Longitudinal Outcome over Two Decades of Unrelated Allogeneic Stem Cell Transplantation for Relapsed/Refractory Acute Myeloid Leukemia: An ALWP/EBMT Analysis

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ABSTRACT

Purpose: We evaluated outcomes of unrelated transplantation for primary refractory/relapsed (ref/rel) acute myeloid leukemia (AML), comparing two cohorts according to the year of transplant, 2000–2009 and 2010–2019.

Patients and Methods: Multivariable analyses were performed using the Cox proportional-hazards regression model.

Results: 3,430 patients were included; 876 underwent a transplant between 2000–2009 and 2554 in 2010–2019. Median follow-up was 8.7 (95% CI, 7.8–9.4) and 3.4 (95% CI, 3.1–3.6) years ($P < 0.001$). Median age was 52 (18–77) and 56 (18–79) years ($P > 0.0001$); 45.5% and 55.5% had refractory AML while 54.5% and 44.5% had relapsed AML. Conditioning was myeloablative in 60% and 52%, respectively. Neutrophil recovery and day 100 incidence of acute and 2-year incidence of chronic graft-versus-host disease (GvHD) were similar between the two periods. Two-year relapse incidence was higher for patients undergoing transplant in the 2000–2009 period versus those undergoing transplant in 2010–2019: 50.2% versus 45.1% (HR, 0.85; 95% CI, 0.74–0.97; $P = 0.002$). Leukemia-free survival; overall survival; and GvHD-free, relapse-free survival were lower for the 2000–2009 period: 26% versus 32.1% (HR, 0.87; 95% CI, 0.78–0.97; $P = 0.01$), 32.1% versus 38.1% (HR, 0.86; 95% CI, 0.77–0.96; $P = 0.01$), and 21.5% versus 25.3% (HR, 0.89; 95% CI, 0.81–0.99; $P = 0.03$), respectively. Two-year non-relapse mortality was not significantly different (23.8% vs. 23.7%; HR, 0.91; 95% CI, 0.76–1.11; $P = 0.34$).

Conclusions: Outcome of unrelated transplantation for patients with ref/rel AML has improved in the last two decades, rescuing about one third of the patients.

See related commentary by Adrianzen-Herrera and Shastri, p. 4167

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is the treatment of choice for high-risk acute myeloid leukemia (AML; refs. 1–3). As only 25%–30% of patients in need of HSCT have a human leukocyte antigen (HLA) matched sibling donor most of the HSCT currently performed worldwide are from 9–10/10 HLA compatible unrelated donors (UD; refs. 4–5). Results of HSCT for patients with acute leukemia have incrementally improved over the last three decades (6–8). Specifically, in transplanted patients, the continuing improvement in outcomes was attained by changes in supportive care, including better treatment of fungal and viral infections, refinement of

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Translational Relevance

Allogeneic transplantation prolongs disease-free survival and even cures leukemic patients with primary refractory (ref) or relapsed (rel) disease. Results of unrelated allogeneic transplantation for patients with acute leukemia undergoing transplantation while in complete remission have incrementally improved over the last three decades, whereas similar data for ref/rel acute myeloid leukemia are rather limited. Thus, assessing whether transplantation outcome for this patient category improves over time is of major clinical importance. We evaluated outcomes of unrelated transplantation for ref/rel AML, comparing two cohorts according to the year of transplant 2000–2009 and 2010–2019. Study findings indicate that outcome of unrelated transplantation for patients with ref/rel AML has improved in the last two decades, with significantly improved leukemia-free, overall, as well as graft-versus-host disease-free, relapse-free survival, and reduced relapse incidence, rescuing about one third of the patients. Our novel results convey an important clinical message and provide hope to this devastated group of patients.

conditioning regimens and optimization of stem cell harvesting modalities (6–8). The improvement in transplantation outcomes was achieved mostly due to a significant reduction in transplant-related mortality and less so due to reduction in posttransplantation relapse (9–10). Notably, most of these longitudinal studies demonstrating the improvement in transplantation outcomes for AML over time, were performed in leukemic patients undergoing transplantation while in complete remission (CR), whereas data assessing trends in outcome of UD-HSCT in primary refractory/relapsed (ref/rel) AML are rather limited (6–8). Allogeneic transplantation is a treatment modality that can offer prolonged disease-free survival and even cure leukemic patients with ref/rel AML, although results are significantly worse than in patients transplanted in CR. There is therefore a lot of space for improvement (11–13). Knowing whether transplantation outcomes improve over time in patients with ref/rel AML is therefore of major importance. Recently, Bazarbachi and colleagues assessed the outcome of 8,162 adult patients with relapsed AML post HSCT performed in first CR (14). The authors demonstrated that in patients younger than 50 years of age, the 2-year overall survival (OS) rate from relapse improved from 16% in HSCT performed between 2000 and 2004 to 26% for those transplanted between 2015 and 2018 ($P = 0.001$). It was also shown that outcomes after second HSCT, performed within 2 years after relapse in patients <50 years of age improved and reached 30.7% (14). In this study, we focused on patients with rel/ref AML undergoing their first UD-HSCT over the last 2 decades, 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, outcomes, and follow-ups once a year. EBMT minimum essential data forms are submitted to the registry by transplant centers. EBMT centers commit to obtain informed consent according to the local regulations applicable at the time of transplantation to report data to the EBMT. Accuracy of data is assured by the individual transplant centers and by quality control measures such as regular internal and external audits. The results of disease assessments at transplant are also submitted and form the basis of this report. Relapsed/ref adult AML patients (≥18 years of age) who underwent first allogeneic transplantation from 9–10/10 HLA compatible UD with bone marrow (BM) or peripheral blood (PB) stem cell grafts between 2000 and 2019 were included in the study. The HSCT outcomes were compared according to the period of transplant 2000–2009 and 2010–2019, respectively. As previously defined (12, 13), patients who never achieved CR despite induction and salvage chemotherapy were classified as having primary refractory AML, while patients who initially achieved CR (BM blasts ≤5%) and then experienced relapse were classified as having relapsing AML. Cytogenetic risk at diagnosis was categorized according to the 2017 European LeukemiaNet (ELN) recommendations for AML (15). For this study, all necessary data were collected according to the EBMT guidelines, using the EBMT minimum essential data forms following receiving consent forms from the patients from the individual EBMT participating centers and center institutional review board approval. Variables used in the study included recipients' characteristics (age, gender, donor sex, Karnofsky performance score (KPS), cytogenetic risk group at diagnosis), disease status at transplant, year of transplant, conditioning regimen, patient and donor cytomegalovirus serostatus. The list of institutions contributing data to this study is provided in the Supplementary Appendix.

Statistical analysis

The statistical analysis was performed as previously described (16). Median values and interquartile ranges (IQR) were used to describe quantitative variables and frequencies and percentages to describe categorical variables. Patient-, disease-, and transplant-related characteristics were compared between the two periods 2000–2009 and 2010–2019 using the Wilcoxon test for quantitative variables, and the χ^2 or Fisher exact test for categorical variables. The primary outcome was leukemia-free survival (LFS). Other endpoints were cumulative incidence (CI) of neutrophil recovery, non-relapse mortality (NRM), relapse incidence (RI), OS, CI of acute graft-versus-host disease (aGVHD) grade II–IV, aGVHD grade III–IV chronic (c) and extensive cGVHD, and refined GVHD-free, relapse-free survival (GRFS). All endpoints were measured from the time of transplantation. Neutrophil recovery is defined as achieving an absolute neutrophil count 0.5×10^9/L for three consecutive days. OS is defined as time from HSCT to death from any cause. LFS is defined as survival with no evidence of relapse. NRM is defined as death from any cause without evidence of relapse (16). Finally, GRFS is defined as time to first event of grade III–IV acute GVHD, extensive GvHD, relapse or death (16). For all outcomes, in the absence of an event, patients were censored at time of last follow-up. The median follow-up was calculated using the reverse Kaplan–Meier (KM) estimator. The probabilities of OS, LFS, and GRFS were calculated using the KM estimator. The incidence of neutrophil recovery, RI and NRM were calculated using the CI function in a competing risk setting, death being treated as a competing event for RI and neutrophil recovery, and relapse a competing event for NRM. Due to the expected different follow-up periods between the two decades, outcomes were censored at 2 years after transplant. Univariate comparison of outcomes between periods was performed using the log-rank test for LFS, OS, and GRFS, while Gray test was used for CI. In addition, outcomes are demonstrated as unadjusted measures and

evaluated in multivariate models. Multivariable analyses were performed using the Cox proportional-hazards regression model. All variables differing significantly between the two comparison groups, and known or potential risk factors were included in the multivariable models. Results were expressed as the HR with a 95% confidence interval (95% CI). Center differences were taken into account by including a random effect or frailty into each multivariable model (17). All *P* values were two-sided with a type I error rate fixed at 0.05. Statistical analyses were performed with R 4.0.2 (ref. 18; available from: http://www.R-project.org)

Data availability statement

Data were generated by the ALWP of the EBMT and are available on request.

Results

Patient, transplant, and disease characteristics

A total of 3,430 patients met the inclusion criteria, 876 were transplanted in 2000–2009, and 2,554 in 2010–2019. The median follow-up was 8.7 (95% CI, 7.8–9.4) and 3.4 (95% CI, 3.1–3.6) years for patients transplanted in 2000–2009 and in 2010–2019, respectively ($P < 0.001$). **Table 1** shows the baseline demographic and clinical characteristics. Patients transplanted between 2000 and 2009 were younger in comparison with those transplanted between 2010 and 2019; 52 (18–77) and 56 (18–79) years, respectively ($P < 0.001$) and fewer were male; 51% and 56% ($P = 0.01$), respectively. As for disease status at HSCT, the 2000–2009 group had a lower percentage of patients with ref AML, 46% versus 56%, and a higher percentage with rel AML 55% versus 45% ($P < 0.001$), respectively, in comparison to the 2010–2019 group. Cytogenetic risk did not differ between patients transplanted in 2000–2009 versus those transplanted in 2010–2019 (**Table 1**). Donors were 10/10 in 75% versus 76%, and 9/10 HLA matched UD 25% versus 25% of the transplants in both periods ($P = 0.62$), respectively. Graft source differed between the two groups with fewer PB grafts (91% vs. 94%) and more BM grafts (9% vs. 6%) in patients transplanted between 2000–2009 versus those transplanted between 2010 and 2019 ($P < 0.004$), respectively. KPS ≥90 was 53.1% and 59.5% in patients transplanted between 2000–2009 and 2010–2019, respectively ($P = 0.002$). Sixty-three percent and 66%

Table 1. Patient, transplant, and disease characteristics.

Variables	Levels	Total *N* = 3,430	2000–2009 *N* = 876	2010–2019 *N* = 2,554	Test *P* value
Patient age	Median [IQR]	55.18 [43.3–63.3]	52 [38.8–60.4]	56.2 [45.1–64.1]	<0.001
Patient sex	Female	1,566 (45.7)	432 (49.3)	1,134 (44.4)	0.01
	Male	1,863 (54.3)	444 (50.7)	1,419 (55.6)	
	Missing	1	0	1	
Disease status at HSCT	Primary induction failure/Primary refractory	1,816 (52.9)	399 (45.5)	1,417 (55.5)	<0.001
	Relapse	1,614 (47.1)	477 (54.5)	1,137 (44.5)	
Cytogenetics	Good	115 (3.4)	28 (3.2)	87 (3.4)	0.06
	Intermediate	1,071 (31.2)	267 (30.5)	804 (31.5)	
	NA/failed	1,661 (48.4)	454 (51.8)	1,207 (47.3)	
	Poor	583 (17)	127 (14.5)	456 (17.8)	
Type HSCT	UD 10/10	2,582 (75.3)	654 (74.7)	1,928 (75.5)	0.62
	UD 9/10	848 (24.7)	222 (25.3)	626 (24.5)	
Donor age	Median [IQR]	31.33 [25–40]	35.5 [27.7–43.1]	30.2 [24.5–38.4]	<0.001
	Missing	1,802	529	1,273	
Donor sex	Female	949 (29)	245 (29.3)	704 (28.9)	0.84
	Male	2,320 (71)	591 (70.7)	1,729 (71.1)	
	Missing	161	40	121	
Female-to-male donor	No	2,912 (87.2)	749 (87.6)	2,163 (87.1)	0.69
	Yes	427 (12.8)	106 (12.4)	321 (12.9)	
	Missing	91	21	70	
Karnofsky	<90	1,314 (42.1)	364 (46.9)	950 (40.5)	0.002
	≥90	1,806 (57.9)	412 (53.1)	1,394 (59.5)	
	Missing	310	100	210	
CMV patient	Negative	1,164 (34.8)	313 (36.6)	851 (34.2)	0.22
	Positive	2,178 (65.2)	543 (63.4)	1,635 (65.8)	
	Missing	88	20	68	
CMV donor	Negative	1,885 (56.2)	499 (58.3)	1,386 (55.5)	0.16
	Positive	1,467 (43.8)	357 (41.7)	1,110 (44.5)	
	Missing	78	20	58	
CMV donor match	Neg to Neg	902 (27.3)	237 (28)	665 (27.1)	0.29
	Neg to Pos	947 (28.7)	252 (29.8)	695 (28.3)	
	Pos to Neg	251 (7.6)	71 (8.4)	180 (7.3)	
	Pos to Pos	1,199 (36.3)	285 (33.7)	914 (37.2)	
	Missing	131	31	100	
Cell source	BM	229 (6.7)	77 (8.8)	152 (6)	0.004
	PB	3,201 (93.3)	799 (91.2)	2,402 (94)	

Abbreviations: BM, bone marrow; CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplantation; IQR, interquartile ranges; NA, not available; Neg, negative; PB, peripheral blood; Pos, positive; UD, unrelated donor.

Table 2. Conditioning regimens.

Variables	Levels	Total $N = 3,430$	2000–2009 $N = 876$	2010–2019 $N = 2,554$	Test *P* value
Myeloablative regimen	No	1,535 (46.1)	343 (40.3)	1,192 (48.1)	<0.0001
	Yes	1,794 (53.9)	508 (59.7)	1,286 (51.9)	
	Missing	101	25	76	
Conditioning regimen	TBI based	603 (17.7)	230 (26.4)	373 (14.7)	Not done
	BuFlu based	587 (17.2)	104 (11.9)	483 (19)	
	FluMel based	470 (13.8)	99 (11.4)	371 (14.6)	
	BuCy based	368 (10.8)	100 (11.5)	268 (10.6)	
	Flamsa TBI	329 (9.7)	144 (16.5)	185 (7.3)	
	Treo based	263 (7.7)	60 (6.9)	203 (8)	
	Chemo + Flamsa based	230 (6.7)	39 (4.5)	191 (7.5)	
	BuCy + Flamsa based	225 (6.6)	58 (6.7)	167 (6.6)	
	TBF based	181 (5.3)	5 (0.6)	176 (6.9)	
	Other chemo	153 (4.5)	32 (3.7)	121 (4.8)	
	Missing	21	5	16	

Abbreviations: Ara-C, and amsacrine; Bu, busulfan; Cy, cytoxan; Flu, fludarabine; Flamsa, Flu; Mel, melphalan; TBI, total body irradiation; TBF, thiotepa-busulfan-fludarabine; Treo, treosulfan.

($P = 0.22$) of the patients and 42% and 45% ($P = 0.15$) of the donors were CMV seropositive, respectively, with no difference between the groups. **Table 2** shows results for conditioning regimens. The use of myeloablative conditioning was higher in the 2000–2009 transplants versus the 2010–2019 transplants, with 60% and 52% ($P < 0.0001$), respectively, and it was total body irradiation (TBI)-based in a higher percentage of the HSCTs (43% vs. 22%), respectively. The most frequent conditioning regimen was comprising TBI- at 26.4% followed by a FLAMSA [fludarabine (Flu), Ara-C, and amsacrine] + TBI-based regimen at 16.5%. For the 2010–2019 period, the most frequent conditioning regimens were BuFlu-based at 19%, followed by a TBI-based regimen at 14.7% and Flu+ melphalan (Mel)-based regimen at 14.6%. The most frequent anti-GvHD prophylaxis regimen was cyclosporin A (CSA)-based in 43% and 48%, or CSA with mycophenolate mofetil (MMF)-based in 33% and 28%, respectively. Anti-thymocyte globulin (ATG) was used more frequently in transplants performed between 2010 and 2019 in comparison to those performed in the earlier period (74% vs. 80%, $P < 0.001$), respectively. Posttransplant cyclophosphamide (PTCy) was used in 0.4% and 5.1% of the HSCTs, respectively (**Table 3**).

Transplantation outcomes

Day 30 incidence of neutrophil recovery was 90.7% and 91.4% ($P = 0.45$) for patients transplanted between 2000–2009 and 2010–2019, respectively (**Table 4**). Day 100 incidence of aGVHD grades II–IV and III–IV were 25.2% versus 22.6% ($P = 0.17$) and 8.3% versus 9.7% ($P = 0.21$), respectively. Two-year total and extensive cGvHD, 28.7% versus 26% ($P = 0.09$), and 12.3% versus 10.8% ($P = 0.22$), respectively. Two-year RI was higher for patients transplanted in the 2009–2010 period versus those transplanted in 2010–2019 (50.2% vs. 45.1%, $P = 0.01$). Two-year LFS and OS were lower for the 2000–2009 period with 26.0% versus 31.2% ($P = 0.004$) and 32.1% versus 38.1% ($P = 0.001$), respectively. The 2-year NRM was not statistically different between patients transplanted between 2000 and 2009 and those transplanted between 2010 and 2019 with 23.8% versus 23.7% ($P = 0.91$). GRFS at 2 years was also similar in the two periods with 21.5% versus 25.3% ($P = 0.10$), respectively (**Table 4**; **Fig. 1**).

Multivariable analysis

These results are presented in Table 5A and 5B. The risk hazard of RI was higher for patients transplanted in the 2000–2009 period versus

Table 3. GVHD prophylaxis.

Variables	Levels	Total $N = 3,430$	2000–2009 $N = 876$	2010–2019 $N = 2,554$	Test *P* value
GVHD prophylaxis	CSA based	1,587 (46.8)	367 (42.7)	1,220 (48.2)	<0.001
	CSA MMF based	985 (29.1)	286 (33.3)	699 (27.6)	
	CSA MTX based	329 (9.7)	118 (13.7)	211 (8.3)	
	MMF TACRO based	317 (9.4)	54 (6.3)	263 (10.4)	
	Other	171 (5)	35 (4.1)	136 (5.4)	
	Missing	41	16	25	
PTCY	Yes	129 (3.8)	3 (0.4)	126 (5.1)	<0.001
	No	3,222 (96.2)	853 (99.6)	2,369 (94.9)	
	Missing	79	20	59	
ATG	Yes	2,664 (78.6)	637 (74.1)	2,027 (80.2)	<0.001
	No	725 (21.4)	223 (25.9)	502 (19.8)	
	Missing	41	16	25	

Abbreviations: ATG, anti-thymocyte globulin; CSA, cyclosporin A; MMF, mycophenolate mofetil; MTX, methotrexate; PTCY, posttransplant cyclophosphamide; TACRO, tacrolimus.

Table 4. Transplantation outcomes according to transplant period.

Outcomes	Total estimation (IC 95%)	Period 2000–2009	Period 2010–2019	Test *P* value
Median FU (y)[a]	4 (3.8–4.2)	8.7 (7.8–9.4)	3.4 (3.1–3.6)	<0.001
LFS (2 y)[a]	29.8 (28.1–31.5)	26 (22.9–29.1)	31.2 (29.2–33.2)	0.004
OS (2 y)[a]	36.5 (34.8–38.2)	32.1 (28.9–35.3)	38.1 (36–40.1)	0.001
RI (2 y)[b]	46.5 (44.6–48.3)	50.2 (46.7–53.7)	45.1 (43–47.2)	0.01
NRM (2 y)[b]	23.7 (22.2–25.3)	23.8 (20.9– 26.8)	23.7 (21.9–25.5)	0.91
aGVHD-II/IV (100 d)[b]	23.3 (21.7–24.9)	25.2 (22–28.6)	22.6 (20.8–24.5)	0.17
aGVHD-III/IV (100 d)[b]	9.4 (8.4–10.5)	8.3 (6.5–10.5)	9.7 (8.5–11.1)	0.21
Poly recovery (30 d)[b]	91.2 (90.2–92.1)	90.7 (88.6–92.5)	91.4 (90.2–92.4)	0.45
GRFS (2 y)[a]	24.3 (22.7–25.9)	21.5 (18.6–24.5)	25.3 (23.4–27.2)	0.10
cGVHD (2 y)[b]	26.7 (25.1–28.4)	28.7 (25.4–32)	26 (24.1–27.9)	0.09
cGVHD Ext (2 y)[b]	11.2 (10–12.4)	12.3 (10–14.9)	10.8 (9.5–12.2)	0.22

Abbreviations: aGVHD, acute GVHD; cGVHD, chronic GVHD; d, day; Ext, extensive; FU, follow-up; GRFS, GVHD-free, relapse-free survival; LFS, leukemia-free survival; NRM, nonrelapse mortality; OS, overall survival; Poly, polymorphonuclear leukocytes; RI, relapse incidence; y, year.
[a]Log rank test.
[b]Gray test.

those transplanted in 2010–2019 [HR = 0.85; 95% CI, 0.74–0.97, $P = 0.02$]. The risk hazard of LFS (HR, 0.87; 95% CI, 0.78–0.97; $P = 0.01$), OS (HR, 0.86; 95% CI, 0.77–0.96; $P = 0.01$) and GRFS (HR, 0.89; 95% CI, 0.81–0.99; $P = 0.03$) were lower for the 2000–2009 period. There was no significant statistical difference between the periods for the risk hazard of NRM (HR, 0.91; 95% CI, 0.76–1.1; $P = 0.34$), aGVHD II–IV (HR, 0.82; 0.67–1.01; $P = 0.06$), aGVHD III–IV (HR, 1.16; 0.84–1.6; $P = 0.38$) and cGVHD (HR, 0.97; 0.86–1.10; $P = 0.65$). Similar results were observed dividing the study period into shorter intervals (2000–2009; 2010–2014; and 2015–2019; Supplementary Table S1) and for patients with refractory and relapsed AML transplanted in 2000–2009 versus 2010–2019 (Supplementary Table S2). Other significant prognostic factors were poor- compared with good-risk cytogenetics for RI, LFS, OS, aGVHD III–IV and GRFS; rel AML and use of TBI for higher relapse incidence; 9/10 versus 10/10 UD for higher NRM and aGVHD (all grades), and lower LFS, OS and GRFS. A PB stem cell graft was

Table 5A. Multivariable analysis.

Variable	Modalities	LFS HR (95% CI)	*P*	OS HR (95% CI)	*P*	RI HR (95% CI)	*P*	NRM HR (95% CI)	Test *P*
Period HSCT	2000–2009	1		1		1		1	
	2010–2019	0.87 (0.78–0.97)	0.01	0.86 (0.77–0.96)	0.01	0.85 (0.74–0.97)	0.02	0.91 (0.76–1.1)	0.34
Age of patient at transplant (by 10 years)		1.01 (0.98–1.05)	0.46	1.05 (1.01–1.09)	0.01	0.94 (0.9–0.98)	0.006	1.2 (1.12–1.29)	0.001
Female-to-male donor	No	1		1		1		1	
	Yes	0.94 (0.82–1.07)	0.35	0.95 (0.82–1.09)	0.45	0.96 (0.81–1.13)	0.63	0.88 (0.7–1.12)	0.31
Type of HSCT	UD 10/10	1		1		1		1	
	UD 9/10	1.14 (1.03–1.27)	0.01	1.2 (1.08–1.33)	0.001	1.06 (0.93–1.2)	0.4	1.31 (1.1–1.56)	0.002
CMV donor	Negative	1		1		1		1	
	Positive	0.99 (0.9–1.1)	0.92	0.99 (0.89–1.09)	0.8	1.04 (0.93–1.18)	0.49	0.9 (0.76–1.06)	0.21
CMV patient	Negative	1		1		1		1	
	Positive	1.13 (1.02–1.25)	0.02	1.2 (1.07–1.33)	0.001	1.02 (0.9–1.15)	0.81	1.39 (1.16–1.67)	0.001
Cell source	BM	1		1		1		1	
	PB	0.86 (0.72–1.03)	0.09	0.82 (0.69–0.99)	0.04	0.89 (0.71–1.1)	0.28	0.82 (0.6–1.11)	0.2
Myeloablative regimen	No	1		1		1		1	
	Yes	1.1 (0.99–1.23)	0.06	1.1 (0.99–1.22)	0.09	1.09 (0.96–1.24)	0.18	1.13 (0.95–1.35)	0.18
TBI	No	1		1		1		1	
	Yes	1.11 (0.99–1.24)	0.07	1.09 (0.97–1.23)	0.13	1.2 (1.04–1.38)	0.01	0.96 (0.79–1.17)	0.67
Disease status at HSCT	Prim ind fail	1		1		1		1	
	Relapse	1.1 (1–1.21)	0.047	1.06 (0.96–1.17)	0.22	1.21 (1.08–1.36)	0.001	0.91 (0.77–1.07)	0.24
In vivo T-cell depletion	No	1		1		1		1	
	Yes	0.99 (0.87–1.11)	0.81	0.93 (0.82–1.05)	0.25	1.08 (0.93–1.26)	0.31	0.84 (0.69–1.02)	0.08
Cytogenetics	Good	1		1		1		1	
	Interm	1.05 (0.8–1.38)	0.7	0.94 (0.72–1.24)	0.68	1.37 (0.97–1.95)	0.08	0.65 (0.42–1)	0.049
	Poor	1.51 (1.14–1.99)	0.004	1.33 (1.01–1.77)	0.04	1.96 (1.37–2.81)	0.001	0.93 (0.6–1.45)	0.76
	NA/failed	1.18 (0.9–1.54)	0.23	1.14 (0.87–1.49)	0.36	1.49 (1.05–2.11)	0.03	0.77 (0.5–1.17)	0.22

Abbreviations: BM, bone marrow; CMV, cytomegalovirus; HSCT, hematopoietic stem cell transplantation; LFS, leukemia-free survival; NRM, nonrelapse mortality; OS, overall survival; PB, peripheral blood; RI, relapse incidence; TBI, total body irradiation; primary induction failure/primary refractory; UD, unrelated donor; *In vivo* T-cell depletion, anti-thymocyte globulin (ATG).

Table 5B. Multivariable analysis.

Variable	Modalities	aGVHD 2–4 HR (95% CI)	*P*	aGVHD 3–4 HR (95% CI)	*P*	cGVHD HR (95% CI)	*P*	GRFS HR (95% CI)	*P*
Period HSCT	2000–2009	1		1		1		1	
	2010–2019	0.82 (0.67–1.01)	0.06	1.16 (0.84–1.6)	0.38	0.97 (0.86–1.1)	0.65	0.89 (0.81–0.99)	0.03
Age of patient at transplant (by 10 years)		0.95 (0.89–1.02)	0.17	1.04 (0.94–1.16)	0.46	0.99 (0.95–1.03)	0.69	1.02 (0.99–1.06)	0.23
Female-to-male donor	No	1		1		1		1	
	Yes	1.2 (0.96–1.51)	0.11	1.36 (0.98–1.88)	0.07	0.91 (0.78–1.07)	0.25	0.96 (0.85–1.09)	0.53
Type of HSCT	UD 10/10	1		1		1		1	
	UD 9/10	1.19 (0.99–1.43)	0.06	1.52 (1.16–1.99)	0.002	1.08 (0.96–1.21)	0.22	1.13 (1.03–1.25)	0.01
CMV donor	Negative	1		1		1		1	
	Positive	0.92 (0.77–1.09)	0.34	0.85 (0.65–1.11)	0.24	1.02 (0.91–1.14)	0.74	1.01 (0.92–1.1)	0.83
CMV patient	Negative	1		1		1		1	
	Positive	1.12 (0.93–1.34)	0.24	1.23 (0.93–1.62)	0.16	1.14 (1.02–1.28)	0.03	1.1 (1–1.21)	0.049
Cell source	BM	1		1		1		1	
	PB	1.4 (0.97–2.01)	0.07	1.1 (0.64–1.86)	0.74	0.77 (0.63–0.94)	0.01	0.96 (0.81–1.14)	0.64
Myeloablative regimen	No	1		1		1		1	
	Yes	1.05 (0.86–1.28)	0.64	0.94 (0.7–1.25)	0.67	1.11 (0.98–1.25)	0.1	1.04 (0.94–1.14)	0.47
TBI	No	1		1		1		1	
	Yes	1.11 (0.89–1.37)	0.35	1.15 (0.83–1.58)	0.4	1.06 (0.93–1.21)	0.36	1.08 (0.98–1.2)	0.13
Disease status at HSCT	Prim ind fail	1		1		1		1	
	Relapse	0.9 (0.75–1.07)	0.22	0.96 (0.74–1.24)	0.74	0.98 (0.88–1.09)	0.68	1.03 (0.94–1.12)	0.51
In vivo T-cell depletion	No	1		1		1		1	
	Yes	0.72 (0.58–0.89)	0.003	0.64 (0.47–0.87)	0.005	1.05 (0.91–1.2)	0.51	0.85 (0.76–0.95)	0.004
Cytogenetics	Good	1		1		1		1	
	Interm	1.36 (0.84–2.21)	0.21	1.91 (0.83–4.42)	0.13	1.03 (0.77–1.38)	0.85	1.04 (0.81–1.32)	0.78
	Poor	1.59 (0.97–2.62)	0.07	2.41 (1.03–5.64)	0.04	1.18 (0.87–1.6)	0.29	1.44 (1.12–1.86)	0.004
	NA/failed	0.46 (0.27–0.77)	0.003	0.51 (0.21–1.24)	0.14	1.19 (0.89–1.6)	0.24	1.05 (0.82–1.33)	0.71

Abbreviations: aGVHD, acute GVHD; cGVHD, chronic GVHD; CMV, cytomegalovirus; BM, bone marrow; GRFS, GVHD-free, relapse-free survival; PB, peripheral blood; TBI, total body irradiation; UD, unrelated donor; primary induction failure/primary refractory; *In vivo* T-cell depletion, anti-thymocyte globulin (ATG).

associated with a lower incidence of cGVHD and OS and *in vivo* T-cell depletion with lower incidence of all grades aGVHD and better GRFS. Patient CMV seropositivity was a prognostic factor for higher NRM and lower LFS and OS. We did not observe a center effect.

Cause of death

A total of 643 (73.4%) patients in the 2000–2009 cohort and 1,597 (62.5%) patients in the 2010–2019 cohort died during the study period. Original disease was the main cause of death being 51.8% and 51.1% of the deaths in 2000–2009 versus 2010–2019, respectively. Transplant-related deaths accounted for 16.6% and 13.4% of the deaths, respectively. GvHD accounted for 11.4% versus 12.9%, while infections were the cause of death in 9.8% versus 15.3%, respectively. Other causes accounted for 9.5% and 6.1% of deaths, respectively, and approximately 1% of deaths in both periods was due to secondary malignancies. Cause of death was missing for 12 (1.9%) and 43 (2.7%) patients, respectively.

Discussion

Relapse and primary refractoriness are the major limitations in AML treatment (13, 15, 19–21). The prognosis in primary refractory and relapsed AML is generally poor and depends mainly on the possibility of HSCT (19–22). A quite recent analysis by the Center for International Blood and Marrow Transplant Research (CIBMTR) showed that of 1,788 patients with AML relapsing after allografts, survival at 1 year after relapse was only 23% (23). Overall, HSCT results in this group of patients are not satisfactory and need improvement (11, 19–23). Transplantation results have improved over the years, but this has been due mainly to a reduction in NRM and organ toxicity and less to a reduction in posttransplantation relapse (6–10). This improvement in transplantation outcomes was therefore applicable mainly to patients with AML transplanted while in CR and less so for those with ref/rel disease. As HSCT is currently still the best therapeutic option for patients with ref/rel AML, demonstrating improvement in transplantation outcomes in this patient category is of major importance and will help in patient consultations. In the current study, comparing outcome of HSCTs from UD 10/10 and UD 9/10 in patients with ref/rel AML undergoing transplantation in 2000–2009 versus 2010–2019, we were able to show significant improvement in transplantation outcomes with reduction in RI from 50% to 45%, increase in OS from 32% to 38%, and in LFS from 26% to 32%. Of note, transplantation was able to rescue about one third of the patients with rel/ref AML. Nonrelapse mortality was reasonable at about 24% at 2 years.

These results are concordant with previous literature. A similar study from the EBMT included 168 patients with ref AML who underwent UD transplantation between 1994 and 2006. The 5-year OS for the whole group was 22% (24). The CIBMTR analyzed 1,673 patients with AML not in remission at the time of conditioning and reported a 3-year OS ranging from 6% to 42% with HSCT from donors other than siblings being a poor prognostic factor (25). In a subsequent study the Gruppo Italiano Trapianto Di Midollo Osseo (GITMO) analyzed 523 patients undergoing transplantation while not in remission and reported a 3-year OS of 18%–40% (26). More recently, Brissot and colleagues assessed the results of HSCT from 9–10/10 HLA compatible UD donors performed between 2007 and 2014 in patients with ref AML and reported a 2-year OS of 35% and LFS of 28% (12).

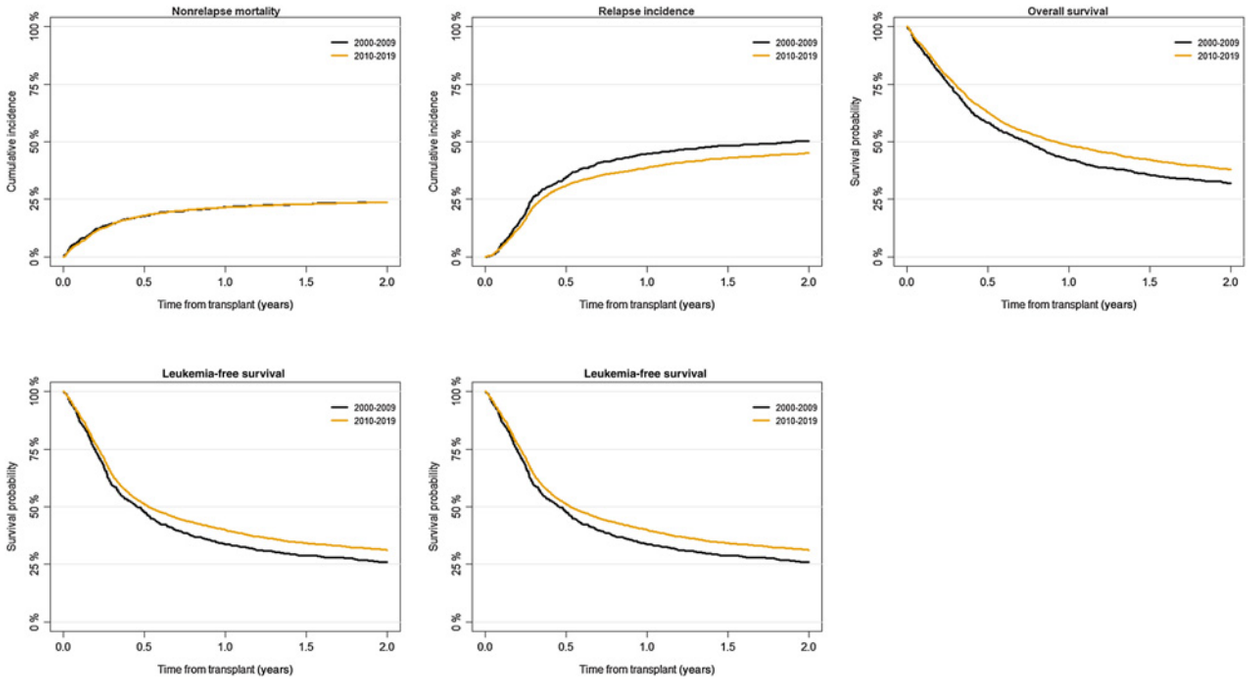

Figure 1.

Results of unrelated transplantation in patients with relapsed/refractory AML, comparing outcomes of two cohorts according to the period of transplant (2000–2009 and 2010–2019); 2-year nonrelapse mortality (NRM); relapse incidence (RI); overall survival (OS); leukemia-free survival (LFS); and GvHD-free, relapse-free survival (GRFS).

Poiani and colleagues looked at transplantation outcome in patients with rel/ref AML transplanted from HLA-matched siblings or UD between 2000 and 2017 demonstrating a 2-year OS of 30%, LFS of 25%, and GRFS of 18% (13). Finally, the East German Study Group Hematology and Oncology (OSHO) analyzed 1,621 patients with AML from two prospective clinical trials (AML02, $n = 740$ and AML04, $n = 881$) and reported that OS after HSCT was 39.3% (31.8–48.6) at 5 years (27).

The 10% or so reduction in the post HSCT relapse rate we observed in the HSCTs performed for ref/rel AML in more recent years is encouraging. Our current findings agree with a recent publication from the EBMT that assessed 8,162 adult patients below 50 years of age with AML who relapsed after HSCT between 2000 and 2018. The study demonstrated continuous improvement in the 2-year OS rate from relapse, increasing from 16% between 2000 and 2004, to 18% for 2005–2009, to 21% for 2010–2014, and to 26% for 2015–2018 ($P = 0.001$; ref. 14). The significant reduction in RI that we observed in transplants performed in 2010–2019 versus 2000–2009 may be attributed to changes in transplant technique and more frequent use of prevention strategies including prophylactic or preemptive donor lymphocyte infusions or by pharmacologic means (21, 22, and 28). Notably, despite the significant improvement in transplantation outcomes in the more recent period, the RI remains high, being 45% at 2 years. It is conceivable that with the use of hypomethylating agents like azacitidine and decitabine and targeted therapies such as tyrosine kinase inhibitors (TKI; sorafenib, midostaurin, gilteritinib, and quizartinib) and the new AML treatment landscape comprising the recently approved novel compounds like venetoclax or Vyxeos (CPX-351), posttransplant RI will be reduced even further in the future (28–30).

The additional prognostic factors we observed for predicting transplantation outcome in rel/ref AML including poor cytogenetics, increasing age, and transplantation from mismatched UD were observed in previous publications and are part of the CIBMTR published predictive score for transplantation in AML patients not in remission (24–26, 12–13). Similarly, patient CMV seropositivity is an additional known poor prognostic factor for outcome of HSCT in ref AML patients (24). Likewise, the currently observed prognostic factors for lower incidence of GVHD including T-cell depletion and PTCy, and the higher GVHD incidence with mismatched UD are all well-known prognostic factors for GvHD (31, 32).

As this was a retrospective and transplantation registry-based study, the analysis suffers from several limitations including unavailability of data, such as first-line therapies, molecular versus hematologic relapses or percentage of blasts as well as comorbidity index risk score and the use of use of donor lymphocyte infusions. Furthermore, as cytogentic risk data is missing for about 50% of study patients, although unlikely, we cannot absolutely exclude the possibility that the outcome differences, we observed are not due to disproportionate distribution of high-risk patients in the 2000–2009 cohort. Nevertheless, based on this relatively large registry-based, retrospective analysis we conclude that the outcome of UD-HSCT for patients with ref/rel AML has improved over the last two decades. The procedure allows for rescuing about one third of the patients. With the recently approved novel agents, it may be possible to further reduce posttransplantation RI and improve HSCT results in rel/ref AML.

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Authors' Contributions

A. Nagler: Conceptualization, investigation, writing–original draft, writing–review and editing. **M. Ngoya:** Conceptualization, formal analysis, investigation, writing–review and editing. **J.-E. Galimard:** Conceptualization, formal analysis, writing–review and editing. **M. Labopin:** Conceptualization, formal analysis, investigation, writing–review and editing. **M. Bornhäuser:** Resources, writing–review and editing. **M. Stelljes:** Resources, writing–review and editing. **J. Finke:** Resources, writing–review and editing. **A. Ganser:** Resources, writing–review and editing. **H. Einsele:** Resources, writing–review and editing. **N. Kröger:** Resources, writing–review and editing. **A. Brecht:** Resources, writing–review and editing. **W. Bethge:** Resources, writing–review and editing. **M. Edinger:** Resources, writing–review and editing. **A. Kulagin:** Resources, writing–review and editing. **J. Passweg:** Resources, writing–review and editing. **I.W. Blau:** Resources, writing–review and editing. **A. Elmaagacli:** Resources, writing–review and editing. **K. Schäfer-Eckart:** Resources, writing–review and editing. **U. Platzbecker:** Resources, writing–review and editing. **T. Schroeder:** Resources, writing–review and editing. **D. Bunjes:** Resources, writing–review and editing. **J. Tischer:** Resources, writing–review and editing. **S. Martin:** Resources, writing–review and editing. **A. Spyridonidis:** Resources, writing–review and editing. **S. Giebel:** Resources, writing–review and editing. **B. Savani:** Resources, writing–review and editing. **M. Mohty:** Resources, writing–review and editing.

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Note

Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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