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Optimal donor for African Americans with hematologic malignancy: HLA-haploidentical relative or umbilical cord blood transplant

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Abstract

While hematopoietic cell transplant from an HLA-matched unrelated donor is potentially curative for hematologic malignancy, survival is lower for African Americans compared to Caucasians. As only about 20% of African Americans will have an HLA-matched unrelated donor many of these patients undergo HLA-haploidentical relative or umbilical cord blood transplantation. Thus, the current analyses studied transplant-outcomes after HLA-haploidentical relative (n=249) and umbilical cord blood (n=118) transplants for African Americans with hematologic malignancy between 2008 and 2016. The predominant disease was acute myeloid leukemia for both donor types. Grade II-IV and III-IV acute graft versus host disease was higher after umbilical cord blood (56% and 29%, respectively) compared to HLA-haploidentical relative transplantation (33% and 11%), p<0.0001. The 2-year incidence of transplant-related mortality adjusted for age and conditioning regimen intensity was higher after umbilical cord blood compared to HLA-haploidentical relative transplantation (31% versus 18%, p=0.008). However, there were no differences in the 2-year adjusted incidence of relapse (30% versus 34%, p=0.51), overall survival (54% versus 57%, p=0.66), or disease-free survival (43% versus 47%, p=0.46). HLA-haploidentical and umbilical cord blood extend access to transplantation with comparable leukemia-free and overall survival for African Americans with hematologic malignancy.

INTRODUCTION

For many patients with advanced hematologic malignancies, allogeneic hematopoietic cell transplantation is an effective curative treatment. Although transplants utilizing a matched sibling donor have historically resulted in the best outcomes, only about a third of patients who are likely to benefit from allogeneic transplantation will have a matched sibling.[1] The remaining patients must pursue an alternative donor that includes matched or mismatched adult unrelated donors, HLA-haploidentical relative, or banked unrelated umbilical cord blood. As the likelihood of identifying an HLA matched unrelated donor for African Americans is approximately 20% most patients of African-American descent rely on HLA-haploidentical relatives or mismatched unrelated umbilical cord blood for allogeneic transplantation.[2–4] Evidence from previously published registry studies have shown inferior survival for African Americans compared to Caucasians with hematological malignancy after HLA-matched unrelated donor that was attributed to higher transplant-related mortality.[5] Although others reported lower survival after umbilical cord blood transplantation in African Americans, this effect was mitigated with transplantation of an adequately dosed umbilical cord blood unit (total nucleated cell dose $>2.5 \times 10^7$/kg) implying the previously observed lower survival in African Americans may be less evident with more recent transplantations that use two cord blood units to overcome the cell dose barrier.[6] Increasing the use of HLA-haploidentical relatives has expanded access to transplantation especially for minorities.[7] In a recent report from a single-center, survival after HLA-haploidentical transplantation with post-transplant cyclophosphamide was better for patients of African American compared to Caucasian descent.[8] This posed the question of whether patients of African American descent should be offered HLA-haploidentical transplantation with post-transplant cyclophosphamide when an HLA-matched sibling or HLA-matched unrelated donor is not available. Thus, the current analysis was undertaken to

examine whether there are differences in survival between HLA-haploidentical relative compared to cord blood transplantation in African Americans with hematologic malignancy.

PATIENTS AND METHODS

Patients

The Center for International Blood and Marrow Transplant Research is a group of over 400 transplant centers worldwide that contribute data prospectively on consecutive transplants performed at each center. Patients are followed until death or lost to follow up. Eligible patients were those who self-identified as African American, aged 18 – 70 years with acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome or non-Hodgkin lymphoma and transplanted in the United States from an HLA-haploidentical relative or umbilical cord blood between 2008 and 2016. HLA-haploidentical relative donor transplants were T-cell replete, used bone marrow or peripheral blood with post-transplant cyclophosphamide, calcineurin inhibitor and mycophenolate for graft-versus-host disease (GVHD) prophylaxis. Umbilical cord blood transplants included one (total nucleated cell [TNC] dose $>2.5 \times 10^7$/kg) or two (TNC dose $>1.5 \times 10^7$/kg for each unit) units, T-replete, and GVHD prophylaxis included calcineurin inhibitor and mycophenolate. Transplant conditioning regimen intensity were myeloablative or non-myeloablative classified based on published criteria.[9] Excluded were non-African American, and recipients of T-cell depleted transplants (*ex vivo* including CD34 selected peripheral blood graft or *in vivo* with anti-thymocyte globulin or alemtuzumab). All patients provided written informed consent for research. The institutional review board of the National Marrow Donor Program approved the study.

End Points

The primary endpoint was overall survival, death from any cause was considered an event and surviving patients censored at last follow-up. Secondary endpoints include hematopoietic recovery (absolute neutrophil count $\geq 0.5 \times 10^9$/L and platelets $\geq 20 \times 10^9$/L unsupported), transplant-related mortality (death in remission), relapse (morphologic, cytogenetic or molecular disease recurrence of disease), disease-free survival (alive in remission) and acute and chronic graft-versus-host disease (GVHD).[10,11] GVHD-free, relapse-free survival endpoints included grade III-IV acute GVHD, chronic GVHD requiring systemic treatment, relapse or death.

Statistical Methods

Patient, disease and transplant characteristics between donor types were compared using the Chi-square statistic for categorical variables. The probabilities of neutrophil and platelet recovery were calculated using the cumulative incidence estimator to accommodate competing risks.[12] Cox regression models[13] were built to study the effect of donor type on overall survival, transplant-related mortality, relapse, disease-free survival, acute and chronic GVHD. Other factors that were considered in Cox regression models were age, sex, performance score, comorbidity score, cytomegalovirus (CMV) serostatus, disease, disease risk index, and transplant period. All variables that attained p-value ≤ 0.05 were held in the final multivariate model except for the variable for donor type which was held in all steps of

model building and the final model regardless of the level of significance. The probabilities of overall survival, transplant-related mortality, relapse, disease-free survival acute and chronic GVHD adjusted for other significant factors were calculated from the Cox model.[14,15] An effect of transplant center on survival was tested using the frailty model.[16] All p-values are two-sided. All analyses were done using SAS version 9.4 (Cary, NC).

RESULTS

Patient, Disease and Transplant Characteristics

The characteristics of patients, their disease and transplantation by donor type are shown in Table 1. Compared to recipients of HLA-haploidentical relative donor transplants, umbilical cord blood recipients were younger, less likely to be cytomegalovirus seropositive and more likely to have performance scores of 90 or 100 and receive myeloablative conditioning regimen. The median age at transplantation for recipients of HLA-haploidentical relative donor transplants was 50 years and for umbilical cord blood, 40 years. Acute myeloid leukemia was the predominant indication for transplantation for both treatment groups and recipients of HLA-haploidentical transplantation were more likely to report poor-risk cytogenetics for acute myeloid and acute lymphoblastic leukemia (54% versus 36%). There were no differences in disease type or disease risk index by donor type. Myeloablative regimens were predominantly total body irradiation (TBI) containing, cyclophosphamide ± fludarabine and the non-TBI regimens, alkylating agent (busulfan or melphalan) with fludarabine. Only one non-myeloablative regimen was used, low dose TBI, cyclophosphamide and fludarabine for both treatment groups. GVHD prophylaxis included post-transplant cyclophosphamide, calcineurin inhibitor and mycophenolate for HLA-haploidentical relative and calcineurin inhibitor and mycophenolate for umbilical cord blood transplant. Treatment groups did not differ regarding sex, hematopoietic transplant co-morbidity index and disease type. Bone marrow (45%) and peripheral blood (55%) were equally likely to be used for HLA-haploidentical relative donor transplant and donors-recipients were HLA-mismatched at ≥2 HLA loci. The median TNC for bone marrow grafts was 2.53×10^8/kg (interquartile range [IQR] 1.99 – 3.12) and the median CD34+ for peripheral blood grafts was 5.03×10^6/kg (IQR 4.52 – 7.67). Among recipients of HLA-haploidentical relative donor transplants, 38% received grafts from a sibling, 49% from offspring and 13% from a parent. Most umbilical cord blood transplants (103 of 118, 87%) used two cord blood units and most (106 of 118, 80%) were mismatched at two HLA-loci considering low-resolution HLA-match at A and B loci and allele-level at DRB1. HLA-match at C locus was not considered. The median total nucleated cell dose of umbilical cord blood transplants was 4.25×10^7/kg (IQR: 3.61 – 5.38). The median time to transplant did not differ between donor types, 9 months for HLA-haploidentical relative and 8.5 months for umbilical cord blood transplant. HLA-haploidentical relative donor transplants were more common after 2012. Consequently, the median follow-up of HLA-haploidentical relative donor transplants was 25 months compared to 47 months after umbilical cord blood transplants.

Hematopoietic recovery

The median times to neutrophil and platelet recovery were shorter after HLA-haploidentical relative compared to umbilical cord blood transplant, 16 versus 19 days for neutrophil (p=0.002) and 22 versus 41 days for platelet recovery (p <0.0001). The day-28 incidence of neutrophil recovery was 92% (95% CI 89 – 95) and 75% (95% CI 67 – 82) for HLA-haploidentical relative donor and umbilical cord blood transplant, respectively, p<0.0001. The corresponding day-100 incidence of platelet recovery was 89% (95% CI 85 – 93) and 71% (95% CI 63 – 79), p <0.0001.

Acute and chronic GVHD

Compared to HLA-haploidentical relative donor transplant, grade II-IV acute GVHD was higher after umbilical cord blood transplant (HR 2.40, 95% CI 1.70 – 3.38, p<0.0001). The only other factor associated with grade II-IV acute GVHD risk was conditioning regimen intensity. Compared to myeloablative conditioning regimens, non-myeloablative regimens were associated with lower risks for acute grade II-IV (HR 0.57, 95% CI 0.39 – 0.82, p=0.003). The day-100 incidence of grade II-IV adjusted for conditioning regimen intensity was 33% (95% CI 27 – 39) and 56% (95% CI 46 – 64) after HLA-haploidentical relative donor and umbilical cord blood transplant, respectively (p<0.0001). Similarly, Grade III-IV acute GVHD was also higher after umbilical cord blood transplant (HR 3.12, 95% CI 1.85 – 5.26, p <0.0001), adjusted for conditioning regimen intensity. The day-100 incidence of grade III-IV adjusted for conditioning regimen intensity was 11% (95% CI 7 – 15) and 29% (95% CI 22 – 38) after HLA-haploidentical relative donor and umbilical cord blood transplant, respectively, p<0.0001. The risk for chronic GVHD did not differ by donor type (HR 0.73, 95% CI 0.47 – 1.13, p=0.15). The only factor associated with chronic GVHD was conditioning regimen intensity. Compared to myeloablative conditioning regimens, non-myeloablative regimens were associated with lower risks for chronic GVHD (HR 0.53, 95% CI 0.36 – 0.79, p=0.001). The 2-year incidence of chronic GVHD adjusted for conditioning regimen intensity was 35% (95% CI 29 – 41) after HLA-haploidentical relative donor and 26% (95% CI 18 – 34%) after umbilical cord blood transplant (p=0.08).

Transplant related mortality and relapse

Compared to HLA-haploidentical relative donor transplant, transplant-related mortality was higher after umbilical cord blood transplant (Table 2). Independent of donor type, transplant-related mortality was higher in patients aged 50 – 70 years compared to 18 – 40 years (HR 2.33, 95% CI 1.45 – 3.77, p=0.001) and lower after non-myeloablative compared to myeloablative regimens (HR 0.57, 95% CI 0.35 – 0.94, p=0.03). The 2-year incidence of transplant-related mortality adjusted for age and conditioning regimen intensity after HLA-haploidentical relative donor and umbilical cord blood transplant were 18% (95% CI 14 – 23) and 31% (95% CI 23 – 40), Figure 1A (p=0.008). Overall relapse risks did not differ by donor type (Table 2). Independent of donor type, relapse risks were higher in patients with high/very high disease risk index compared to low/intermediate disease risk (HR 1.70, 95% CI 1.16 – 2.49, p=0.007) and after non-myeloablative compared to myeloablative conditioning regimens (HR 1.60, 95% CI 1.09 – 2.35, p=0.020). The 2-year incidence of relapse adjusted for disease risk index and conditioning regimen intensity after HLA-

haploidentical relative donor was 34% (95% CI 28 – 40) compared to 30% (95% CI 20 – 39) after umbilical cord blood transplant, Figure 1B (p=0.51).

Overall survival and disease-free survival

Compared to HLA-haploidentical relative donor overall survival and disease-free survival did not differ by donor type (Table 2). Independent of donor type, overall mortality was higher in patients aged 50 – 70 years compared to 18 – 40 years (HR 1.66, 95% CI 1.22 – 2.26, p=0.001) and with high/very high disease risk index compared to low/intermediate disease risk (HR 1.73, 95% CI 1.25 – 2.39, p=0.0009). The 2-year probability of overall survival adjusted for age and disease risk index after HLA-haploidentical relative donor and umbilical cord blood transplant were 57% (95% CI 51 – 63) and 54% (95% CI 45 – 663), Figure 2A, p=0.66. Treatment failure (inverse of disease-free survival) was also higher in patients aged 50 – 70 years compared to 18 – 40 years (HR 1.54, 95% CI 1.16 – 2.05, p=0.003) and with high/very high disease risk index compared to low/intermediate disease risk (HR 1.64, 95% CI 1.22 – 2.22, p=0.001). The 2-year adjusted probability of disease-free survival after HLA-haploidentical relative donor and umbilical cord blood transplant were 47% (95% CI 40 – 53) and 43% (95% CI 33 – 51), Figure 2B, p=0.46.

GVHD-free, relapse-free survival

GVHD-free relapse-free survival (GRFS) did not differ by donor type (HR 1.28, 95% CI 0.98 – 1.67, p=0.07). The only factor associated with GRFS was conditioning regimen intensity. Compared to myeloablative conditioning regimens, non-myeloablative regimens were associated with lower risks for GRFS (HR 0.77, 95% CI 0.60 – 0.99, p=0.04). The 2-year probability of GRFS adjusted for conditioning regimen intensity after HLA-haploidentical relative donor and umbilical cord blood transplant was 23% (95% CI 18 – 29) and 22% (95% CI 15 – 30), p=0.81.

Subset analysis of recipients of umbilical cord blood transplant

We examined whether outcomes after umbilical cord blood transplantation differed between African Americans included in the current analysis and Caucasians (n=715) who met the study's eligibility criteria. The characteristics of the cohort are shown in a Supplemental Table 1. The median TNC of cord blood unit(s) for Caucasians (4.45×10^7/kg [IQR 3.72 – 5.49]) and did not differ from that for African Americans (p=0.27). African Americans were more likely to receive unit(s) mismatched at 2 HLA-loci compared to Caucasians (80% versus 56%, P<0.001). Results of multivariate analysis confirmed transplant-related mortality (HR 1.04, 95% CI 0.72 – 1.49, p=0.85), relapse (HR 1.07, 95% CI 0.73 – 1.56, p=0.73), disease-free (HR 1.08, 95% CI 0.83 – 1.40, p=0.58) and overall survival (HR 0.92, 95% CI 0.69 – 1.22, p=0.56) were not different between African Americans and Caucasians.

DISCUSSION

The current analysis sought to study whether survival after HLA-haploidentical related donor transplant would be better when compared to umbilical cord blood transplant for African Americans with hematologic malignancy. Although we did not record differences in survival between the two donor types, grade II-IV and III-IV acute GVHD and transplant-

related mortality were higher after umbilical cord blood transplants. It is noteworthy that with longer follow up, the early adverse effect on survival after umbilical cord blood transplantation is negated by lower relapse rate although this did not reach the level of significance set for the current analysis. Relatively low relapse rates after umbilical cord blood has been documented by others and thought to be attributed to graft-versus-leukemia effect.[17–20] Intensified immunosuppression with post-transplant cyclophosphamide after HLA-haploidentical related donor transplant may blunt the CD4+ T-cell response and dampening of graft-versus-leukemia activity.[21] With 2-year overall survival of 57% and 54% after HLA-haploidentical relative and umbilical cord blood transplantation both donor options should be considered. Whether preference should be given to an HLA-haploidentical relative when available to lower the burden of morbidity associated with acute GVHD and lower transplant-related mortality or umbilical cord blood with an advantage for relapse control merits a careful discussion with the patient. Although it is assumed that all patients have a suitable HLA-haploidentical relative there are challenges. A single-center in the United States that prospectively studied donor availability in potential transplant recipients reported only 44% of African Americans were able to identify a suitable HLA-haploidentical relative.[22]

As an earlier report recorded worse survival for African Americans compared to Caucasians after umbilical cord blood transplantation, we compared outcomes of African American recipients in the current analysis to a comparable group of Caucasians and observed similar outcomes. The cell dose of unit(s) was comparable but African Americans were more likely to receive units mismatched at 2 HLA-loci. Most transplants mismatched at 1 or 2-HLA-loci at lower resolution are mismatched at 3 or more HLA-loci considering allele-level HLA match and associated with higher transplant-related mortality.[23] Therefore, we hypothesize that higher transplant-related mortality after umbilical cord blood compared to HLA-haploidentical relative donor transplantation may in part be explained by a higher rate of acute GVHD[24] infections[25] and HLA-disparity[23] after umbilical cord blood. The high rates of acute GVHD after umbilical cord blood transplants is explained by exclusion of anti-thymocyte globulin to transplant regimens and the predominant use of myeloablative conditioning regimens.[24] The use of post-transplant cyclophosphamide for GVHD prophylaxis for HLA-haploidentical relative transplants led to the low rates of grade II-IV and III-IV acute GVHD.[26] The feasibility of using lower dose post-transplant cyclophosphamide for umbilical cord blood transplant is being investigated.[27]

We performed a carefully controlled analysis but acknowledge the modest numbers of African Americans although this the largest to-date that is known to us. Although the study population included acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome and non-Hodgkin lymphoma, half of the study population had acute myeloid leukemia. We did not observe differences in outcome by disease type but with modest numbers of patients in each of the disease categories this study does not have statistical power to detect significant differences by disease type. We do not have data on immune reconstitution for either donor type and it is plausible delayed immune reconstitution after umbilical cord blood transplantation may have contributed to higher transplant-related mortality although none received in vivo T-cell depletion.[28] In summary, both donor types

offer comparable overall survival and strategies to improve outcomes after HLA-haploidentical relative and umbilical cord blood are desirable.

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Highlights

- HLA-haploidentical and umbilical cord blood extend access to transplantation
- Higher grade II-IV and III-IV acute GVHD after umbilical cord blood transplantation
- Higher transplant-related mortality after umbilical cord blood transplantation

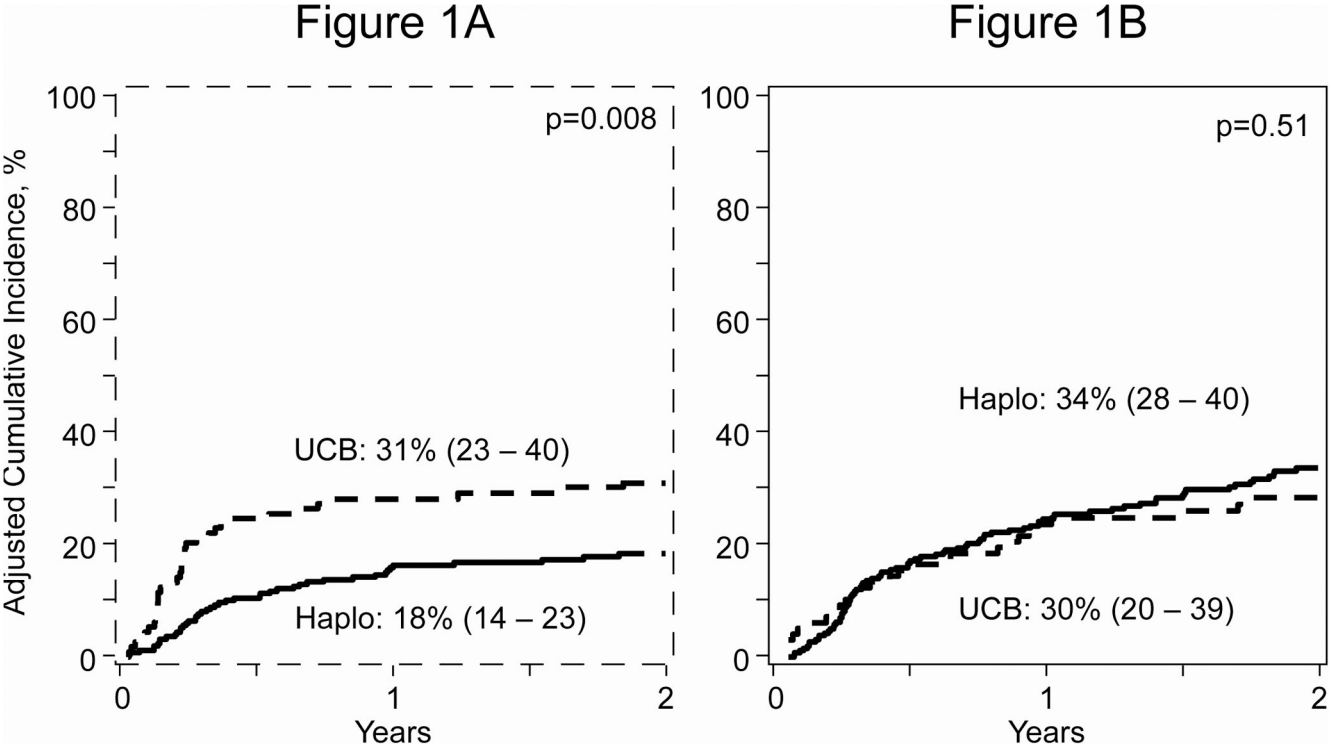

Figure 1.

A: Transplant-related mortality. The 2-year incidence of transplant-related mortality adjusted for age and conditioning regimen intensity was 18% (95% CI 14 – 23) for HLA-haploidentical related donor and 31% (95% CI 23 – 40) for umbilical cord blood. B: Relapse. The 2-year incidence of relapse adjusted for disease risk index and conditioning regimen intensity was 34% (95% CI 28 – 40) for HLA-haploidentical related donor and 30% (95% CI 20 – 39) for umbilical cord blood.

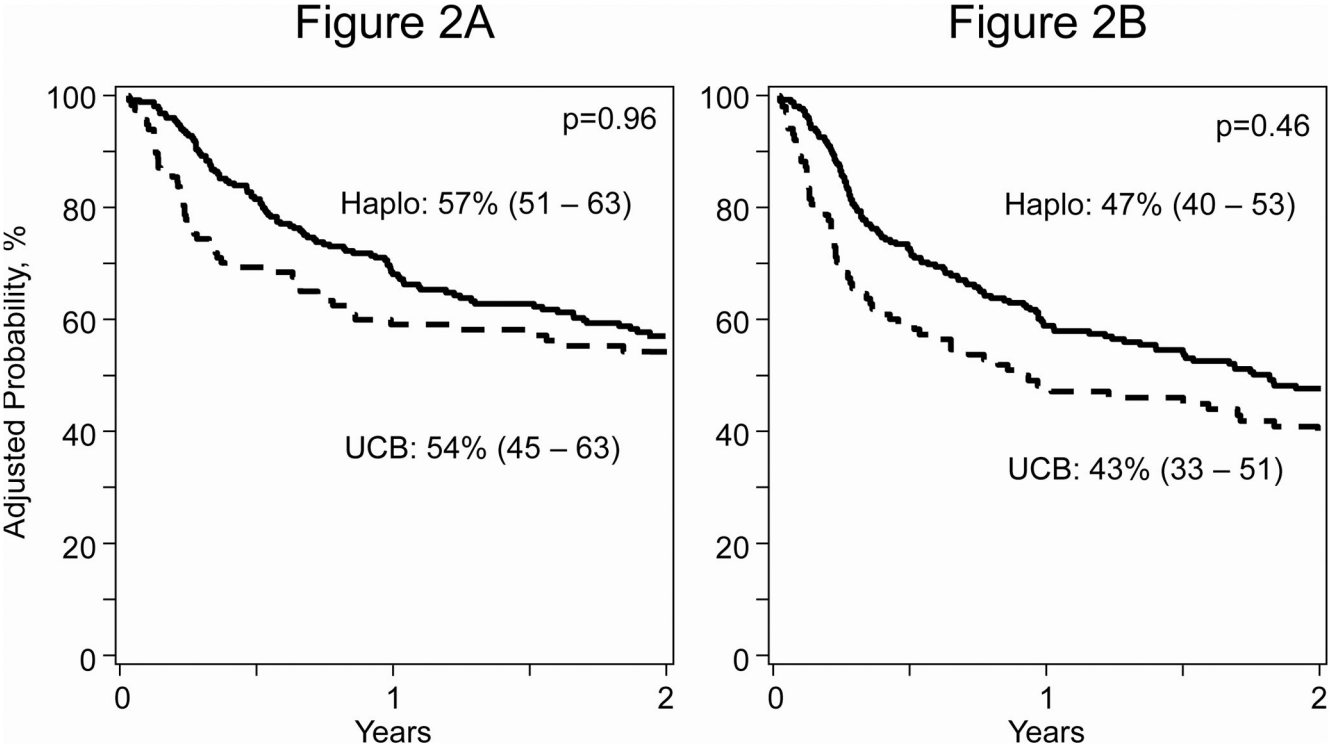

Figure 2.

A: Overall survival. The 2-year probability of overall survival adjusted for age and disease risk index was 57% (95% CI 51 – 63) for HLA-haploidentical related donor and 54% (95% CI 45 – 63) for umbilical cord blood. B: Disease-free survival. The 2-year probability of disease-free survival adjusted for age and disease risk index was 47% (95% CI 40 – 53) for HLA-haploidentical related donor and 43% (95% CI 33 – 51) for umbilical cord blood.

Table 1.

Patient, disease and transplant characteristics

	HLA-haploidentical relative	Umbilical cord blood	p-value
Number	249	118	
Age, years			<0.001
18 – 30	47 (19%)	27 (23)	
31 – 40	33 (13%)	35 (30)	
41 – 50	48 (19%)	29 (25)	
51 – 60	67 (27%)	14 (12)	
61 – 70	54 (22%)	13 (11)	
Sex, male/female	115 (46%)/134 54%)	58 (49%)/60 (51%)	0.59
Performance score			0.02
90 – 100	140 (56%)	83 (70)	
≤80	100 (40%)	34 (29)	
Not reported	9 (4%)	1 (<1)	
HCT - comorbidity index			0.75
≤2	137 (55%)	67 (57%)	
≥3	112 (45%)	51 (43%)	
Cytomegalovirus serostatus			0.007
Positive	192 (77%)	33 (28)	
Negative	57 (23%)	81 (69)	
Not reported	____	4 (3)	
Disease			0.56
Acute myeloid leukemia	130 (52%)	56 (47)	
Acute lymphoblastic leukemia	47 (19%)	26 (22)	
Myelodysplastic syndrome	34 (14%)	13 (11)	
Non-Hodgkin lymphoma	38 (15%)	23 (19)	
Disease risk index			0.08
Low	16 (6%)	9 (8)	
Intermediate	156 (63%)	80 (68)	
High	64 (26%)	29 (25)	
Disease status at transplant			
Acute myeloid/lymphoblastic leukemia			0.24
1st complete remission	121 (68%)	50 (61)	
2nd complete remission	56 (32%)	32 (39)	
Myelodysplastic syndrome			0.85
RA/RARS/RCMD	6 (18%)	2 (15)	
RAEB-1/RAEB-2	28 (82%)	11 (85)	
Non-Hodgkin lymphoma			0.004

	HLA-haploidentical relative	Umbilical cord blood	p-value
Complete remission	14 (37%)	11 (48)	
Partial remission	14 (37%)	—	
Progressive disease	10 (26%)	12 (52)	
Conditioning regimen			<0.001
Myeloablative	103 (41%)	85 (72)	
Non-myeloablative	146 (59%)	33 (28)	
Transplant period			<0.001
2008 – 2012	56 (22%)	65 (55)	
2013 – 2016	193 (78%)	53 (45)	
Follow-up. median (range), mo	25 (9 – 96)	47 (12 – 110)	

Table 2.

Transplant-related mortality, relapse, disease-free and overall survival by donor type

Outcome	Events/Evaluable	Hazard Ratio (95% confidence interval)	p-value
Transplant-related mortality *			
HLA-haploidentical relative	47/246	1.00	
Umbilical cord blood	36/111	1.99 (1.25 – 3.17)	0.004
Relapse #			
HLA-haploidentical relative	90/246	1.00	
Umbilical cord blood	31/111	0.99 (0.65 – 1.53)	0.99
Disease-free survival //			
HLA-haploidentical relative	137/246	1.00	
Umbilical cord blood	67/111	1.35 (0.99 – 1.83)	0.06
Overall survival ≠			
HLA-haploidentical relative	118/249	1.00	
Umbilical cord blood	66/118	1.24 (0.89 – 1.73)	0.20

* adjusted for age at transplant and conditioning regimen intensity

adjusted for disease risk index and conditioning regimen intensity

// adjusted for age at transplant and disease risk index

≠ adjusted for age at transplant and disease risk index