table 3; Figs. 1, 2). Outcomes were similar between patients aged ≥50 years old and those aged <50 years (Supplementary Table S4).

Multivariate analysis

The incidence of total cGVHD was reduced for HSCTs performed ≥2015 compared to those performed in 2005–2009 (hazard ratio [HR] =0.74, 95% CI 0.56–0.99, $p = 0.046$) and GRFS improved for patients transplanted in 2010–2014 *vs.* those transplanted in 2005–2009, HR = 0.74 (95% CI 0.56–0.98, $p = 0.037$) (Table 3). All other HSCT outcomes including NRM, RI, LFS, and OS did not differ with no improvement in the period ≥2015 compared to 2010–2014 (Table 3). LFS, OS, and GRFS were inferior in patients with t (8:21) with HR = 1.32 (95% CI 1.03–1.68, $p = 0.026$), HR = 1.38 (95% CI 1.04–1.83, $p = 0.027$) and HR = 01.25 (95% CI 1.02–1.53, $p = 0.035$), respectively. Other significant poor prognostic factors were older patient age (by 10 years) for NRM and OS; 10/10 and 9/10 UD vs. MSD for aGVHD II-IV (9/10 also for III-IV aGVHD) and Haplo *vs.* MSD for NRM, OS, aGVHD II-IV, and total cGVHD. The combination of female donors to male patients was associated with poor prognosis with respect to NRM, OS, GRFS,aGVHD III-IV, cGVHD, and, extensive cGVHD. In vivo, T-cell depletion was a positive prognostic factor for GRFS, aGVHD, and, cGVHD. PTCy was associated with a lower risk of cGVHD and extensive cGVHD, and PB grafts with an increased risk of total cGVHD (Table 3). There was no interaction between the cytogenetic/molecular group and the year of HSCT (data not shown).

Cause of death

A total of 55 (25%) patients in the 2005–2009 cohort, 80 (20%) patients in the 2009–2014 cohort, and 261 (21%) patients in 2015–2021 died within 3 years after transplant (Table 4). Original disease was the main cause constituting 60.0%, 42.9%, and 42.3% of the deaths in each group, respectively. The second and third causes of death in all three periods were GVHD and infections.

Table 2. Transplantation outcome: univariate analysis.

		3 years				
		Relapse	**NRM**	**LFS**	**OS**	**GRFS**
Year of HSCT	2005–2009	25.3%[19.7–31.3]	7.9%[4.8–12.1]	66.7%[60–72.6]	73.7%[67.2–79.2]	50.8%[43.9–57.2]
	2010–2014	17.7%[13.9–22]	11.7%[8.5–15.3]	70.6%[65.5–75.1]	76.4%[71.4–80.6]	57.1%[51.6–62.1]
	2015–2021	20.3%[17.9–22.9]	13%[11–15.2]	66.6%[63.6–69.5]	73.9%[70.9–76.6]	53.6%[50.3–56.7]
	P value	0.11	0.14	0.42	0.62	0.29
Cytogenetic and mutation groups	inv(16)	18.5%[15–22.3]	11.2%[8.4–14.4]	70.3%[65.7–74.4]	76.8%[72.4–80.6]	57.4%[52.6–61.9]
	t(8;21)	23%[19.4–26.7]	12.9%[10.2–16]	64.1%[59.7–68.1]	71.1%[66.8–75]	50.9%[46.4–55.2]
	FLT3-wt NPM1pos	19.8%[16.7–23]	11.7%[9.3–14.4]	68.6%[64.7–72.1]	75.4%[71.7–78.7]	54.4%[50.3–58.3]
	P value	0.18	0.6	0.07	0.11	0.19
Type of donor	MSD	22.7%[19.5–26]	10.7%[8.5–13.3]	66.6%[62.8–70.1]	74.9%[71.3–78.2]	52.9%[48.9–56.7]
	UD 10/10	19.3%[16.2–22.6]	10.5%[8.2–13.2]	70.2%[66.2–73.7]	76.7%[72.9–80]	55.4%[51.2–59.4]
	UD 9/10	18.7%[12.8–25.4]	14.9%[9.6–21.2]	66.4%[58–73.6]	69.5%[61.1–76.5]	54.4%[45.9–62]
	Haplo	17.5%[12.6–23.2]	18.6%[13.2–24.6]	63.9%[56.5–70.4]	69.4%[61.9–75.6]	54.4%[47–61.3]
	P value	0.44	0.011	0.22	0.05	0.69
HCT-CI	HCT-CI = 0	21.6%[18.6–24.7]	12.6%[10.2–15.2]	65.8%[62.1–69.3]	74.3%[70.7–77.6]	53.1%[49.2–56.8]
	HCT-CI = 1 or 2	19.2%[14.8–24]	12.1%[8.6–16.1]	68.8%[63–73.9]	72.4%[66.5–77.4]	54.5%[48.4–60.1]
	HCT-CI > = 3	18.1%[13.3–23.5]	12.7%[8.6–17.6]	69.2%[62.5–74.9]	76%[69.5–81.2]	52.6%[45.5–59.2]
	P value	0.51	0.98	0.73	0.65	0.94
Karnofsky score	<90	23%[18.3–27.9]	12.1%[8.7–16]	64.9%[59.2–70.1]	73.1%[67.6–77.8]	52.7%[46.9–58.2]
	>=90	19.9%[17.6–22.2]	12.3%[10.4–14.3]	67.9%[65.1–70.6]	74.5%[71.7–77]	53.8%[50.8–56.7]
	P value	0.31	0.89	0.33	0.46	0.77
Patient sex	Male	19.9%[17.3–22.7]	12.3%[10.2–14.6]	67.8%[64.5–70.8]	72.9%[69.7–75.9]	53.7%[50.3–57]
	Female	21%[18.1–24.1]	11.5%[9.2–14]	67.5%[63.8–70.9]	76.4%[73–79.4]	54.8%[50.9–58.5]
	P value	0.81	0.66	0.91	0.19	0.24
Donor sex	donor male	20.8%[18.4–23.4]	10.3%[8.5–12.3]	68.9%[65.9–71.7]	75.8%[72.9–78.4]	55.3%[52.2–58.4]
	donor female	19.9%[16.7–23.4]	14.9%[12.1–18.1]	65.2%[60.9–69.1]	71.8%[67.6–75.5]	51.6%[47.2–55.8]
	P value	0.75	0.009	0.12	0.09	0.1
Female to male combination	no F- > M	20.5%[18.4–22.8]	10.9%[9.3–12.7]	68.6%[65.9–71]	76.1%[73.6–78.4]	55.1%[52.3–57.8]
	F- > M	19.8%[15.3–24.7]	16.5%[12.2–21.3]	63.7%[57.5–69.3]	66.8%[60.4–72.4]	49.8%[43.6–55.7]
	P value	0.97	0.016	0.1	0.005	0.033
Cell source	BM	17.9%[13.2–23.1]	9.5%[6.1–13.7]	72.6%[66.3–77.9]	80.5%[74.6–85.2]	58.7%[51.9–64.8]
	PB	20.9%[18.8–23.2]	12.4%[10.7–14.3]	66.7%[64–69.2]	73.4%[70.8–75.7]	53.3%[50.5–56]
	P value	0.32	0.26	0.11	0.024	0.21
Conditioning intensity	MAC	20.3%[17.9–23]	10.1%[8.4–12.1]	69.5%[66.5–72.3]	77.4%[74.5–80]	55.8%[52.6–58.9]
	RIC	20.9%[17.7–24.2]	14.7%[11.9–17.7]	64.5%[60.4–68.2]	69.6%[65.6–73.3]	51.3%[47.1–55.3]
	P value	0.82	0.021	0.09	0.001	0.19
MRD pre HCT	MRD neg	18.6%[15.2–22.3]	12.4%[9.6–15.5]	69%[64.6–73]	75.6%[71.3–79.3]	54.9%[50.3–59.4]
	MRD pos	21.4%[18.2–24.7]	12%[9.6–14.8]	66.6%[62.7–70.3]	74.3%[70.5–77.6]	53.2%[49.1–57.1]
	P value	0.17	0.7	0.35	0.72	0.41

Table 2. continued

		3 years				
		Relapse	**NRM**	**LFS**	**OS**	**GRFS**
PTCY	No PTCy	20.6%[18.5–22.9]	10.9%[9.3–12.7]	68.4%[65.8–70.9]	75.5%[73–77.8]	54.4%[51.6–57.1]
	PTCy	18.3%[13.5–23.7]	15.5%[11–20.8]	66.1%[59.3–72.1]	70.8%[64–76.6]	56%[49.1–62.4]
	P value	0.63	0.03	0.25	0.06	0.66
In vivo T cell depletion	no in vivo TCD	20.5%[17.6–23.7]	12%[9.7–14.5]	67.5%[63.8–70.9]	75%[71.4–78.2]	50.3%[46.4–54.1]
	in vivo TCD	20.4%[17.8–23.2]	11.5%[9.5–13.8]	68%[64.8–71.1]	74.4%[71.2–77.2]	57.4%[54–60.6]
	P value	0.82	0.55	0.5	0.95	0.002

		180 days		3 years	
		Acute GVHD II-IV	**Acute GVHD III-IV**	**chronic GVHD**	**ext. chronic GVHD**
Year of HSCT	2005–2009	18.2%[13.4–23.7]	5.1%[2.7–8.7]	49.3%[42.1–56.1]	22.7%[17.1–28.9]
	2010–2014	21.1%[17.1–25.4]	5.7%[3.6–8.4]	50.4%[44.7–55.8]	20.7%[16.4–25.3]
	2015–2021	21.6%[19.3–24]	7.3%[5.9–8.9]	39.2%[36.1–42.3]	18.6%[16–21.2]
	P value	0.68	0.4	0.001	0.2
Cytogenetic and mutation groups	inv(16)	22.5%[19–26.3]	7%[5–9.4]	44.3%[39.4–49.1]	18.4%[14.7–22.4]
	t(8;21)	21.1%[17.9–24.5]	5.2%[3.6–7.2]	42.5%[38.1–46.9]	20.5%[16.9–24.3]
	FLT3-wt NPM1pos	20%[17.1–23.1]	7.9%[6–10.1]	41.9%[37.8–45.9]	19.1%[15.9–22.5]
	P value	0.56	0.17	0.52	0.77
Type of donor	MSD	18.9%[16.1–21.8]	6.2%[4.6–8.1]	46.7%[42.6–50.6]	21.5%[18.2–24.9]
	UD 10/10	22.1%[19–25.3]	6.7%[5–8.8]	40.8%[36.7–44.9]	20%[16.7–23.5]
	UD 9/10	22.1%[16.1–28.8]	8.6%[4.9–13.6]	38.2%[30-46.3]	15.3%[9.8–21.9]
	Haplo	25.1%[19.4–31.2]	7.3%[4.2–11.3]	39.3%[32.1-46.4]	13%[8.5–18.5]
	P value	0.15	0.57	0.1	0.08
HCT-CI	HCT-CI = 0	21.6%[18.8–24.5]	8.2%[6.4–10.2]	42.1%[38.2–45.8]	18.5%[15.5–21.7]
	HCT-CI = 1 or 2	19.6%[15.4–24.1]	5.9%[3.7–8.9]	37.9%[32.1–43.7]	20.3%[15.7–25.3]
	HCT-CI > = 3	23.2%[18.1–28.7]	6.6%[3.9–10.2]	45.5%[38.6–52.1]	23.6%[17.7–30.1]
	P value	0.61	0.45	0.38	0.33
Karnofsky score	<90	19%[15–23.4]	6%[3.8–8.9]	38.6%[32.9–44.3]	16.8%[12.6–21.5]
	>=90	21.5%[19.3–23.8]	7%[5.7–8.4]	44.5%[41.5–47.4]	20.6%[18.2–23.1]
	P value	0.35	0.64	0.059	0.19
Patient sex	Male	21.3%[18.7–23.9]	7.4%[5.9–9.2]	43.2%[39.8–46.6]	20.6%[17.8–23.5]
	Female	20.9%[18.1–23.8]	5.7%[4.3–7.5]	42.3%[38.5–46]	17.9%[15–21]
	P value	0.94	0.24	0.34	0.09
Donor sex	donor male	20.1%[17.8–22.5]	5.7%[4.5–7.2]	41%[37.9–44.1]	17.8%[15.4–20.3]
	donor female	23%[19.8–26.4]	8.6%[6.6–11]	46%[41.6–50.2]	22.4%[18.7–26.2]
	P value	0.14	0.012	0.044	0.058
Female to male combination	no F- > M	20.7%[18.6–22.8]	5.8%[4.7–7.1]	41.5%[38.7–44.3]	17.9%[15.8–20.2]
	F- > M	22.9%[18.3–27.7]	10.8%[7.6–14.6]	49.1%[42.7–55.2]	26.6%[21–32.5]
	P value	0.52	0.003	0.003	0.001

Table 2. continued

		180 days		3 years	
		Acute GVHD II-IV	**Acute GVHD III-IV**	**chronic GVHD**	**ext. chronic GVHD**
Cell source	BM	23.4%[18.2–29]	4.7%[2.5–7.9]	39.3%[32.8–45.8]	18.2%[13.4–23.7]
	PB	20.8%[18.7–22.8]	7%[5.8–8.4]	43.4%[40.7–46.2]	19.6%[17.4–21.9]
	P value	0.33	0.17	0.37	0.85
Conditioning intensity	MAC	21.7%[19.3–24.2]	6.3%[5–7.9]	43.9%[40.6–47.1]	19.8%[17.2–22.5]
	RIC	20.1%[17.2–23.3]	7.5%[5.6–9.6]	41%[36.9–45]	18.7%[15.5–22.1]
	P value	0.39	0.26	0.31	0.45
MRD pre HCT	MRD neg	19.9%[16.7–23.3]	6%[4.2–8.2]	41.7%[37.1–46.2]	18.9%[15.3–22.7]
	MRD pos	22.8%[19.7–26]	6.6%[4.9–8.6]	44.1%[40–48]	20.2%[16.9–23.6]
	P value	0.26	0.7	0.41	0.76
PTCY	No PTCy	20.6%[18.6–22.7]	6.2%[5.1–7.6]	43.8%[41.1–46.6]	20.3%[18.1–22.7]
	PTCy	23.5%[18.5–28.8]	9%[5.9–12.9]	36.7%[30.1–43.4]	13.3%[8.9–18.6]
	P value	0.39	0.13	0.052	0.018
In vivo T cell depletion	no in vivo TCD	23.2%[20.3–26.3]	8.7%[6.8–10.8]	51.4%[47.4–55.3]	24.4%[21–27.9]
	in vivo TCD	19.4%[17–21.9]	5.3%[4–6.8]	36.3%[33–39.6]	15.4%[13.1–18]
	P value	0.056	0.005	0.001	0.001

Outcomes were censored at 3 years for comparisons. Unless otherwise stated, results are expressed as frequencies (%).
HSCT hematopoietic stem cell transplantation, *UD* unrelated donor, *MSD* matched sibling donor, *Haplo* haploidentical donor, *PTCy* post transplant cyclophosphamide, *pos* positive, *neg* negative, *MAC* myeloablative conditioning, *RIC* reduced intensity conditioning, *MRD* measurable residual disease, *F* female, *M* male, *GVHD* graft-versus-host disease, a-acute, *NRM* non-relapse mortality, *LFS* leukemia-free survival, *OS* overall survival, *ext.* extensive, *GRFS* GVHD-free and relapse-free survival, *FLT3* ITD Fms related receptor tyrosine kinase 3 internal tandem duplication mutation, *NPM1* nucleophosmin mutation, *HCT CI* Hematopoietic Cell Transplantation specific Comorbidity Index, *TCD* T cell depletion, *BM* bone marrow, *PB* peripheral blood.

Table 3. Transplantation outcomes: multivariate analysis.

	RELAPSE		NRM		LFS	
	HR (95% CI)	***p* value**	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
year 2005–2009 (reference)	1		1		1	
2010–2014	0.67 (0.44–1.01)	0.056	1.04 (0.56–1.94)	0.9	0.77 (0.55–1.09)	0.14
2015–2021	0.86 (0.6–1.24)	0.41	0.91 (0.51–1.63)	0.76	0.86 (0.64–1.18)	0.36
2015–2021 vs. 2010–2014	1.29 (0.93–1.78)	0.12	0.88 (0.58–1.33)	0.54	1.12 (0.87–1.44)	*0.39*
inv(16) reference	1		1		1	
t(8;21)	1.34 (0.98–1.82)	0.064	1.34 (0.9–2)	0.15	1.32 (1.03–1.68)	0.026
FLT3-wt/NPM1pos	1.34 (0.98–1.83)	0.068	0.87 (0.57–1.32)	0.51	1.14 (0.89–1.46)	0.31
Patient age (per 10 y)	0.91 (0.83–1.01)	0.072	1.34 (1.16–1.55)	<0.0001	1.04 (0.96–1.13)	0.32
KPS > = 90	0.86 (0.65–1.14)	0.3	1.12 (0.76–1.66)	0.57	0.95 (0.76–1.19)	0.65
Donor MSD (reference)	1		1		1	
UD 10/10	0.95 (0.72–1.27)	0.75	1.13 (0.74–1.72)	0.56	1.01 (0.8–1.28)	0.94
UD 9/10	0.91 (0.58–1.43)	0.68	1.58 (0.9–2.78)	0.11	1.11 (0.78–1.58)	0.56
Haplo	0.83 (0.47–1.46)	0.52	3.05 (1.54–6.06)	0.001	1.41 (0.92–2.16)	0.11
Female to male R	1.04 (0.77–1.42)	0.79	1.56 (1.06–2.28)	0.023	1.22 (0.97–1.55)	0.095
in vivo TCD	0.92 (0.69–1.23)	0.57	0.99 (0.65–1.5)	0.96	0.95 (0.75–1.2)	0.65
PTCY vs. No	1.02 (0.63–1.67)	0.92	0.76 (0.39–1.5)	0.43	0.9 (0.61–1.34)	0.61
RIC vs. MAC	1.16 (0.89–1.53)	0.27	1 (0.7–1.44)	0.98	1.11 (0.9–1.37)	0.34
PB vs. BM	1.14 (0.79–1.64)	0.49	1.27 (0.76–2.13)	0.37	1.16 (0.86–1.55)	0.33
Pat. CMV pos	1.14 (0.86–1.5)	0.36	1.39 (0.94–2.04)	0.1	1.21 (0.97–1.51)	0.097
Don. CMV pos	1 (0.78–1.29)	0.98	1.07 (0.76–1.51)	0.69	1.03 (0.84–1.26)	0.78
	OS		**GRFS**		**Acute GVHD II-IV**	
year 2005–2009 (reference)	1		1		1	
2010–2014	0.76 (0.52–1.13)	0.18	0.74 (0.56–0.98)	0.037	1.43 (0.89–2.29)	0.14
2015–2021	0.77 (0.54–1.1)	0.15	0.85 (0.65–1.1)	0.21	1.53 (0.98–2.4)	0.06
2015–2021 vs. 2010–2014	1.01 (0.75–1.35)	0.97	1.15 (0.93–1.42)	0.21	1.08 (0.8–1.44)	0.62
inv(16) reference	1		1		1	
t(8;21)	1.38 (1.04–1.83)	0.027	1.25 (1.02–1.53)	0.035	0.94 (0.71–1.25)	0.67
FLT3-wt/NPM1pos	1.1 (0.82–1.47)	0.52	1.19 (0.97–1.47)	0.1	0.9 (0.68–1.2)	0.48
Patient age (per 10 y)	1.12 (1.02–1.23)	0.019	1.04 (0.97–1.11)	0.28	0.99 (0.9–1.08)	0.79
KPS > = 90	1 (0.77–1.3)	0.99	1.02 (0.84–1.24)	0.84	1.2 (0.9–1.61)	0.21
donor MSD (reference)	1		1		1	
UD 10/10	1.13 (0.85–1.49)	0.41	1.16 (0.95-1.42)	0.15	1.53 (1.14–2.05)	0.005
UD 9/10	1.46 (0.99–2.17)	0.058	1.33 (0.98–1.79)	0.066	1.81 (1.19–2.75)	0.005
Haplo	1.66 (1.01–2.74)	0.045	1.41 (0.96–2.06)	0.078	1.74 (1.05–2.9)	0.032
Female to male R	1.51 (1.16–1.97)	0.003	1.28 (1.05–1.56)	0.016	1.06 (0.79–1.41)	0.71
in vivo TCD	1 (0.75–1.32)	0.98	0.72 (0.58–0.88)	0.001	0.67 (0.5–0.89)	0.007
PTCY vs. No	1.03 (0.65–1.62)	0.91	0.75 (0.53–1.06)	0.1	0.71 (0.45–1.13)	0.15

Table 3. continued

	OS		GRFS		Acute GVHD II-IV	
RIC vs. MAC	1.22 (0.95–1.57)	0.12	1.06 (0.88–1.27)	0.56	0.95 (0.73–1.23)	0.69
PB vs. BM	1.3 (0.91–1.86)	0.16	1.17 (0.91–1.5)	0.22	0.98 (0.69–1.39)	0.93
Pat. CMV pos	1.27 (0.97–1.65)	0.078	1.02 (0.85–1.23)	0.8	0.92 (0.71–1.18)	0.51
Don. CMV pos	1.02 (0.81–1.29)	0.87	1.18 (0.99–1.4)	0.062	0.9 (0.71–1.14)	0.39
	Acute GVHD III-IV		**Chronic GVHD**		**Extensive chronic GVHD**	
year 2005–2009 (reference)	1		1		1	
2010–2014	0.81 (0.37–1.79)	0.61	0.91 (0.67–1.23)	0.53	0.84 (0.54–1.3)	0.43
2015–2021	1.09 (0.54–2.23)	0.81	0.74 (0.56–0.99)	0.046	0.81 (0.53–1.22)	0.31
2015–2021 vs. 2010–2014	1.34 (0.77–2.35)	0.3	0.82 (0.66–1.03)	0.082	0.96 (0.69–1.34)	0.82
inv(16) reference	1		1		1	
t(8;21)	0.88 (0.53–1.49)	0.65	1.06 (0.85–1.32)	0.61	1.29 (0.92–1.8)	0.14
FLT3-wt/NPM1pos	1.22 (0.74–2.01)	0.44	1.07 (0.85–1.33)	0.56	1.29 (0.91–1.81)	0.15
Patient age (per 10 y)	1.02 (0.86–1.21)	0.82	1.01 (0.94–1.09)	0.71	1.07 (0.95–1.2)	0.25
KPS > = 90	1.37 (0.81–2.31)	0.24	1.14 (0.91–1.43)	0.26	1.17 (0.84–1.65)	0.35
donor MSD (reference)	1		1		1	
UD 10/10	1.68 (1–2.82)	0.051	1.16 (0.93–1.45)	0.19	1.36 (0.98–1.88)	0.066
UD 9/10	2.68 (1.36–5.29)	0.004	1.18 (0.83–1.68)	0.37	1.17 (0.68–2.01)	0.57
Haplo	1.48 (0.6–3.65)	0.39	1.86 (1.19-2.9)	0.007	1.33 (0.65–2.7)	0.43
Female to male R	1.99 (1.28–3.08)	0.002	1.38 (1.11–1.72)	0.004	1.71 (1.26–2.33)	0.0006
in vivo TCD	0.42 (0.25–0.7)	0.0009	0.49 (0.39–0.62)	<0.0001	0.5 (0.36–0.69)	<0.0001
PTCY vs. No	0.76 (0.35–1.63)	0.48	0.47 (0.31–0.71)	0.0004	0.42 (0.22–0.79)	0.007
RIC vs. MAC	1.19 (0.76–1.87)	0.45	0.88 (0.71–1.08)	0.22	0.83 (0.61–1.13)	0.24
PB vs. BM	1.74 (0.84–3.58)	0.13	1.58 (1.19–2.1)	0.001	1.32 (0.88–1.98)	0.19
Pat. CMV pos	0.8 (0.52–1.24)	0.32	0.83 (0.68–1.02)	0.072	0.95 (0.7–1.29)	0.72
Don. CMV pos	1.08 (0.71–1.64)	0.73	1.12 (0.93-1.35)	0.24	1.31 (0.98–1.76)	0.066

Outcomes were censored at 3 years for comparisons. Unless otherwise stated, results are expressed as frequencies (%).
HR hazard ratio, *CI* confidence interval, *HSCT* hematopoietic stem cell transplantation, *y* year, *vs.* versus, *UD* unrelated donor, *MSD* matched sibling donor, *Haplo* haploidentical donor, *PTCy* post transplant cyclophosphamide, *pos*positive, *neg* negative, *MAC* myeloablative conditioning, *RIC* reduced intensity conditioning, *MRD* measurable residual disease, *R* recipient, *GVHD* graft-versus-host disease, *a* acute, *NRM* non-relapse mortality, *LFS* leukemia-free survival, *OS* overall survival, *GRFS* GVHD-free and relapse-free survival, *FLT3* ITD Fms related receptor tyrosine kinase 3 internal tandem duplication mutation, *NPM1* nucleophosmin mutation, *HCT-CI* Hematopoietic Cell Transplantation specific Comorbidity Index, *TCD* T cell depletion, *BM* bone marrow, *PB* peripheral blood.

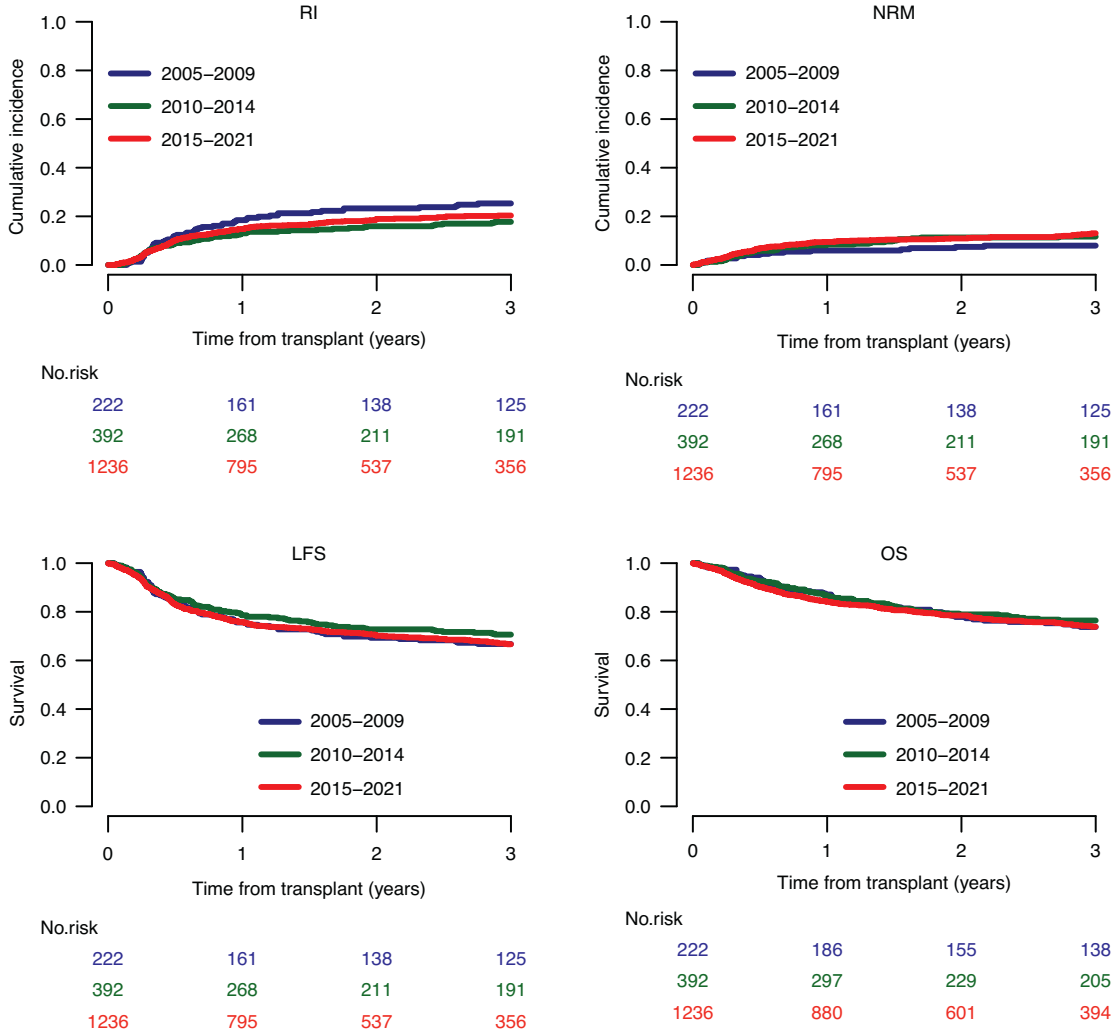

Fig. 1 Allogeneic stem cell transplantation for favorable risk acute myeloid leukemia in first complete remission comparing outcomes according to the period of transplant during three time periods: 3-year outcomes: relapse incidence (RI), non-relapse mortality (NRM), leukemia-free survival (LFS), and overall survival (OS). Three-year NRM was similar in patients transplanted in 2005–2009 *vs*. those transplanted in 2010–2024 and 2015–2021 ($p = 0.14$) as was 3-year RI ($p = 0.11$), LFS ($p = 0.42$) and OS ($p = 0.62$).

Other transplant-related causes of death were infrequent (<~4%) and included veno-occlusive disease of the liver, graft failure, interstitial pneumonitis, cardiac toxicity, hemorrhage, and lymphoproliferative disorders, with no difference between the three groups (Table 4).

DISCUSSION

In this study focusing on 1850 patients with favorable risk AML transplanted in CR1 from MSD, UD, or Haploidentical donors, we performed a longitudinal assessment of transplantation outcomes over 16 years comparing post-HSCT outcomes between patients transplanted in 2005–2009, 2010–2014, and more recently in 2015–2021. We observed an increased number of transplants in patients ≥60 years, from UD and Haplo with PB grafts and in vivo T cell depletion or PTCy as GVHD prophylaxis. Most importantly, 3-year GRFS improved from 2010 and total cGVHD reduced from 2015, while other HSCT outcome parameters including NRM, RI, LFS,OS, and GRFS have not changed.

Changes in transplantation activity in favorable risk AML in the recent compared to earlier periods include the increased number of HSCTs in patients aged > 60 years old and the increased number of HSCTs from alternative donors including HaploHSCT, and the use of in vivo T cell depletion or PTCy as GVHD prophylaxis. These changes are similar to those witnessed in high and intermediate-risk AML in which transplantation is the recommended procedure in CR1 [13, 20, 32–35].

The reduction in cGVHD from 2015 and the improvement in GRFS may be related to those trends and are of clinical importance as allogeneic transplantation has a better anti-leukemic effect and is associated with a significant reduction in RI compared to conventional therapy also in favorable risk AML [9, 36]. Indeed, either in vivo T cell depletion or PTCy as GVHD prophylaxis have been shown to significantly reduce the incidence of GVHD which is still a major obstacle for successful allogeneic transplantation [37–39].

Our results are in agreement with some recent publications assessing longitudinal outcomes post alternative donor HSCT in other AML categories with higher risk demonstrating improvement in the composite endpoint of GRFS in recent years [17, 19, 22].

Overall, the ~70% 3-year LFS and OS that we observed in this current study is marginally better than those reported by Gorin et al. in a previous ALWP/EBMT study that analyzed results in a smaller cohort of 64 patients with inv16, and 81 patients with t (8:21), undergoing HSCT between 1990-2004 with a 5-year LFS of

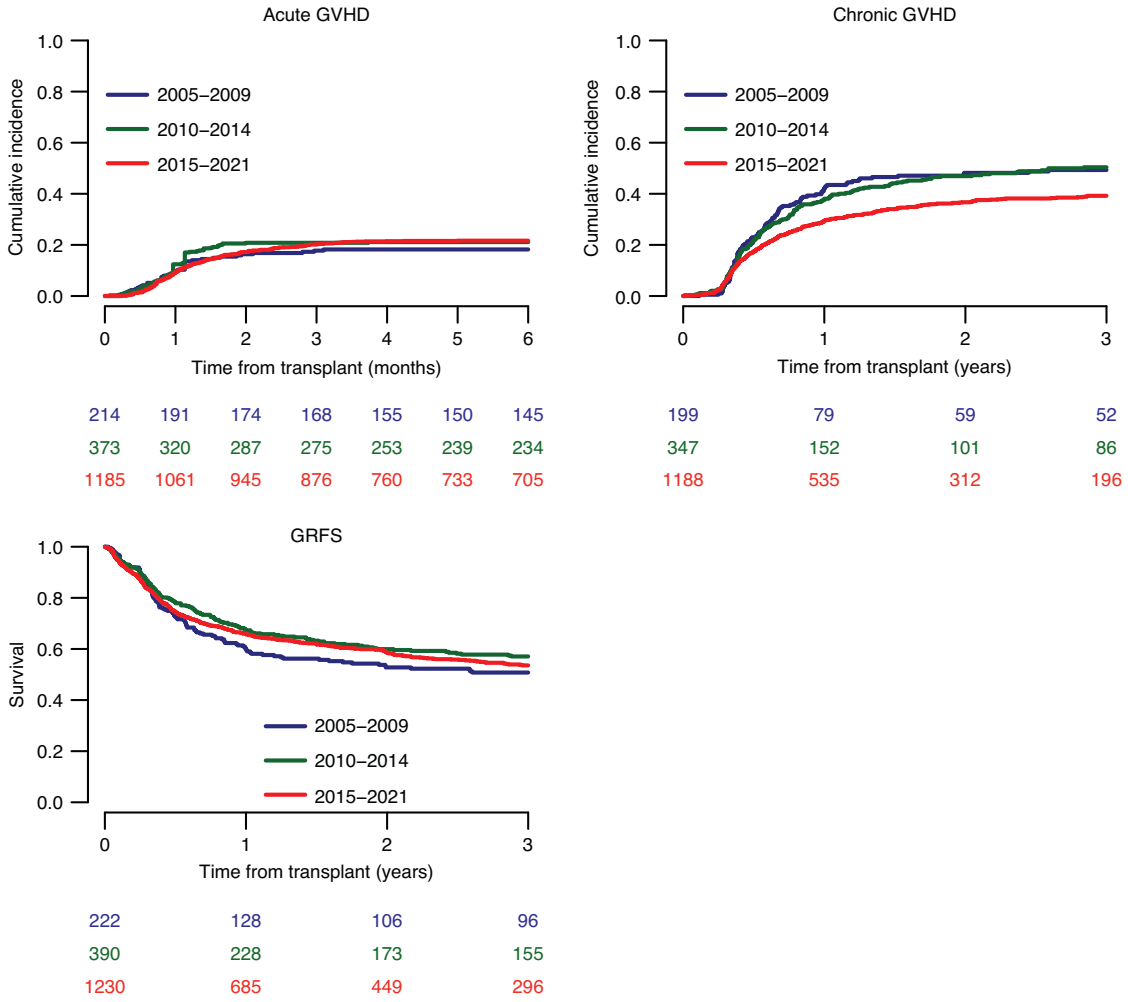

Fig. 2 Allogeneic stem cell transplantation for favorable risk acute myeloid leukemia in first complete remission comparing outcomes according to the period of transplant during three time periods: graft-versus-host disease, chronic GVHD, and GVHD-free relapse-free survival. Day 180 incidence of aGVHD grade II–IV and III–IV did not differ between transplants performed during the 3 time periods ($p = 0.68$ and $p = 0.4$, respectively). The 3-year total cGVHD incidence was significantly lower in transplants performed>2015 ($p = 0.001$), while 3-year extensive cGVHD did not differ ($p = 0.2$). GRFS was comparable between the three groups ($p = 0.29$).

60% [40] and in another French AML Intergroup survey of 116 patients with inv16, 16 of whom had an HSCT with a 3-year LFS of 56% in the transplanted patients [41]. Notably, results were better in patients younger than 35 years of age [41]. Similar results were reported by Schlenk et al. who reported on behalf of the Center for International Blood and Marrow Transplant Research (CIBMTR) on 118 AML patients with t (8:21) receiving HSCT between 1990-2002 with a 5-year relapse-free survival (RFS) of 55% [36].

We observed a rather low 3-year NRM of up to 13% with no significant difference between the three analyzed periods. The fact that we have not seen a reduction in NRM with time may be because the age of the transplanted patients increased over time going from a median of 40.4 years in the earlier period (2005–2009) to a median of 50.9 years in those transplanted in 2015–2021. Of note, of the total number of transplanted patients, the percentage of those aged ≥60 years increased from 8.1% to 25.4%, respectively. These results are in agreement with a recent study by Bazarbachi et al. that recently assessed post-transplantation outcomes over two decades in AML patients aged 65-80 years, demonstrating significant improvement in LFS and OS while NRM was not significantly affected [19]. The correlation between age and transplant-related mortality is well established regardless of the leukemic risk. For example, in a study reported by Schetelig et al., the cumulative incidence of NRM for patients aged under 45 years at transplant was 7% rising to 25% for patients aged over 65 years [42].

As for patients with NPM1 and normal karyotype, in another recent study from the ALWP analyzing transplantation outcomes in 2782 such patients with a median age of 54 (18–83) years transplanted between 2005 and 2021, the 2-year NRM was 13.3% [43]. Interestingly, longitudinal assessment of post-transplantation outcomes showed improvement in LFS and OS in $FLT3^{mut}$ $NPM1^{wild}$ patients but failed to do so in those with $NPM1^{mut}$ [18]. German colleagues reported on 17 elderly $NPM1^{mut}$ AML patients with a median age of 67 (range, 61-76) years transplanted between 1998-2018 with a 2-year NRM of 12%, LFS of 81%, and OS of 88% [44].

Of note, we have not seen a reduction in RI over time, which is in agreement with our recent publication assessing HSCT outcomes of 106,188 patients with hematological malignancies,~60% with acute leukemia, over three periods with no significant improvement in RI in patients transplanted from MSD, UD or Haplo donors [20]. Furthermore, the intensity of the conditioning being RIC or MAC had no impact on the RI which may be related to the favorable cytogenetic risk and being in CR1. Indeed relapse remains the main hurdle to successful

Table 4. Cause of death within 3 years post HSCT.

	2005–2009 ($n = 55$)	2010–2014 ($n = 80$)	2015–2021 ($n = 261$)	Overall ($n = 396$)
Original disease	33 (60%)	33 (42.9%)	107 (42.3%)	173 (44.9%)
GVHD	8 (14.5%)	14 (18.2%)	48 (19%)	70 (18.2%)
Infection	7 (12.7%)	18 (23.4%)	51 (20.2%)	76 (19.7%)
Cardiac toxicity	0 (0%)	0 (0%)	2 (0.8%)	2 (0.5%)
Hemorrhage	0 (0%)	1 (1.3%)	2 (0.8%)	3 (0.8%)
Failure/Rejection	1 (1.8%)	0 (0%)	1 (0.4%)	2 (0.5%)
VOD	0 (0%)	2 (2.6%)	3 (1.2%)	5 (1.3%)
IP	2 (3.6%)	1 (1.3%)	1 (0.4%)	4 (1%)
Lymphoproliferative disorder	0 (0%)	1 (1.3%)	0 (0%)	1 (0.3%)
Other second malignancy	0 (0%)	0 (0%)	4 (1.6%)	4 (1%)
MOF	0 (0%)	2 (2.6%)	5 (2%)	7 (1.8%)
Other transp related	2 (3.6%)	3 (3.9%)	7 (2.8%)	12 (3.1%)
Non HSCT related	2 (3.6%)	2 (2.6%)	22 (8.7%)	26 (6.8%)
Missing	0	3	8	11

HSCT hematopoietic stem cell transplantation, *VOD* veno occlusive disease of the liver, *GVHD* graft-versus-host disease, *MOF* multiorgan failure; trans-transplantation, *IP* interstitial pneumonitis.

transplantation. It is also intriguing that we have seen a significant reduction in cGVHD that was not translated into a reduction in RI speaking for a dissociation of GVHD and the graft versus leukemia effect with PTCy [45]. Emerging strategies for earlier detection of relapse, potentially based on MRD, and early intervention with pharmacological means including recently approved novel agents and targeted therapies or immunologically based cellular therapies may hopefully lead to a reduction in the post-HSCT relapse incidence improving transplantation outcome [46, 47]. The intensity of the pre-transplant conditioning may also be tailored according to the MRD, as patients with positive MRD may benefit from more intense conditioning. Unfortunately being a registry-based study we miss MRD data for close to a third of the study patients and thus could not correlate the RI to the pre-HSCT MRD and the intensity of the conditioning.

LFS, OS, and GRFS were superior in patients with t (8:21) which is in contrast to previous publications demonstrating worse outcomes for AML with t (8:21) compared to those with inv16 due to higher RI and differences in co-operating mutational profiles. Translocation (8; 21) AML is more often associated with epigenetic/chromatin modulator/cohesion mutations while inv16 AML is more frequently associated with kinase mutations [14, 48–50]. Unfortunately, being a transplantation-based registry, molecular information was lacking.

The additional factors we observed for predicting inferior transplantation outcomes in favorable risk AML included increasing age, alternative donors, and the combination of female donor to a male patient are in agreement with previous publications and have been previously reported as prognostic factors for poor outcomes of HSCT in AML [16, 42, 51, 52]. As for GVHD, PTCy was associated with a lower incidence of cGVHD; PB grafts with an increased risk of total cGVHD and in vivo T cell depletion with lower risk of acute and cGVHD in agreement with previous publications [37–39, 53, 54]. UD and HaploHSCT were risk factors for aGVHD as previously reported [51, 55].

This being a retrospective and transplantation registry-based study, had several limitations including the risk of selection bias, the possibility of unavailable data that have not been considered, such as frontline therapies and co-mutation profiling including the KIT mutation, as well as MRD and HCT-CI that are missing for a substantial number of patients, especially those transplanted in the earlier periods. The lack of mutation data is of particular importance as CBF AML including t 8;21 leukemia is a genetically heterogenous disease entity partially due to activating kinase mutations like KIT, FLT3, and NRAS as well as epigenetic regulators like ASXL2 and ZBTB7A, that were identified in patients with 8;21 AML but not in those with inv(16), and have been demonstrated to affect the disease biology and characteristics and may affect clinical outcomes [56, 57].

In conclusion, in this large registry-based retrospective analysis of HSCT patients with favorable risk AML in CR1, transplanted between the years 2005 to 2022, we observed an increased number of HSCTs in patients ≥60 years, from UD and Haplo with PB grafts and in vivo T cell depletion or PTCy as GVHD prophylaxis. Most importantly, 3-year GRFS improved from 2010 and total cGVHD reduced from 2015, while other HSCT outcome parameters including NRM, RI, LFS, OS, and GRFS have not changed. have not changed.

Hopefully, with these recent encouraging results and evolving novel strategies including gemtuzumab ozogamicin that was recently shown to improve survival in CBF AML [58], as well as hypomethylating agents (azacitidine or decitabine), the Bcl2 inhibitor venetoclax, the multikinase inhibitor dasatinib for patients with t(8;21) AML with KIT mutations, as well as quizartinib, sorafenib for those with FLT3 co mutations or gilteritinib for those with FLT3 co mutations and positive MRD, it may be possible to further improve outcomes in favorable risk AML [59–65].

DATA AVAILABILITY

AN, ML and MM had full access to all the data in the study (available upon data specific request).

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AUTHOR CONTRIBUTIONS

AN wrote the manuscript, designed the study, and interpreted the data. ML and MM designed the study, performed the statistical analyses, interpreted the data, and edited the manuscript US, DW, DB, AR, PR, EF, RPdL, PC, PvdB, DB, CS, JM, NK, GB, MA, JV, KH, and FC reviewed the manuscript and provided clinical data. All authors approved the final version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The scientific boards of the ALWP of the EBMT approved this study. The study was performed in accordance with the Declaration of Helsinki and approved by the Sheba Medical Center Helsinki committee (SMC-770920). Informed consent was obtained from all subjects.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41409-024-02379-z.

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