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RESEARCH ARTICLE

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Human leukocyte antigen-haploidentical transplantation for relapsed/refractory acute myeloid leukemia: Better leukemia-free survival with bone marrow than with peripheral blood stem cells in patients ≥55 years of age

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Abstract

The best stem cell source for T-cell replete human leukocyte antigen (HLA)-haploidentical transplantation with post-transplant cyclophosphamide (PTCy) remains to be determined. In this European Society for Blood and Marrow Transplantation retrospective study, we analyzed the impact of stem cell source on leukemia-free survival (LFS) in adult patients with primary refractory or relapsed acute myeloid leukemia (AML) given grafts from HLA-haploidentical donors with PTCy as graft-versus-host disease (GVHD) prophylaxis. A total of 668 patients (249 bone marrow [BM] and 419 peripheral blood stem cells [PBSC] recipients) met the inclusion criteria. The use of PBSC was associated with a higher incidence of grade II–IV (HR = 1.59,

$p = .029$) and grade III–IV (HR = 2.08, $p = .013$) acute GVHD. There was a statistical interaction between patient age and the impact of stem cell source for LFS ($p < .01$). In multivariate Cox models, among patients <55 years, the use of PBSC versus BM resulted in comparable LFS (HR = 0.82, $p = .2$). In contrast, in patients ≥55 years of age, the use of PBSC versus BM was associated with higher non-relapse mortality (NRM) (HR = 1.7, $p = .01$), lower LFS (HR = 1.37, $p = .026$) and lower overall survival (HR = 1.33, $p = .044$). In conclusions, our data suggest that in patients ≥55 years of age with active AML at HLA-haploidentical transplantation, the use of BM instead of PBSC as stem cell source results in lower NRM and better LFS. In contrast among younger patients, the use of PBSC results in at least a comparable LFS.

1 | INTRODUCTION

Despite recent advances in the field,[1] allogeneic hematopoietic stem cell transplantation (allo-HCT) has remained the best treatment option for fit patients with primary refractory or relapsed acute myeloid leukemia (AML).[2–4] This treatment option relies largely on immune-mediated graft-versus-leukemia (GVL) effects to eradicate leukemic cells resistant to chemotherapy.[5] Consequently, one could hypothesize that selecting transplantation approaches providing the highest GVL activity might be particularly suited for relapsed/refractory AML patients.

Human leukocyte antigen (HLA)-haploidentical hematopoietic cell transplantation (Haplo-HCT) is frequently used as treatment for relapsed/refractory AML patients who lack an HLA-identical sibling donor. While post-transplant cyclophosphamide (PTCy) has revolutionized the Haplo-HCT field,[6–11] the best stem cell source (bone marrow [BM] or peripheral blood stem cells [PBSC]) for Haplo-HCT with PTCy as graft-versus-host disease (GVHD) prophylaxis has remained under debate. Ruggeri et al. found similar outcomes (besides higher incidence of acute GVHD in PBSC patients) with both stem cell sources.[12] In contrast, a large retrospective study from the Center for International Blood and Marrow Transplant Research observed a higher relapse risk with BM than with PBSC.[13] This finding suggests that the use of PBSC might be the optimal stem cell source for Haplo-HCT in patients with active AML at transplantation. Here, we challenged this hypothesis and compared outcomes of Haplo-HCT with BM versus Haplo-HCT with PBSC, in a large cohort of patients with active AML at transplantation.

2 | PATIENTS AND METHODS

2.1 | Study design and inclusion criteria

This study reports the results of a multicenter retrospective analysis using the data set of the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (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. The EBMT Med A/B standardized data collection forms are submitted to the registry by transplant center personnel following written informed consent from patients in accordance with center ethical research guidelines. 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 transplantation were also submitted and form the basis of this report.

Inclusion criteria included adult patients (defined as ≥18 years of age at transplantation), first allogeneic Haplo-HCT between 2010 and 2020 using PTCy as GVHD prophylaxis, primary refractory or relapsed AML (i.e., all patients had active disease at the time of transplant conditioning initiation), and no in vivo T-cell depletion. The primary endpoint was leukemia-free survival (LFS).

2.2 | Ethics

The scientific board of the ALWP of the EBMT approved this research project. The study was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines.

2.3 | Definitions

Reduced intensity conditioning was defined as regimens combining fludarabine with either <6 Gy total body irradiation (TBI), ≤8 mg/kg busulfan, or ≤140 mg/m^2 melphalan or with other nonmyeloablative drugs as previously reported.[10,11] Acute and chronic GVHD were graded according to previously reported criteria.[12] Comorbidities at transplantation were determined using the hematopoietic cell transplantation-specific comorbidity-index (HCT-CI) score.[14] Cytogenetic risk was stratified according to the MRC-UK classification, as previously reported.[15,16]

2.4 | Statistical analyses

All patients meeting the inclusion criteria were included in the study. Start time was the day of allo-HCT for all endpoints. Patients were

censored at the time of last follow-up. Primary endpoint was LFS. Relapse incidence was defined as the time to first documentation of active disease (i.e., presence of 5% BM and/or reappearance of the underlying disease) after transplantation.[17] Non-relapse mortality (NRM) was defined as death without evidence of relapse or progression. Overall survival (OS) was defined as the time from allo-HCT to death, regardless of the cause. Events in the LFS endpoint included relapse (as defined above) and death, whichever occurred first. Events in the composite endpoint GVHD-free and relapse-free survival (GRFS) included grade III-IV acute GVHD, severe chronic GVHD, relapse and death, whichever occurred first.[18,19] Engraftment was defined as absolute neutrophil count ≥500/mm^3 achieved for three consecutive laboratory values. The Kaplan–Meier method was used to estimate probabilities of LFS, GRFS, and OS.[20]

Cumulative incidence functions were used to estimate relapse incidence and NRM in a competing risk setting. Relapse and death were treated as competing events for analyses assessing cumulative incidences of acute and chronic GVHD. Death was the competing event for engraftment.

Comparison between the two groups were performed using cause-specific Cox models. Results were expressed as the hazard ratio (HR) with the 95% confidence interval (95% CI). We checked the interaction between the main effect and the other significant covariates. As we found a qualitative interaction between source of stem cells and patient age less or more than 55 years, we run the analyses separately in the two age groups. All tests were two sided with the type I error rate fixed at 0.05 for the determination of factors associated with time-to-event outcomes. Statistical analyses were performed with SPSS 26.0 (SPSS Inc), R 4.0.1 (R Core Team [2019]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/).

3 | RESULTS

3.1 | Patients

A total of 668 patients (249 BM and 419 PBSC recipients) met the inclusion criteria (Table S1). This included 380 patients with primary refractory AML, 229 in first relapse and 59 in second or more advanced relapse at transplantation. Median follow-up was 36 months. Median age at transplantation was 57 years (interquartile range, 45–64 years).

3.2 | Engraftment & GVHD

The 60-day incidence of neutrophil engraftment was 88% in BM versus 89% in PBSC recipients ($p = .06$) (Figure S1A).

The 180-day cumulative incidences of grade II-IV and grade III-IV acute GVHD were 18% and 7%, respectively, in BM recipients, versus 32% ($p = .001$) and 14% ($p = .004$), respectively, in PBSC recipients (Figure S1B,C). In multivariate analysis, the use of PBSC was associated with a higher incidence of grade II-IV (HR = 1.59, 95% CI: 1.05–2.41, $p = .029$) and grade III-IV (HR = 2.08, 95% CI: 1.17–3.70, $p = .013$) acute GVHD.

The 2-year cumulative incidences of chronic and extensive chronic GVHD were 20% and 9%, respectively, in BM recipients, versus 24% ($p = .36$) and 12% ($p = .09$), respectively, in PBSC recipients (Figure S1D). In multivariate analysis, PBSC was not significantly associated with higher risks of chronic (HR = 1.34, 95% CI: 0.89–2.01, $p = .16$) nor extensive chronic (HR = 1.57, 95% CI: 0.85–2.91, $p = .15$) GVHD.

3.3 | Relapse, NRM, LFS, OS, GRFS

Relapse, NRM, LFS, OS, and GRFS were not significantly impacted by stem cell source in the whole cohort (Table S2). However, there was a statistical interaction between patient age and stem cell source for LFS (the primary endpoint); $p < .01$ for age < or ≥55 years). No other significant interactions between the variable of interest (stem cell source) and other covariates were present for the LFS endpoint. In particular, there was no interaction between conditioning and stem cell source for LFS. The analyses for relapse incidence, NRM, LFS, OS, and GRFS were thus performed separately for patients < or ≥55 years of age.

3.4 | BM versus PBSC in patients <55 years of age

3.4.1 | Patients

This subgroup included 301 patients. In comparison to BM recipients ($n = 114$), PBSC patients ($n = 187$) were transplanted more recently (median year 2017 vs. 2015, $p < .0001$). Median patient age was 44 years in BM recipients versus 43 years in PBSC recipients ($p = .19$). There was no difference in distribution of disease status ($p = .94$), the proportion of patients with primary refractory AML was 53% and 54% in BM versus PBSC patients, respectively (Table 1).

3.4.2 | GVHD

The 180-day cumulative incidences of grade II–IV and grade III–IV acute GVHD were 19% and 7%, respectively, in BM recipients, versus 34% ($p = .003$) and 12% ($p = .12$), respectively, in PBSC recipients. The 2-year cumulative incidences of chronic and extensive chronic GVHD were 21% and 7%, respectively, in BM recipients, versus 28% ($p = .19$) and 12.5% ($p = .07$), respectively, in PBSC recipients.

3.4.3 | Relapse and NRM

Two-year cumulative incidences of relapse and NRM were 58% and 17%, respectively, in BM recipients, versus 50% ($p = .29$) and 16% ($p = .88$), respectively, in PBSC recipients (Figure 1). Factors associated with relapse incidence in multivariate analysis included adverse

TABLE 1 Patient characteristics among patients <55 years of age at transplantation

		BM ($n = 114$)	PB ($n = 187$)	p
Follow-up (mo)	Median (95% CI)	43.2 (21–6.8)	35.0 (26.3–41.0)	.16
Year transplant	Median (min–max)	2015 (2010–2020)	2017 (2010–2020)	<.0001
Patient age (years)	Median (min–max) [IQR]	44.4 (18.2–54.8) [33.1–50.6]	42.7 (18.1–54.7) [32.4–48.7]	.19
Status at transplantation	P refr.	60 (52.6%)	101 (54%)	.94
	Rel1	41 (36%)	67 (35.8%)	
	Rel2+	13 (11.4%)	19 (10.2%)	
Cytogenetics	Intermediate	42 (61.8%)	94 (64.8%)	.66
	Poor	26 (38.2%)	51 (35.2%)	
	NA/failed	46	42	
FLT3	FLT3-wt	34 (69.4%)	62 (62.6%)	.42
	FLT3-ITD	15 (30.6%)	37 (37.4%)	
	Missing	65	88	
NPM1	NPM1 absent	37 (82.2%)	61 (66.3%)	.052
	NPM1 present	8 (17.8%)	31 (33.7%)	
	Missing	69	95	
Karnofsky score	<90	52 (45.6%)	72 (38.5%)	.22
	≥90	62 (54.4%)	115 (61.5%)	
HCT-CI	HT-CI = 0	36 (53.7%)	70 (53%)	.84
	HT-CI = 1 or 2	16 (23.9%)	36 (27.3%)	
	HT-CI ≥ 3	15 (22.4%)	26 (19.7%)	
	Missing	47	55	
Patient sex	Male/female	62 (54.4%)/52 (45.6%)	100 (53.5%)/87 (46.5%)	.88
Donor sex	Male/female	72 (63.2%)/42 (36.8%)	94 (50.5%)/92 (49.5%)	.033
Female to male	F->M	25 (21.9%)	49 (26.2%)	.40
Patient CMV	Pat. CMV neg.	23 (20.2%)	44 (23.8%)	.47
	Pat. CMV pos	91 (79.8%)	141 (76.2%)	
	Missing	0	2	
Donor CMV	Don. CMV neg.	39 (34.5%)	60 (32.8%)	.76
	Don. CMV pos	74 (65.5%)	123 (67.2%)	
	Missing	1	4	
Conditioning	MAC	65 (57.5%)	127 (67.9%)	.069
	RIC	48 (42.5%)	60 (32.1%)	
	Missing	1	0	
TBI	Chemotherapy	83 (73.5%)	157 (84%)	
	TBI	30 (26.5%)	30 (16%)	
	Missing	1	0	
CD34+ infused (10e6/kg)	Median (min–max) [IQR]	2.8 (1.1–10.1) [1.9–4.1]	7 (2.4–12.6) [5.1–8.6]	<.0001
	Missing	81	118	

Abbreviations: BM, bone marrow; CMV, cytomegalovirus; FLT3-ITD, FLT3 internal tandem duplication; FLT3-wt, Fms-like tyrosine kinase 3 (FLT3) wild type; HCT-CI, hematopoietic cell transplant-specific comorbidity index; MAC, myeloablative conditioning; mo, months; NA, not applicable; neg, negative; NPMI, nucleophosmin; P refr, primary refractory; PBSC, peripheral blood stem cells; pos, positive; Rel1, first relapse; Rel2+, second or more advanced relapse; RIC, reduced-intensity conditioning; TBI, total body irradiation.

cytogenetics (HR = 1.65, 95% CI: 1.15–2.36; $p = .006$) and year of transplantation (HR = 0.93, 95% CI: 0.87–0.99; $p = .032$) (Table S3). Factors associated with NRM in multivariate analysis included older age at transplantation (per 10 years, HR = 1.65, 95% CI: 1.14–2.38; $p = .007$) while a Karnofsky performance score ≥90 at transplantation was associated with lower NRM (HR = 0.42, 95% CI: 0.22–0.81; $p = .01$). Interestingly, neither conditioning intensity nor the use of TBI were significantly associated with relapse or NRM.

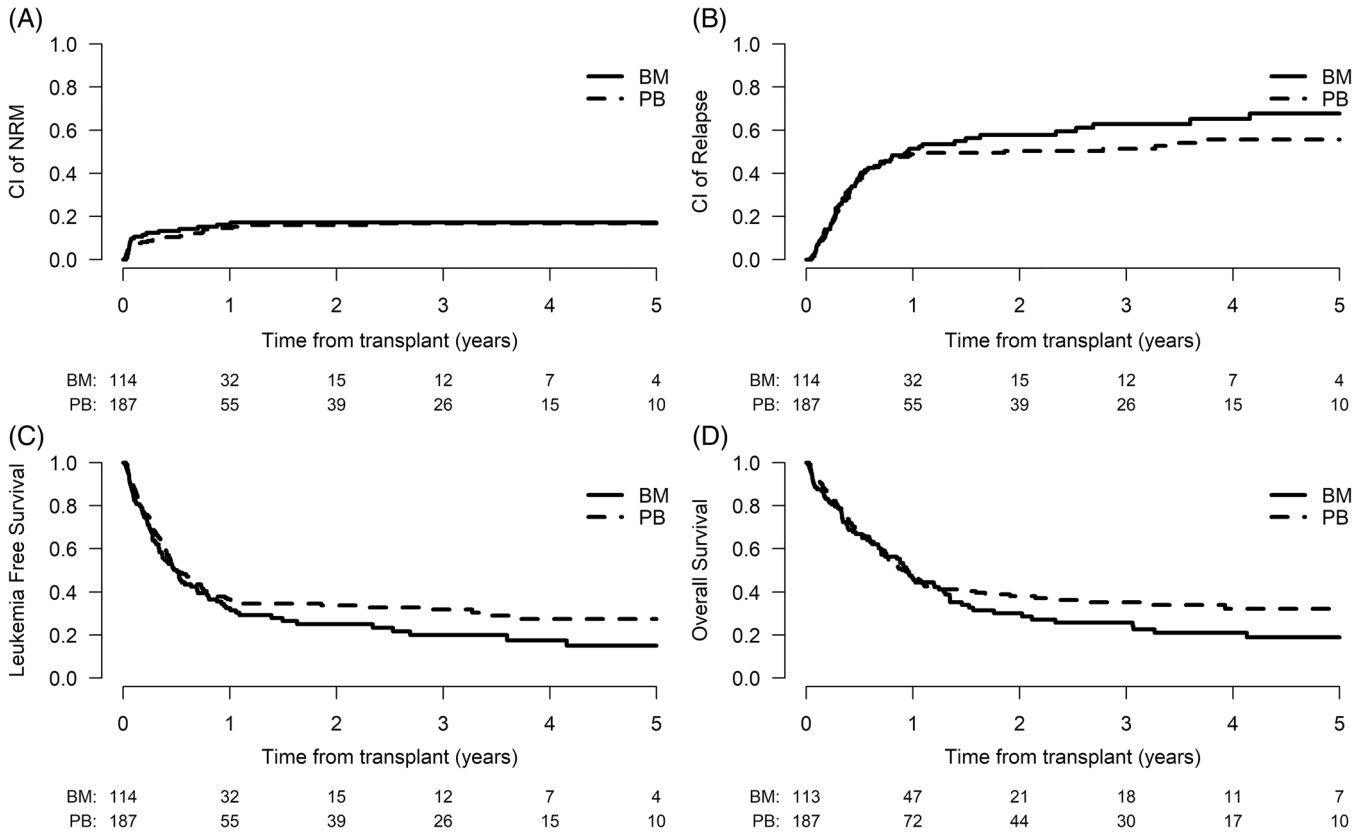

FIGURE 1 Hematopoietic cell transplantation outcomes in patients <55 years old at transplantation. (A) Cumulative incidence of non-relapse mortality. (B) Cumulative incidence of relapse. (C) Leukemia-free survival. (D) Overall survival

3.4.4 | LFS, OS, and GRFS

Two-year LFS and OS were 25% and 30%, respectively, in BM recipients, versus 34% ($p = .17$) and 38% ($p = .21$) in PBSC recipients (Figure 1). The only factor associated with LFS in multivariate analysis was adverse cytogenetics (HR = 1.44, 95% CI: 1.03–2.02; $p = .034$) while adverse cytogenetics (HR = 1.48, 95% CI: 1.04–2.11; $p = .03$) and older age at transplantation (per 10 years, HR = 1.21, 95% CI: 1.03–1.41; $p = .018$) were associated with OS (Table S3). Causes of death were comparable between the groups with the exception of higher mortality due to GVHD in the PBSC group (8.2% vs. 2.5%) (Table S4).

Two-year GRFS was 22% in BM patients versus 24% in PBSC recipients. No factors were associated with GRFS in multivariate analyses (Table S3).

3.5 | BM versus PBSC in patients ≥55 years of age

3.5.1 | Patients

This subgroup comprised 367 patients. In comparison to BM recipients ($n = 135$), PBSC patients ($n = 232$) were transplanted more recently (median year of transplantation 2018 vs. 2017, $p = .0002$) (Table 2). Median patient age was 64 years in BM recipients versus 63 years in PBSC recipients ($p = .30$). The proportion of patients with primary refractory AML was 56% and 62% in BM versus PBSC patients, respectively ($p = .60$).

3.5.2 | GVHD

The 180-day cumulative incidences of grade II–IV and grade III–IV acute GVHD were 16% and 6%, respectively, in BM recipients, versus 30% ($p = .005$) and 15% ($p = .015$), respectively, in PBSC recipients. The 2-year cumulative incidences of chronic and extensive chronic GVHD were 20% and 10%, respectively, in BM recipients, versus 22% ($p = 1$) and 12% ($p = .5$), respectively, in PBSC recipients.

3.5.3 | Relapse and NRM

Two-year cumulative incidences of relapse and NRM were 36% and 30%, respectively, in BM recipients, versus 40% ($p = .36$) and 34% ($p = .11$), respectively, in PBSC recipients (Figure 2). Adverse cytogenetics (HR = 2.51, 95% CI: 1.71–3.69; $p < .0001$) and TBI-based conditioning (HR = 2.01, 95% CI: 1.31–3.15; $p = .002$) were associated with higher relapse incidence in multivariate analysis while older age at transplantation (HR = 0.67, 95% CI: 0.46–0.98; $p = .037$) was

TABLE 2 Patient characteristics among patients ≥55 years of age at transplantation

		BM ($n = 135$)	PB ($n = 232$)	p
Follow-up (mo)	Median (95% CI)	39.3 (28.5–57.0)	29.5 (25.1–47.8)	.29
Year transplant	Median (min–max)	2017 (2010–2020)	2018 (2010–2020)	.0002
Patient age (years)	Median (min–max) [IQR]	64 (55.3–74.3) [59.7–68.1]	62.8 (55–78.8) [59.8–67.4]	.30
Status at transplantation	P refr.	76 (56.3%)	143 (61.6%)	.60
	Rel1	48 (35.6%)	73 (31.5%)	
	Rel2+	11 (8.1%)	16 (6.9%)	
Cytogenetics	Intermediate	76 (74.5%)	128 (66.7%)	.17
	Poor	26 (25.5%)	64 (33.3%)	
	NA/failed	33	40	
FLT3	FLT3-wt	43 (72.9%)	86 (76.8%)	.57
	FLT3-ITD	16 (27.1%)	26 (23.2%)	
	Missing	76	120	
NPM1	NPM1 absent	34 (60.7%)	83 (75.5%)	.049
	NPM1 present	22 (39.3%)	27 (24.5%)	
	Missing	79	122	
Karnofsky score	<90	68 (50.4%)	108 (46.6%)	.48
	≥90	67 (49.6%)	124 (53.4%)	
HCT-CI	HT-CI = 0	43 (48.9%)	72 (40.4%)	.21
	HT-CI = 1 or 2	20 (22.7%)	36 (20.2%)	
	HT-CI ≥ 3	25 (28.4%)	70 (39.3%)	
	Missing	47	54	
Patient sex	Male/female	82 (61.2%)/52 (38.8%)	137 (59.1%)/95 (40.9%)	.69
Donor sex	Male/female	89 (66.4%)/45 (33.6%)	154 (66.4%)/45 (33.6%)	.99
Female to male	F->M	24 (18%)	44 (19%)	.83
Patient CMV	Neg.	25 (18.8%)	55 (24.2%)	.23
	Pos	108 (81.2%)	172 (75.8%)	
	Missing	2	5	
Donor CMV	Neg.	65 (49.2%)	102 (45.3%)	.47
	Pos	67 (50.8%)	123 (54.7%)	
	Missing	3	7	
Conditioning	MAC	42 (31.1%)	71 (30.7%)	.94
	RIC	93 (68.9%)	160 (69.3%)	
	Missing	0	1	
TBI	Chemotherapy	118 (87.4%)	190 (82.3%)	.19
	TBI	17 (12.6%)	41 (17.7%)	
	Missing			
CD34+ infused (10e6/kg)	Median (min–max) [IQR]	3.2 (1.2–8.2) [2.6–4.6]	6.3 (2.3–17.2) [5–8]	<.0001
	Missing	95	143	

Abbreviations: BM, bone marrow; CMV, cytomegalovirus; FLT3-ITD, FLT3 internal tandem duplication; FLT3-wt, Fms-like tyrosine kinase 3 (FLT3) wild type; HCT-CI, hematopoietic cell transplant-specific comorbidity index; MAC, myeloablative conditioning; mo, months; NA, not applicable; neg, negative; NPMI, nucleophosmin; P refr, primary refractory; PBSC, peripheral blood stem cells; pos, positive; Rel1, first relapse; Rel2+, second or more advanced relapse; RIC, reduced-intensity conditioning; TBI, total body irradiation.

associated with lower relapse incidence. Factors associated with higher NRM in multivariate analysis included PBSC as stem cell source (HR = 1.7, 95% CI: 1.14–2.54; $p = .01$) and older age (per 10 years) at transplantation (HR = 2.06, 95% CI: 1.39–3.04; $p = .0003$) (Table S5). Interestingly, conditioning intensity (RIC vs. MAC) was not significantly associated with relapse or NRM.

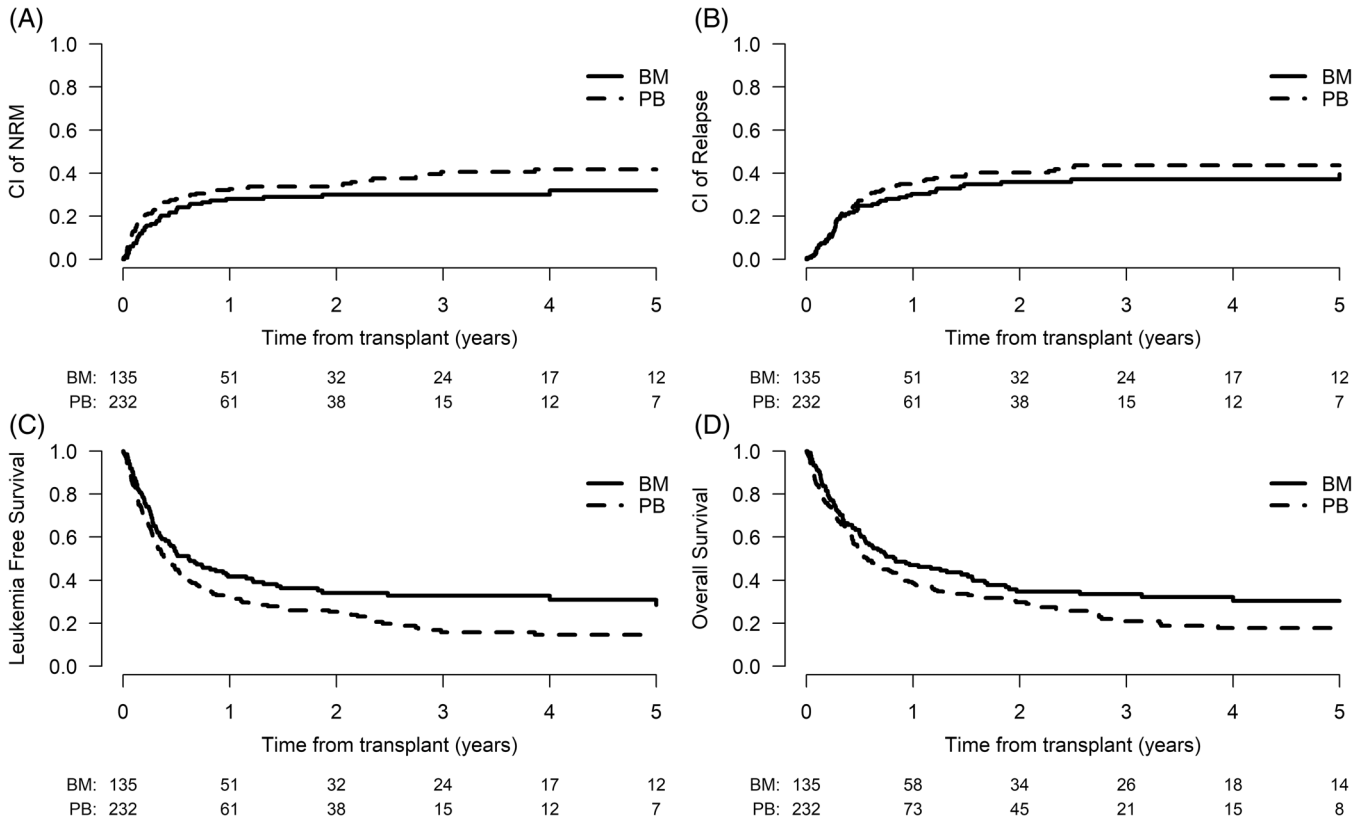

FIGURE 2 Hematopoietic cell transplantation outcomes in patients ≥55 years old at transplantation. (A) Cumulative incidence of non-relapse mortality. (B) Cumulative incidence of relapse. (C) Leukemia-free survival. (D) Overall survival

3.5.4 | LFS, OS, and GRFS

Two-year LFS and OS were 34% and 35%, respectively, in BM recipients, versus 25% ($p = .01$) and 30% ($p = .035$), respectively, in PBSC recipients (Figure 2). Two-year GRFS was 29% in BM patients versus 19% in PBSC recipients ($p = .002$). As observed in the whole study group, there was no significant interaction between conditioning intensity and stem cell source for LFS ($p = .49$). In multivariate analyses (Table S5), PBSC as the graft source was associated with lower LFS (HR = 1.37, 95% CI: 1.04–1.8; $p = .026$), lower OS (HR = 1.33, 95% CI: 1.01–1.76; $p = .044$) and lower GRFS (HR = 1.43, 95% CI: 1.1–1.86; $p = .008$). This was also the case for adverse cytogenetics (LFS: HR = 1.55, 95% CI: 1.16–2.06; $p = .003$; and OS: HR = 1.44, 95% CI: 1.08–1.93; $p = .014$). In contrast, a Karnofsky performance score ≥90% was associated with better LFS (HR = 0.74, 95% CI: 0.58–0.95; $p = .02$) and OS (HR = 0.73, 95% CI: 0.56–0.94; $p = .016$).

Causes of death were comparable between the groups (Table S6).

4 | DISCUSSION

Allo-HCT is the best treatment option for fit patients with primary refractory or relapsed AML. This approach relies mainly on immune-mediated GVL effects for tumor eradication.[21,22] Several studies have assessed the impact of stem cell source (BM vs. PBSC) on allo-HCT outcomes.[23–25] In an individual-patient data meta-analysis using data from nine randomized trials including a total of 1111 adult patients given grafts from HLA-identical sibling after myeloablative conditioning, the use of PBSC versus BM was associated with a higher incidence of grade III-IV acute GVHD, higher incidence of chronic GVHD, and lower relapse incidence.[23] This translated to better LFS and OS in the subgroup of patients with advanced disease at transplantation.[23] In a large phase III trial of 551 patients given grafts from unrelated donors mainly after myeloablative conditioning, the use of PBSC was associated with a higher incidence of chronic GVHD leading to worse quality of live without reducing the relapse rate, thus not improving OS or LFS.[24,26] Finally, in a large retrospective study focusing on patients given grafts after reduced-intensity conditioning ($n = 9848$), the use of PBSC versus BM was associated with lower relapse incidence translating to better LFS and OS.[25]

Haplo-HCT is increasingly used in patients with active AML at transplantation.[27] While PTCy is highly efficient at preventing GVHD it also has a strong impact on immune reconstitution after transplantation by rendering alloreactive T-cells functionally impaired.[28,29] It is thus unclear whether observations made by prior studies comparing BM to PBSC on GVL effects outside of the PTCy setting hold true in the PTCy-based Haplo-HCT setting. Here, we hypothesized that in the latter scenario, the use of PBSC rather than BM will be associated with higher GVL effects and thus lower relapse incidence, translating to better LFS. To challenge this hypothesis, we performed a large

EBMT registry study. To avoid confounding effects of in vivo T-cell depletion on the impact of stem cell source,[30,31] in vivo T-cell depletion was a study exclusion criterion. Several observations were made.

A first observation was that the use of PBSC as the stem cell source was associated with higher incidences of grade II-IV and grade III-IV acute GVHD.[12,13,32] This observation is in concordance with prior observations and is probably due to the higher T-cell content in PBSC grafts. Interestingly, stem cell source was not statistically significantly associated with chronic GVHD in our study. This could be due to a lack of statistical power although it should be noted that prior studies assessing the impact of stem cell source in the Haplo-HCT PTCy setting have yielded disparate results: some observed an association between use of PBSC and higher incidence of chronic GVHD[13,32] while others did not.[12,33]

Another important observation was that in contrast to the study hypothesis, the use of PBSC was not associated with a lower relapse incidence. This could be related to the low and relatively comparable incidence of chronic GVHD observed in patients given PBSC or BM. Indeed, prior studies have demonstrated a strong association between GVL effects and chronic GVHD in AML patients, including in the Haplo-PTCy setting[34] (a transplantation platform in which grade II acute GVHD was also associated with GVL effects[34]). Further studies are needed to better characterize the mechanisms of GVL effects in the PTCy setting. As an example, a recent elegant study observed that a transcriptional exhaustion phenotype in $CD8^+$ T-cells, lowered natural killer (NK) cell counts, and a loss of inflammatory gene signatures in NK cells predicted relapse incidence in that setting.[35] Whether these phenotypes are impacted by stem cell source remains to be determined.

We observed a strong interaction between age and the association between stem cell source and LFS (the primary endpoint of our study). While in younger patients both stem cell sources yielded comparable NRM, LFS, and OS; in the subgroup of patients ≥55 years at transplantation the use of PBSC was significantly associated with higher NRM leading to significantly lower LFS, OS, and GRFS. This is of importance since it suggests that BM could be the best stem cell source for Haplo-HCT in patients aged ≥55 years. It should be however stressed that this was not the case for patients <55 years of age at transplantation for which outcomes tended to be better with PBSC than with BM as stem cell source, without reaching the predefined threshold of significant difference ($p < .05$).

As expected, relapse was by far the leading cause of treatment failure and of death in both groups. Beyond strategies aimed at maximizing GVL effects, post-transplant maintenance therapies, for example, with FLT3 tyrosine-kinase inhibitors in the case of FLT3-ITD AML,[36,37] hypomethylating agents[38,39] or pre-emptive donor lymphocyte infusion[40–42] should be investigated in this group of patients.

In conclusion, our study shows that the use PBSC instead of BM is associated with higher incidences of grade II–IV and grade III–IV acute GVHD. Furthermore, in patients ≥55 years old, use of PBSC was associated with higher NRM leading to lower LFS, GRFS, and OS. In contrast, transplantation outcomes were at least as good with PBSC than with BM in patients <55 years old.

AUTHOR CONTRIBUTIONS

Frédéric Baron wrote the manuscript, designed the study and interpreted the data. Myriam Labopin designed the study, performed the statistical analyses, interpreted the data and edited the manuscript. Mohamad Mohty designed the study, interpreted the data, and edited the manuscript. Johanna Tischer, Fabio Ciceri, Anna Maria Raiola, Didier Blaise, Simona Sica, Jan Vydra, Renato Fanin, Friedrich Stölzel, Alessandro Busca, Jose Luis Diez-Martin, Yener Koc, and Arnon Nagler reviewed the manuscript and provided clinical data. All authors approved the final version of the manuscript.

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CONFLICT OF INTEREST

Frédéric Baron has received travel grants and/or speaker honoraria from Celgene, Abbvie, Novartis, Pfizer, and Sanofi. The other authors declare that they have no relevant conflict of interest.

DATA AVAILABILITY STATEMENT

Data presented in the current study are available upon reasonable data specific request. Data request should be sent to Dr Myriam Labopin (myriam.labopin@upmc.fr).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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