Nonmyeloablative Alternative Donor Transplantation for Hodgkin and Non-Hodgkin Lymphoma: From the LWP-EBMT, Eurocord, and CIBMTR

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abstract

PURPOSE To compare the outcomes of patients with Hodgkin or non-Hodgkin lymphoma undergoing non-myeloablative haploidentical or unrelated cord blood (UCB) hematopoietic cell transplantation.

PATIENTS AND METHODS We retrospectively studied 740 patients with Hodgkin lymphoma (n = 283, 38%) and non-Hodgkin lymphoma (n = 457, 62%) age 18-75 years who received transplantations from 2009 to 2016. Data were reported to the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation, Eurocord, or Center for International Blood and Marrow Transplant Research. Of the 526 patients who received haploidentical transplantation, 68% received bone marrow and 32% received peripheral blood. All patients received a uniform transplantation conditioning regimen (2 Gy of total-body irradiation, cyclophosphamide, and fludarabine) and graft-versus-host disease prophylaxis (calcineurin inhibitor and mycophenolate). In addition, patients who received a haploidentical transplantation received posttransplantation cyclophosphamide.

RESULTS Compared with haploidentical bone marrow and peripheral-blood transplantations and adjusted for age, lymphoma subtype, and disease status, survival was lower after UCB transplantation (hazard ratio [HR], 1.55; $P = .001$; and HR, 1.59; $P = .005$, respectively). Similarly, progression-free survival was lower after UCB transplantations compared with haploidentical bone marrow and peripheral-blood transplantations (HR, 1.44; $P = .002$; and HR, 1.86; $P < .0001$), respectively. The 4-year overall and progression-free survival rates after UCB transplantation were 49% and 36%, respectively, compared with 58% and 46% after haploidentical bone marrow transplantation and 59% and 52% after peripheral-blood transplantation, respectively. Lower survival was attributed to higher transplantation-related mortality after UCB transplantation compared with haploidentical bone marrow and peripheral-blood transplantation (HR, 1.91; $P = .0001$; and HR, 2.27; $P = .0002$, respectively).

CONCLUSION When considering HLA-mismatched transplantation for Hodgkin or non-Hodgkin lymphoma, the data support haploidentical related donor transplantation over UCB transplantation.

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INTRODUCTION

Despite recent advances in the treatment of Hodgkin and non-Hodgkin lymphoma, such as targeted therapies and chimeric antigen receptor T-cell therapy, allogeneic hematopoietic cell transplantation offers long-term cure. Approximately one fourth of whites and most ethnic minorities do not have an available HLA-matched related or unrelated donor.[1] For these patients, unrelated cord blood (UCB) or a haploidentical relative are donor options for allogeneic hematopoietic cell transplantation. Both donor sources are readily available, tolerance has been demonstrated for donor-recipient HLA disparity, and reports suggest comparable outcomes between the 2 donor types for hematologic malignancy.[2-11] Donor selection (UCB or haploidentical relative) is often based on transplantation center experience, donor availability, and the cost associated with transplantation, although there are no comparative economic analyses to date. However, several reports included heterogenous conditioning regimens

and graft-versus-host disease (GVHD) prophylaxis. Therefore, the aim of the current analysis was to compare outcomes after UCB and haploidentical transplantations in a relatively homogenous population (Hodgkin or non-Hodgkin lymphoma [diffuse large B-cell, follicular, mantle cell, or T-cell subtypes]) with low-intensity conditioning regimens.

PATIENTS AND METHODS

Patients and Donors

Data were obtained from the Center for International Blood and Marrow Transplant Research (CIBMTR), the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation (LWP-EBMT), and Eurocord. Participating centers reported consecutive transplantations, and patients were followed longitudinally. Data were collected on standardized reporting forms. One hundred twenty-six centers contributed patients (Appendix Fig A1, online only). Of these, 111 centers contributed < 10 patients; 11 centers, 10-20 patients; 3 centers, 31-40 patients; and 1 center, 138 patients. Patients age 18-75 years with Hodgkin lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, or T-cell lymphoma receiving their first allogeneic hematopoietic cell transplantation from 2009 to 2016 were included in the study. Recipients of haploidentical donor transplantation received bone marrow or peripheral-blood grafts. Recipients of UCB transplantation received 1 or 2 units of UCB to achieve a minimum total nucleated cell (TNC) dose of 3.0×10^7/kg of recipient body weight. All patients received conditioning regimens with cyclophosphamide, fludarabine, and 2 Gy of total-body irradiation (TBI). UCB recipients received cyclophosphamide 50 mg/kg and fludarabine 200 mg/m^2. Haploidentical recipients received cyclophosphamide 29 mg/kg and fludarabine 150 mg/m^2. GVHD prophylaxis included calcineurin inhibitor with mycophenolate for UCB transplantation and posttransplantation cyclophosphamide (100 mg/kg), calcineurin inhibitor, and mycophenolate for haploidentical transplantation. Recipients of in vivo T-cell depletion or ex vivo graft manipulation including expanded UCB units were excluded. Patients provided written informed consent for research. The Institutional Review Board of the National Marrow Donor Program approved the study.

Outcomes

Overall survival was the primary end point. Death from any cause was an event, and surviving patients were censored at last follow-up. Progression-free survival was defined as survival without relapse or progression. Progression or relapse was defined as progressive disease or recurrence after a complete remission; death without relapse or progression was the competing risk. Transplantation-related mortality was defined as death from any cause without relapse or progression; relapse or progression was the competing risk. Acute grade 2-4 GVHD and chronic GVHD were assigned and graded using standard criteria.[12,13]

Statistical Analysis

The incidence of acute and chronic GVHD, relapse or progression, and transplantation-related mortality was calculated using the cumulative incidence estimator to accommodate competing risks.[14] Multivariable analyses were performed using Cox proportional hazards models for overall and progression-free survival, acute and chronic GVHD, relapse or progression, and transplantation-related mortality to examine the effect of donor type on transplantation outcomes.[15] A stepwise model-building approach was adopted, and variables that attained a $P \le .05$ were retained in the final model. The variables tested were donor-graft type (haploidentical bone marrow v haploidentical peripheral blood v UCB), age, sex, performance score, recipient cytomegalovirus serostatus, lymphoma subtype (Hodgkin v diffuse large B-cell v follicular v mantle cell v T-cell non-Hodgkin lymphoma), disease status, prior autologous transplantation, and transplantation period (Table 1). All variables met the assumption of proportional hazards, and there were no first-order interactions between the variables held in final Cox models. The effect of acute and chronic GVHD on survival was examined by fitting acute and chronic GVHD as time-dependent variables in the final Cox model for overall survival. The probabilities of overall and progression-free survival were calculated from the final Cox model. Transplantation center effect on survival and transplantation-related mortality was tested using the frailty model[16] and sensitivity analysis using Cox proportional hazards regression.[5] All P values are 2-sided, and all analyses were done using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient, Disease, and Transplantation Characteristics

The characteristics of the patients and their disease by donor-graft type are listed in Table 1. Haploidentical bone marrow transplantations were more common for Hodgkin lymphoma and less likely for T-cell lymphoma compared with haploidentical peripheral-blood and UCB transplantations. UCB transplantations were more common for follicular lymphoma. Although most transplantations occurred during complete or partial remission, haploidentical peripheral blood recipients were more likely to have chemotherapy-refractory disease. Bone marrow was the predominant graft for haploidentical transplantations. Most UCB transplantations (66%) were mismatched at 2 HLA loci considering low-resolution typing at A and B and high-resolution typing at DRB1. The remaining UCB transplantations were mismatched at 1 HLA locus (30%) or matched (3%). There were 22 single-unit UCB transplantations with a median TNC dose of 4×10^7/kg (interquartile range [IQR], 3.6-4.5 $\times 10^7$/kg), and there were 192 double-unit UCB transplantations with a median TNC dose of 5×10^7/kg (IQR, 4.4-5.9 $\times 10^7$/kg). The frequency of UCB transplantations decreased over time, whereas the opposite

TABLE 1. Patient and Disease Characteristics

| | No. of Patients (%) | | | |
Characteristic	Haploidentical Bone Marrow Transplantation (n = 357)	Haploidentical Peripheral-Blood Transplantation (n = 169)	Umbilical Cord Blood Transplantation (n = 214)	P
Age, years				.15
Median (range)	48 (18-75)	48 (19-75)	48 (18-73)	
18-30	84 (23)	39 (23)	41 (19)	
31-40	56 (16)	26 (15)	37 (17)	
41-50	49 (14)	26 (15)	38 (18)	
51-60	79 (22)	46 (27)	52 (24)	
61-70	75 (21)	31 (18)	45 (21)	
71-75	14 (4)	1 (1)	1 (< 1)	
Sex				.45
Male	223 (37)	115 (68)	136 (64)	
Female	134 (37)	54 (32)	78 (36)	
Performance score				.02
90-100	265 (74)	105 (62)	148 (69)	
≤ 80	78 (22)	59 (35)	54 (25)	
Not reported	14 (4)	5 (3)	12 (6)	
Cytomegalovirus serostatus				.61
Positive	153 (43)	63 (37)	91 (43)	
Negative	199 (56)	104 (62)	122 (57)	
Not reported	5 (1)	2 (1)	1 (< 1)	
Disease				< .001
Hodgkin lymphoma	156 (44)	65 (39)	62 (29)	
Non-Hodgkin lymphoma				
Diffuse large B-cell	106 (30)	34 (20)	47 (22)	
Follicular	35 (10)	16 (9)	41 (19)	
Mantle cell	28 (8)	20 (12)	17 (8)	
T-cell	32 (9)	34 (20)	47 (22)	
Disease status				.02
Complete remission	172 (48)	78 (46)	113 (53)	
Partial remission	141 (40)	57 (34)	75 (35)	
Chemotherapy refractory	36 (10)	29 (17)	15 (7)	
Untreated	8 (2)	5 (3)	11 (5)	
Prior autologous transplantation	192 (52)	94 (56)	127 (59)	.43
Transplantation period				< .001
2009-2012	166 (46)	24 (14)	137 (64)	
2013-2016	191 (54)	145 (86)	77 (36)	
Median follow-up, months (range)	43 (3-100)	30 (3-87)	48 (3-112)	

was observed for haploidentical peripheral-blood transplantations. The median follow-up time of recipients of haploidentical peripheral-blood transplantations was 30 months, compared with 43 months for haploidentical bone marrow transplantations and 48 months for UCB transplantations.

Hematopoietic Recovery

The median times to neutrophil recovery after UCB, haploidentical bone marrow, and peripheral-blood transplantations were 20, 19, and 17 days, respectively. The day 28 neutrophil recovery rate was lower after UCB transplantation (69%; 95% CI, 58% to 78%) compared with haploidentical bone marrow and peripheral blood transplantations (85% [95% CI, 79% to 91%] and 92% [95% CI, 86% to 97%], respectively; $P <$ .0001). The day 100 platelet recovery rate was also lower after UCB transplantation (67%; 95% CI, 57% to 77%) compared with haploidentical bone marrow and peripheral-blood transplantations (91% [95% CI, 85% to 96%] and 90% [95% CI, 83% to 96%], respectively; $P <$ .0001).

GVHD

The day 100 grade 2-4 acute GVHD rate was higher after UCB transplantation compared with haploidentical bone marrow transplantation (43% [95% CI, 36% to 50%] v 20% [95% CI, 16% to 25%], respectively; $P <$ .0001). Acute grade 2-4 GVHD did not differ after UCB and haploidentical peripheral-blood transplantation (35%; 95% CI, 28% to 43%; $P =$ .17). Multivariable analysis confirmed a higher risk of grade 2-4 GVHD after UCB transplantation compared with haploidentical bone marrow transplantation after adjusting for age, the only variable that was significantly associated with acute grade 2-4 GVHD (Table 2). The incidence of grade 3-4 acute GVHD was higher after UCB transplantation compared with haploidentical transplantation either with bone marrow or with peripheral blood (Table 2). The day 100 grade 3-4 acute GVHD rates were 18% (95% CI, 13% to 24%) after UCB, 5% (95% CI, 3% to 8%) after haploidentical bone marrow, and 6% (95% CI, 3% to 11%) after peripheral-blood transplantations ($P <$ .0001). The median time to onset of chronic GVHD was 5 months (IQR, 4-8 months) after UCB transplantation compared with 6 months (IQR, 4-11 months) and 6 months (IQR, 4-9 months) after haploidentical bone marrow and peripheral-blood transplantations. The 6-month incidence of chronic GVHD was higher after UCB transplantation (17%; 95% CI, 12% to 23%) compared with haploidentical bone marrow transplantation (11%; 95% CI, 8% to 14%; $P =$ .04), but not after haploidentical peripheral-blood transplantation (18%; 95% CI, 12% to 24%; $P =$ .91); the corresponding 4-year chronic GVHD rates were 28% (95% CI, 22% to 34%), 24% (95% CI, 19% to 29%; $P =$ .31), and 32% (95% CI, 25% to 40%; $P =$ .42). The 2-year incidence of severe chronic GVHD was higher after UCB (14%; 95% CI, 10% to 20%) and haploidentical peripheral-blood transplantation (16%; 95% CI, 10% to 22%) compared with haploidentical bone marrow transplantation (8%; 95% CI, 5% to 12%; $P =$ .02). Multivariable analysis showed a higher risk of chronic GVHD after UCB transplantation compared with haploidentical bone marrow transplantation but not haploidentical peripheral-blood transplantation (Table 2). No other factors were associated with chronic GVHD.

Transplantation-Related Mortality and Relapse or Progression

Transplantation-related mortality was higher after UCB transplantation compared with haploidentical transplantation with bone marrow or peripheral blood, adjusted for age, performance score, and prior autologous transplantation (Table 2 and Fig 1A). After adjusting for age, lymphoma subtype, and disease status, the risk of relapse or progression did not differ between UCB and haploidentical bone marrow transplantations (Table 2 and Fig 1B). However, risks were lower after haploidentical peripheral-blood transplantation compared with UCB transplantation.

Overall and Progression-Free Survival

Overall and progression-free survival outcomes were lower after UCB transplantation compared with haploidentical bone marrow and peripheral-blood transplantation after adjusting for age, type of lymphoma. and disease status at transplantation (Table 2 and Figs 2A and 2B). The effect of grade 3-4 acute GVHD on survival confirmed higher mortality after UCB transplantation compared with haploidentical bone marrow (hazard ratio [HR] 1.64; 95% CI, 1.23 to 2.18; $P =$ .0008) and peripheral-blood transplantations (HR, 1.65; 95% CI, 1.17 to 2.33; $P =$ .005). Similarly, chronic GVHD was also associated with a higher mortality after UCB transplantation compared with haploidentical bone marrow (HR, 1.73; 95% CI, 1.13 to 2.30; $P =$ .0002) and peripheral-blood transplantations (HR, 1.76; 95% CI, 1.25 to 2.47; $P =$ .001). Ninety-eight (51%) of 193 recipients of UCB are dead. One hundred fifteen (37%) of 313 recipients of haploidentical bone marrow and 58 (37%) of 159 recipients of haploidentical peripheral blood are dead. Recurrent disease was the most common cause of death in all treatment groups but did not differ between the groups ($P =$ .17). Infection was the second most common cause of death and did not differ between treatment groups ($P =$ .34). The proportion of deaths attributed to GVHD was higher after UCB transplantation (18%) compared with after haploidentical bone marrow and peripheral-blood transplantations (6% and 9%, respectively; $P =$ .01). Other causes of death, including interstitial pneumonitis and organ failure, did not differ between the donor groups (data not shown).

Transplantation center effect. We tested for an effect of transplantation center on survival ($P =$ .25) and transplantation-related mortality ($P =$ .17) using the frailty model and found no effect. Several sensitivity analyses were performed to address transplantation center effects. We first compared risks for overall mortality (1−survival) and transplantation-related mortality at the center that contributed 134 haploidentical transplantations to the risks at the other centers that performed haploidentical bone marrow transplantations and did not find a significant difference (HR, 1.20; 95% CI, 0.81 to 1.79; $P =$ 0.37; and HR, 1.47; 95% CI, 0.84 to 2.57; $P =$ .18, respectively). A second analysis comparing

TABLE 2. Results of Multivariable Analysis

Outcome	HR (95% CI)	P
Grade 2-4 acute GVHD[a]		
UCB *v* haploidentical bone marrow	1.83 (1.37 to 2.44)	< .0001
UCB *v* haploidentical peripheral blood	1.04 (0.76 to 1.43)	.81
Grade 3-4 acute GVHD[a]		
UCB *v* haploidentical bone marrow	2.61 (1.55 to 4.40)	.0003
UCB *v* haploidentical peripheral blood	2.31 (1.18 to 4.54)	.02
Chronic GVHD		
UCB *v* haploidentical bone marrow	1.53 (1.09 to 2.15)	.02
UCB *v* haploidentical peripheral blood	1.01 (0.69 to 1.48)	.97
Transplantation-related mortality[b]		
UCB *v* haploidentical bone marrow	1.91 (1.37 to 2.65)	.0001
UCB *v* haploidentical peripheral blood	2.27 (1.45 to 3.54)	.0002
Relapse or progression[c]		
UCB *v* haploidentical bone marrow	1.11 (0.80 to 1.52)	.54
UCB *v* haploidentical peripheral blood	1.52 (1.03 to 2.26)	.04
Progression-free survival[d]		
UCB *v* haploidentical bone marrow	1.44 (1.14 to 1.82)	.002
UCB *v* haploidentical peripheral blood	1.86 (1.39 to 2.50)	< .0001
Overall survival[e]		
UCB *v* haploidentical bone marrow	1.55 (1.19 to 2.03)	.001
UCB *v* haploidentical peripheral blood	1.59 (1.15 to 2.20)	.005

Abbreviations: GVHD, graft-versus-host disease; HR, hazard ratio; UCB, unrelated cord blood.

[a]Adjusted for age: patients age 60-75 years were at higher risk for grade 2-4 acute GVHD compared with patients age 18-39 years (HR, 1.40; 95% CI, 1.03 to 2.30; $P = .03$). Acute GVHD risks did not differ between patients age 40-59 years and those age 18-30 years (HR, 1.13; 95% CI, 0.85 to 1.52; $P = .40$).

[b]Adjusted for age, performance score, and prior autologous transplantation. Risks were higher for those age 40-59 years (HR, 2.37; 95% CI, 1.56 to 3.60; $P < .0001$) and 60-75 years (HR, 3.19; 95% CI, 2.05 to 4.97; $P < .0001$; interaction $P = .16$); patients with a performance score ≤ 80 compared with 90-100 (HR, 1.45; 95% CI, 1.04 to 2.03; $P = .03$; interaction $P = .91$); and patients with prior autologous transplantation (HR, 1.43; 95% CI, 1.04 to 1.97; $P = .03$; interaction $P = .49$). Transplantation period was not associated with transplantation-related mortality (HR, 1.36; 95% CI, 0.98 to 1.89; $P = .07$).

[c]Adjusted for age, lymphoma subtype, and disease status. Relapse risks were lower for those age 40-59 years (HR, 0.64; 95% CI, 0.46 to 0.91; $P = .01$) and 60-75 years (HR, 0.47; 95% CI, 0.31 to 0.73; $P = .0008$) compared with patients age 18-39 years (interaction $P = .80$); patients with diffuse large B-cell lymphoma (DLBCL; HR, 2.30; 95% CI, 1.58 to 3.36; $P < .0001$) and mantle cell lymphoma (HR, 2.13; 95% CI, 1.22 to 3.71; $P = .007$) compared with Hodgkin lymphoma (interaction $P = .34$; relapse risks did not differ between the other subtypes); and patients with disease status of partial response (HR, 1.93; 95% CI, 1.43 to 2.59; $P < .0001$) and chemotherapy refractory (HR, 3.39; 95% CI, 2.31 to 4.98; $P < .0001$) compared with complete remission (interaction $P = .23$). Transplantation period was not associated with relapse or progression (HR, 0.82; 95% CI, 0.62 to 1.09; $P = .99$).

[d]Adjusted for cytomegalovirus (CMV) serostatus, lymphoma subtype, and disease status. Risks were higher for CMV seropositive recipients (HR, 1.39; 95% CI, 1.13 to 1.71; $P = .002$; interaction $P = .43$); patients with DLBCL (HR, 1.68; 95% CI, 1.31 to 2.16; $P < .0001$) and mantle cell lymphoma (HR, 1.49; 95% CI, 1.04 to 2.14; $P = 0.03$) compared with Hodgkin lymphoma (interaction $P = .26$; risks did not differ between the other subtypes); and patients with a disease status of partial response (HR, 1.59; 95% CI, 1.27 to 1.98; $P < .0001$) and chemotherapy refractory (HR, 2.36; 95% CI, 1.74 to 3.22; $P < .0001$) compared with complete remission (interaction $P = .16$). Transplantation period was not associated with progression-free survival (HR, 1.05; 95% CI, 0.84 to 1.30; $P = .67$).

[e]Adjusted for age, sex, CMV serostatus, lymphoma subtype, and disease status. Risks were higher for those age 60-75 years (HR, 1.64; 95% CI, 1.13 to 2.38; $P = .009$; interaction $P = .15$); CMV seropositive recipients (HR, 1.53; 95% CI, 1.20 to 1.95; $P = .001$; interaction $P = .43$); patients with DLBCL (HR, 1.75; 95% CI, 1.23 to 2.48; $P = .002$) and T-cell lymphoma (HR, 1.64; 95% CI, 1.11 to 2.41; $P = .01$; interaction $P = .81$); and patients with a disease status of partial response (HR, 1.49; 95% CI, 1.16 to 1.91; $P = .002$) and chemotherapy refractory (HR, 2.29; 95% CI, 1.62 to 3.23; $P < .0001$) compared with complete remission (interaction $P = .33$). Transplantation period was not associated with overall survival (HR, 1.09; 95% CI, 0.86 to 1.41; $P = .45$).

the 6 high-volume haploidentical bone marrow transplantation centers to the other centers that performed haploidentical bone marrow transplantation did not identify differences in overall mortality (HR, 1.20; 95% CI, 0.86 to 1.72; $P = .24$), transplantation-related mortality (HR, 1.21; 95% CI, 0.69 to 2.12; $P = .51$), relapse or progression (HR, 1.00; 95% CI, 0.68 to 1.48; $P = .99$), or progression-free survival (HR, 1.06; 95% CI, 0.78 to 1.44; $P = .72$). A third analysis compared the 3 treatment groups without the 6 high-volume centers that performed haploidentical bone
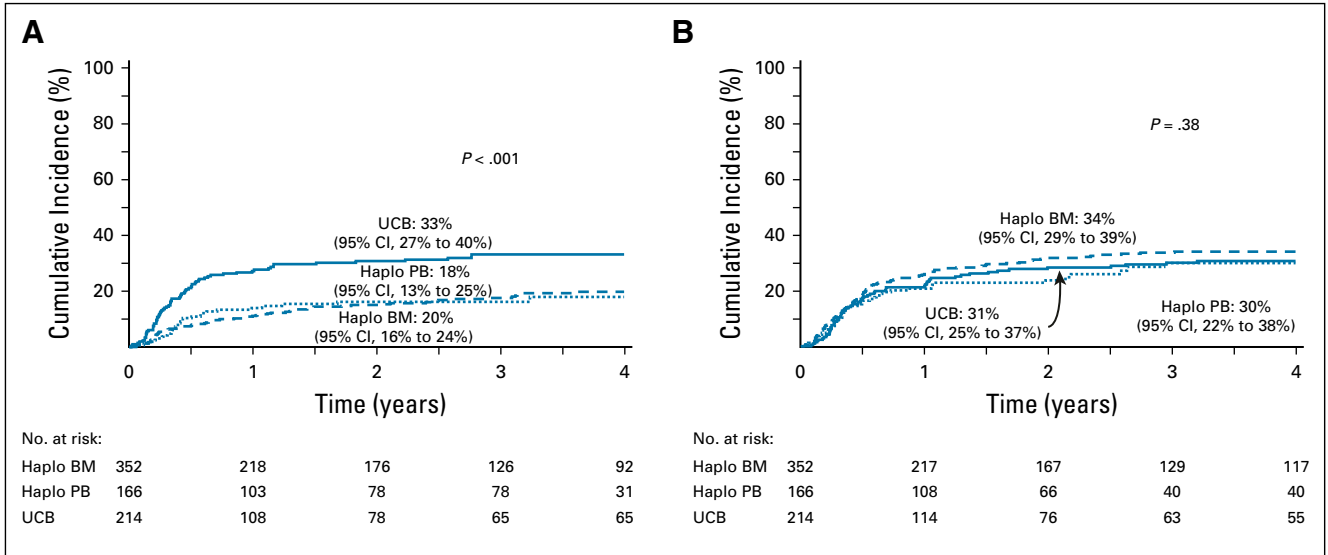
FIG 1. (A) Transplantation-related mortality. The 4-year cumulative incidence of transplantation-related mortality was 20% (95% CI, 16% to 24%) for haploidentical bone marrow (BM) transplantations, 18% (95% CI, 12% to 25%) for haploidentical peripheral-blood (PB) transplantations, and 33% (95% CI, 27% to 40%) for unrelated cord blood (UCB) transplantations. (B) Relapse or progression. The 4-year cumulative incidence of relapse or progression was 34% (95% CI, 29% to 39%) for haploidentical BM transplantations, 30% (95% CI, 22% to 38%) for haploidentical PB transplantations, and 31% (95% CI, 25% to 37%) for UCB transplantations. Haplo, haploidentical.

marrow transplantations (Data Supplement), and the effect of donor type on transplantation outcomes is consistent with the main analysis (Table 2). A fourth analysis compared the 3 treatment groups with transplantation center volume held in the final Cox model (Data Supplement). Centers were considered as those that contributed ≤ 10 patients versus each center that contributed > 10 patients. As with the other

sensitivity analyses, the effects of donor type on transplantation outcomes were consistent with the main analysis (Table 2).

DISCUSSION

Multicenter retrospective studies have compared outcomes after UCB and haploidentical donor transplantation
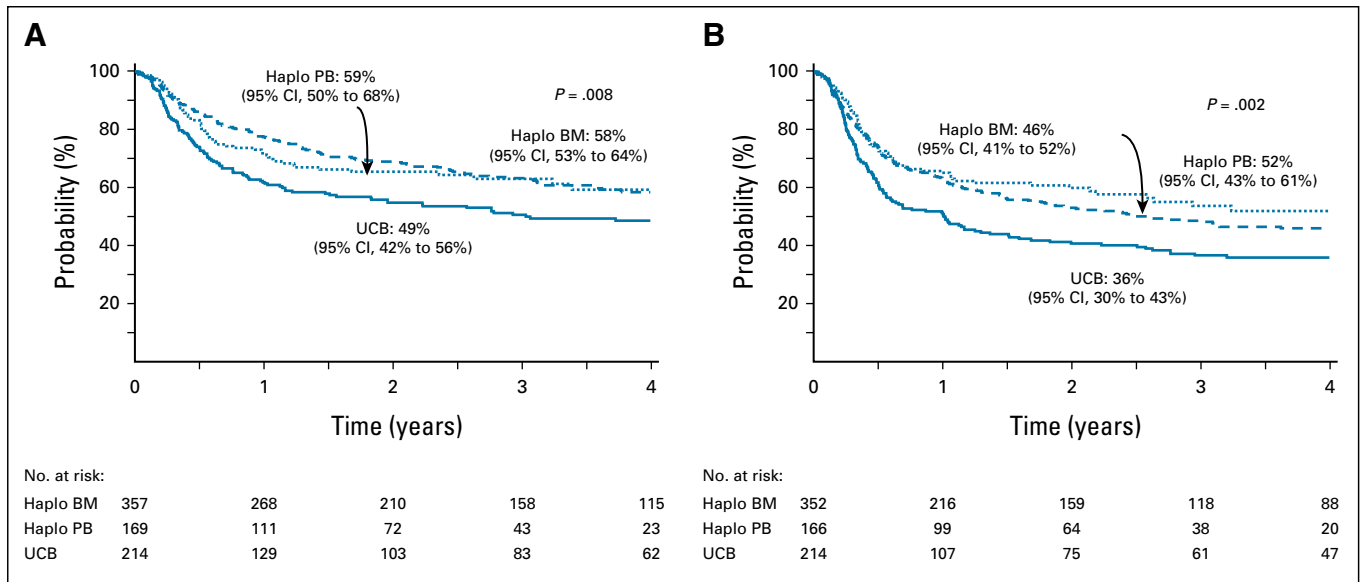

FIG 2. (A) Overall survival. The 4-year probability of overall survival was 58% (95% CI, 53% to 64%) for haploidentical bone marrow (BM) transplantations, 59% (95% CI, 50% to 68%) for haploidentical peripheral-blood (PB) transplantations, and 49% (95% CI, 42% to 56%) for unrelated cord blood (UCB) transplantations. (B) Progression-free survival. The 4-year probability of progression-free survival was 46% (95% CI, 41% to 52%) for haploidentical BM transplantations, 52% (95% CI, 43% to 61%) for haploidentical PB transplantations, and 36% (95% CI, 30% to 43%) for UCB transplantations. Haplo, haploidentical.

with mixed results, although these studies have been largely for leukemia and myelodysplastic syndrome.[17-20] In unselected patients with acute leukemia, survival did not differ after UCB transplantation compared with haploidentical transplantation.[17,18] However, when patients with acute myeloid leukemia received a uniform myeloablative conditioning regimen (thiotepa, busulfan, and fludarabine) or unselected patients with myelodysplastic syndrome, overall and leukemia-free survival were higher after haploidentical transplantation.[19,20] The current analysis, which includes only patients with lymphoma, showed lower overall and progression-free survival after UCB transplantation compared with haploidentical donor transplantation, which to our knowledge has not been previously reported. Differences in overall and progression-free survival were a result of higher transplantation-related mortality and not relapse or progression after UCB transplantation. Lower progression-free and overall survival after UCB transplantation compared with haploidentical donor transplantation was independent of other factors associated with these outcomes including disease type and disease status at transplantation. Compared with Hodgkin lymphoma, transplantation-related mortality and relapse or progression rates were higher and progression-free and overall survival lower in patients with diffuse large B-cell and mantle cell lymphoma but not in patients with other non-Hodgkin lymphoma subtypes. Similarly, relapse or progression was higher for patients who received transplantation in partial remission or who had chemotherapy-refractory disease compared with those in remission. Our analysis confirmed that the effects of disease subtype and disease status are independent of donor type (Table 2). Secondary graft failure was 7% after UCB, compared with 5% and 4% after haploidentical bone marrow and peripheral-blood transplantations, respectively, but its assessment was confounded by relapse and progressive disease. We examined for an effect of transplantation center volume on transplantation outcomes and did not record differences in the effect of donor type on outcomes, leading us to conclude that better outcomes after haploidentical transplantation in the current analyses cannot be explained by transplantation center volume. Our analyses considered a relatively recent period, and many centers may have overcome their learning curve in regard to the donor groups being studied.

A phase III randomized trial designed based on the findings of 2 parallel phase II trials[3] that used conditioning regimens and GVHD prophylaxis similar to transplantations in the current analysis is expected to enroll 205 patients to each arm of the trial (UCB and haploidentical bone marrow transplantation; ClinicalTrials.gov identifier: NCT01597778). Given the enrollment to the phase II trials, we anticipate that approximately 140 patients with lymphoma will be enrolled in the trial. In contrast, the current analysis with 214 UCB and 526 haploidentical transplantation recipients has allowed us to study the effect of donor-graft type in a larger population with lymphoma and is a strength of the current analysis. We are also able to address outcomes through 4 years after transplantation, unlike the phase III trial, which is designed to detect a 15% difference in 2-year progression-free survival. We found 2-year progression-free survival rates of 40% (95% CI, 33% to 47%) and 53% (95% CI, 48% to 59%) after UCB and haploidentical bone marrow transplantations ($P < .001$), respectively, an absolute difference of 13%.

The recorded high incidence of transplantation-related mortality after UCB transplantation is consistent with other reports.[3-5,10] Several factors may have contributed to the higher transplantation-related mortality, including higher grade 3-4 acute and chronic GVHD, higher incidence of bacterial and viral infections,[21] and HLA disparity.[22] Most UCB transplantations were mismatched at 2 HLA loci considering lower resolution HLA match and, therefore, likely to be mismatched at $\geq$ 3 HLA loci considering allele-level match.[22] Although haploidentical transplantations are mismatched at $\geq$ 2 HLA loci, differences in survival have not been reported when compared with HLA-matched sibling transplantations.[8,23] Although slower neutrophil recovery may have increased risk of systemic infection(s) and in part contributed to higher early mortality, the proportion of deaths attributed to infection did not differ between the 3 donor groups. It is plausible that differences in chemotherapy dosing (ie, conditioning and GVHD prophylaxis) could have contributed to the higher transplantation-related mortality in the UCB group. Despite the same dose of TBI (2 Gy), there were differences in the total dose of fludarabine (200 mg/m^2 in the UCB group v 150 mg/m^2 in the haploidentical group) and cyclophosphamide (50 mg/kg in the UCB group v 129 mg/kg in the haploidentical group). Nevertheless, as mentioned earlier, the proportion of deaths as a result of infection and organ failure was not significantly different among the 3 donor groups, making this hypothesis less likely. Another factor known to mitigate early mortality is delivery of adequate TNC dose. The total TNC dose for all UCB transplantations in the current analyses met the minimum required dose of 3×10^7/kg. In fact, the median TNC dose was 4.8×10^7/kg (IQR, 4.0-5.6 $\times$ 10^7/kg).[3,22,24] A recent phase II trial of expanded UCB transplantation (median TNC dose, 4.9 $\times$ 10^7/kg) for leukemia reported lower transplantation-related mortality and higher relapse without a survival advantage compared with a contemporary cohort of nonexpanded UCB transplantations.[25] Thus, a minimum TNC dose is desired for UCB transplantation but perhaps without an added advantage to infusing higher than the desired TNC. Strategies to lower GVHD after UCB transplantation should also be investigated, such as the use of posttransplantation cyclophosphamide.[26]

Our study has several limitations, the first being a retrospective cohort analysis in which treatment choices were physician dependent and/or institutional preference and the second being our inability to adjust for unknown or

unmeasured factors, including consideration of hematopoietic cell transplantation comorbidities (not collected for cord blood recipients reported to Eurocord) known to be associated with survival.[27] We considered prefreeze TNC as that was available for all UCB units and other reports have identified CD34 count of the unit as a better predictor for hematopoietic recovery.[28] Haploidentical transplantations were more recent, and these patients may have received newer therapies before transplantation. However, lower progression-free and overall survival rates after UCB transplantation were a result of differences in mortality and not relapse or progression. We also did not record differences in outcome by transplantation period. Fewer UCB transplantations after 2012 coincide with publication of results of the parallel phase II trials of UCB and haploidentical bone marrow transplantation, which may have prompted increased use of haploidentical donors.[3] A strength of the current analysis is the inclusion of > 700 patients with Hodgkin and non-Hodgkin lymphoma, which allowed us to compare the effect of graft type for haploidentical transplantations (bone marrow and peripheral blood) compared with UCB transplantations. Accruing 700 patients for randomized clinical trials in transplantation can be lengthy and the costs prohibitive. Thus, these data are informative for clinical decision making. Consistent with an earlier report that included primarily patients with acute myeloid leukemia,[29] we did not record an advantage for progression-free survival (HR, 1.28; 95% CI, 0.96 to 1.72; $P = .10$) or overall survival (HR, 1.00; 95% CI, 0.72 to 1.39; $P = .97$) with peripheral blood compared with bone marrow for haploidentical transplantation. Therefore, when considering HLA-mismatched donor transplantation, our data support using a haploidentical relative, with UCB reserved when such a donor is not available.[30,31]

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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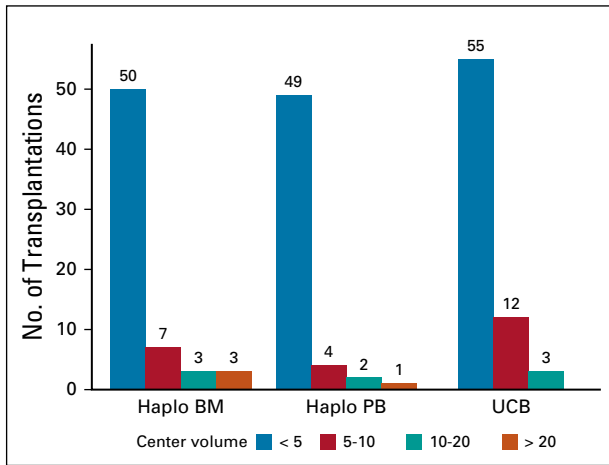No other potential conflicts of interest were reported.

FIG A1. Center volume by donor group. BM, bone marrow; Haplo, haploidentical; PB, peripheral blood; UCB, unrelated cord blood.