Leukemia (2017) **31**, 1408–1414

www.nature.com/leu

ORIGINAL ARTICLE

Outcomes of UCB transplantation are comparable in FLT3+ AML: results of CIBMTR, EUROCORD and EBMT collaborative analysis

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Allogeneic hematopoietic cell transplantation (HCT) from siblings or unrelated donors (URD) during complete remission (CR) may improve leukemia-free survival (LFS) in FMS-like tyrosine kinase 3+ (FLT3+) acute myeloid leukemia (AML), which has poor prognosis because of high relapse rates. Umbilical cord blood (UCB) HCT outcomes are largely unknown in this population. We found that compared with sibling HCT, relapse risks were similar after UCB ($n = 126$) (hazard ratio (HR) 0.86, $P = 0.54$) and URD ($n = 91$) (HR 0.81, $P = 0.43$). UCB HCT was associated with statistically higher non-relapse mortality compared with sibling HCT (HR 2.32, $P = 0.02$), but not vs URD (HR 1.72, $P = 0.07$). All three cohorts had statistically nonsignificant 3-year LFS: 39% (95% confidence interval (CI): 30–47) after UCB, 43% (95% CI: 30–54) after sibling and 50% (95% CI: 40–60) after URD. Chronic graft-versus-host disease rates were significantly lower after UCB compared with either sibling (HR 0.59, $P = 0.03$) or URD (HR 0.49, $P = 0.001$). Adverse factors for LFS included high leukocyte count at diagnosis and HCT during CR2 (second CR). UCB is a suitable option for adults with FLT3+ AML in the absence of an human leukocyte antigen-matched sibling and its immediate availability may be particularly important for FLT3+ AML where early relapse is common, thus allowing HCT in CR1 (first CR) when outcomes are best.

Leukemia (2017) **31,** 1408–1414; doi:10.1038/leu.2017.42

INTRODUCTION

FMS-like tyrosine kinase (FLT3), a receptor tyrosine kinase (TK), is present in early hematopoietic progenitors and influences the survival, proliferation and differentiation of hematopoietic cells. Mutation in the *FLT3* gene (FLT3+) has been reported in acute myeloid leukemia (AML). The internal tandem duplication (FLT3-ITD, 15–35%) and missense point mutations (5–10%) in the TK domain (TKD) are the most commonly detected mutations in the *FLT3* gene.[1,2] These mutations confer ligand-independent constitutive activation of the FLT3 kinase and its downstream signaling pathway, which stimulates AML cell proliferation.[3] Patients with FLT3+ AML share clinical, cytogenetic and molecular common features at diagnosis, typically presenting with high white blood cell (WBC) counts, normal cytogenetics, presence of the nucleophosmin (NPM1) gene mutation and FAB subtypes M4 and M5.[1] However, the prognosis of patients with FLT3+ AML is poor mainly because of frequent and early relapse in both adult and pediatric populations.[4–10]

Allogeneic hematopoietic cell transplantation (HCT) for FLT3+ AML from sibling or unrelated donors (URDs) has been most often reported in first complete remission (CR1) given the poor prognosis of disease.[11–19] Leukemia-free survival (LFS) at 2 years after HCT approximates to 50–60% in most studies,[8,13,20,21] although it ranges widely from 20% (refs 5,15) to 70%.[22] Umbilical cord blood (UCB) HCT has increasingly been used for patients when suitable human leukocyte antigen-matched donors are unavailable and when proceeding to transplantation is urgent,[23–29] potentially as in FLT3 + AML. The outcomes of UCB HCT are reportedly similar to sibling or URD HCT for various diseases.[24,30,31] The outcomes of patients with FLT3+ AML after UCB HCT are largely unknown, except for a recent University of Minnesota report.[32]

In this large retrospective study, we compared the efficacy of UCB HCT with matched sibling and URD grafts in FLT3+ AML using data from three large international observational registries. We hypothesized that relapse and LFS after UCB HCT would be similar to sibling or URD HCT.

PATIENTS AND METHODS

Data collection

The data on sibling and URD HCT were obtained solely from the Center for International Blood and Marrow Transplant Research (CIBMTR), a voluntary

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Received 8 September 2016; revised 11 December 2016; accepted 21 December 2016; accepted article preview online 25 January 2017; advance online publication, 14 February 2017

network of more than 450 transplant centers worldwide that report data on consecutive HCTs. Patient, disease and HCT characteristics and outcome data are reported on standardized forms submitted at the time of HCT (baseline) and at 100 days, 6 months and annually thereafter. Data on UCB HCT were obtained from the CIBMTR, Eurocord and the European Group for Blood and Marrow Transplantation (EBMT). All patients provided written informed consent for research. The Institutional Review Board of the National Marrow Donor Program and Eurocord approved this study.

Inclusion criteria

Included are adult FLT3+ AML patients (aged $\geqslant 18$ years) who received UCB HCT (single or double unit), sibling or URD HCT in CR1 or CR2 (second CR) between 2007 and 2012 as data on FLT3 mutation status was incompletely reported in prior years. The presence of FLT3+ mutation was reported by the transplant center. Assay method and quantitative data are not available. Previous HCT, *ex vivo* manipulated UCB, UCB combined with another source of stem cells and haploidentical donor HCTs were excluded. There were no exclusions regarding conditioning regimen, alemtuzumab or antithymocyte globulin use or regimen intensity.

Definitions

Cytogenetic data (G-banding and/or fluorescence *in situ* hybridization analyses) at diagnosis were classified according to the Southwest Oncology Group/European Leukemia Net.[33,34] LFS and CR were defined according to the International Working Group criteria.[35] Conditioning regimen intensity was based on the report of Bacigalupo *et al.*[36]

End points

Relapse, the primary end point, was defined as morphological recurrence of disease, and non-relapse mortality (NRM) was considered a competing risk. Molecular (*FLT3* mutation) evidence of leukemia as well as TK use before or after HCT was not considered for relapse or measures of minimal residual disease as these data were not available. Secondary end points included LFS, NRM and overall survival (OS). Relapse or death from any cause was considered an event for LFS—the opposite of treatment failure. NRM was defined as death in remission, and disease relapse was considered a competing risk. Neutrophil recovery was defined as achieving an absolute neutrophil count of $\geqslant 0.5\times10^9$/l for the first of three measurements. Platelet recovery was defined as achieving platelets $\geqslant 20\times10^9$/l, unsupported by platelet transfusion for 7 days. Grade II–IV acute and chronic graft-versus-host disease (GVHD) were graded using the standard criteria.[37,38] For neutrophil recovery, platelet recovery, acute and chronic GVHD, death without specific event was considered a competing risk. Study subjects were right-censored if corresponding event was not observed at the end of study.

Statistical analysis

Patient-, disease- and transplant-related variables for donor types were compared using χ^2 statistics for categorical variables and the Kruskal–Wallis test for continuous variables. Probabilities for relapse, NRM and GVHD were calculated using the cumulative incidence estimator to accommodate competing risks. Kaplan–Meier estimates were used to calculate the probability of LFS and OS. The composite end point of GVHD-free (no grade III/IV acute GVHD and no chronic GVHD), relapse-free survival point estimates are provided using unadjusted Kaplan–Meier estimates. Time to event end points were measured from the date of HCT. The Cox proportional hazards regression model was used to identify risk factors associated with acute and chronic GVHD, relapse, NRM, LFS (treatment failure) and OS (overall mortality). As the primary variable of interest was donor type (UCB vs HLA-matched sibling vs URD), this variable was included in all steps of model building regardless of level of significance. For other variables, a forward selection method was used to build the regression models. Variables tested included age (18–29 vs 30–49 vs 50–69 years), gender (male vs female), performance score (90–100 vs <90), WBC count at diagnosis (<10 vs 11–50×10^9/l vs $>50\times10^9$/l), cytogenetic risk group (favorable/intermediate vs adverse), time from diagnosis to CR1 (<5 vs 5–8 vs >8 weeks) and disease status at HCT (CR1 vs CR2). None of the variables violated the assumptions of proportionality. Variables that were statistically significant with *P*-value $\leqslant 0.05$ were retained in the final models. There were no first-order interactions between the main effect (donor type) and variables in the final multivariate models. Adjusted probabilities of LFS and survival, and adjusted cumulative incidence functions of NRM, relapse and acute and chronic GVHD were calculated using the multivariate models, stratified on type of transplant and weighted by the pooled sample proportion value for each prognostic factor.[39,40] These adjusted probabilities estimate likelihood of outcomes in populations with similar prognostic factors. All analyses were carried out using the statistical package SAS version 9.3 (Cary, NC, USA).

RESULTS

A total of 284 FLT3+ AML patients received HCT. Their clinical and treatment characteristics are shown in Table 1. One hundred and twenty-six patients received unrelated UCB (76 (60%) double units UCB grafts), 91 patients received peripheral blood ($n=73$) or bone marrow ($n=18$) from adult URD donors and 67 patients received peripheral blood ($n=64$) or bone marrow ($n=3$) from HLA-matched siblings. The median ages of the three graft-type groups (UCB, sibling, URD) ranged from 41 to 48 years. Approximately 80% of HCTs occurred in CR1 and the most common conventional cytogenetic risk was intermediate (i.e., normal karyotype) in all treatment groups. The median time to achieve CR1 was 5 weeks for the adult donor HCT and 6 weeks for UCB HCT. Among patients transplanted in CR1, approximately half of sibling HCT recipients received their HCT <12 weeks from achieving CR1 (median time to HCT 11 weeks). In contrast, only 20% of UCB and URD recipients received their HCT within 12 weeks from CR1 (median time to HCT 17 and 16 weeks, respectively). Most recipients of sibling and URD HCT received myeloablative-conditioning regimen (MAC), while a third of UCB recipients received a reduced intensity-conditioning (RIC) regimen. Although most patients received calcineurin inhibitor containing GVHD prophylaxis, mycophenolate was the predominant second agent for UCB HCT vs methotrexate for sibling and URD HCT. The median follow-up of survivors in each of the treatment groups was 3 years.

Relapse and LFS

The primary outcome of interest was relapse after HCT. After adjusting for the effects of WBC count at diagnosis and disease status at the time of HCT, there were no significant differences in relapse risks between UCB or HLA-matched siblings or URD donors (Table 2), and no difference between UCB HCT compared with URD (hazard ratio (HR) 1.05, 95% confidence interval (CI): 0.65–1.69, $P=0.84$). The 3-year probabilities of relapse, adjusted for WBC count and remission status were: HLA-matched sibling 44% (95% CI: 31–55); UCB 33% (95% CI: 25–42) and URD 33% (95% CI: 24–42), $P>0.72$ (Figure 1 and Supplementary Table 1). Pairwise comparisons between each donor type were not significant (all $P>0.16$) (Supplementary Table 1). Relapse risks were higher in patients with WBC $>50\times10^9$/l at diagnosis compared with $\leqslant 10\times10^9$/l (HR 2.72, 95% CI: 1.52–4.86, $P=0.0007$) and in those receiving HCT in CR2 compared with CR1 (HR 1.83, 95% CI: 1.17–2.84, $P=0.008$).

After adjusting for the effects of WBC count at diagnosis and disease status at the time of HCT, the risk of treatment failure (relapse or death; inverse of LFS) was similar after UCB and URD HCTs as compared with HLA-matched sibling HCT (Table 2). Similarly, there was no significant difference in the risk of treatment failure after UCB compared with URD HCT (HR 1.27, 95% CI: 0.87–1.85, $P=0.21$). The 3-year probabilities of LFS, after adjusting for WBC count and disease status were 43% (95% CI: 30–54), 39% (95% CI: 30–47) and 50% (95% CI: 40–60) after HLA-matched sibling, UCB and URD HCTs, respectively, $P=0.42$ (Figure 2 and Supplementary Table 1). The risk of treatment failure was greater in patients with WBC $>50\times10^9$/l at diagnosis (HR 2.16, 95% CI: 1.37–3.40, $P=0.0009$) and for patients receiving HCTs in CR2 (HR 1.67, 95% CI: 1.17–2.39, $P=0.005$).

Table 1. Patients characteristics

Variable	*HLA-matched sibling*	*Unrelated donor*	*Umbilical cord blood*	P-*value*
Number	67	91	126	
Gender				0.91
Male	31 (46)	39 (43)	55 (44)	
Female	36 (54)	52 (57)	71 (56)	
Age (years)				0.02
Median (range)	48 (18–59)	43 (19–60)	41 (18–67)	0.002
18–29	5 (7)	21 (23)	34 (27)	
30–49	31 (46)	39 (43)	58 (46)	
50–69	31 (36)	31 (34)	34 (27)	
Performance score				0.04
<90	21 (31)	28 (31)	22 (17)	
90–100	42 (63)	60 (66)	101 (80)	
Not reported	4 (6)	3 (3)	3 (2)	
WBC count at diagnosis				<0.001
$\leqslant 10x10^9$/l	18 (27)	21 (23)	22 (17)	
11–$50x10^9$/l	26 (39)	31 (34)	29 (23)	
$>50x10^9$/l	22 (33)	34 (37)	41 (33)	
Not reported	1 (1)	5 (5)	34 (27)	
Cytogenetic risk				0.65
Favorable	2 (3)	3 (3)	5 (4)	
Intermediate	55 (82)	73 (80)	106 (84)	
Poor	9 (13)	11 (12)	8 (6)	
Missing	1 (1)	4 (4)	7 (6)	
Recipient CMV				0.30
Negative	25 (37)	35 (38)	39 (31)	
Positive	42 (63)	54 (59)	84 (67)	
Missing	0	2 (2)	3 (2)	
Time to CR1 (weeks)				0.02
$\leqslant 5$	36 (54)	44 (48)	37 (29)	
6–8	18 (27)	24 (26)	39 (31)	
>8	8 (12)	16 (18)	36 (29)	
Not reported	5 (7)	7 (8)	14 (11)	
Disease status, HCT				0.82
CR1	52 (78)	73 (80)	97 (77)	
CR2	15 (22)	18 (20)	29 (23)	
Duration of CR1				0.21
<12 months	12 (80)	11 (61)	17 (59)	
$\geqslant 12$ months	2 (13)	5 (28)	3 (10)	
Missing	1 (7)	2 (11)	9 (31)	
Conditioning regimen				
Myeloablative				
TBI+Cy ± other	37 (55)	35 (38)	45 (36)	
TBI+other	2 (3)	0	5 (4)	
Bu+Cy/other	22 (33)	42 (46)	33 (26)	
Other[a]	0	0	3 (2)	
Reduced intensity				
Bu+Flu	4 (6)	8 (9)	0	
TBI 200 cGy ± Flu ± other	0	3 (3)	40 (32)	
Other[a]	2 (3)	3 (3)	0	
Graft type				
Bone marrow	3 (4)	18 (20)		
Peripheral blood	64 (96)	73 (80)		
Umbilical cord blood				
Single			50 (40)	
Double			76 (60)	
GVHD prophylaxis				
CsA/Tac+MMF	10 (15)	17 (19)	97 (77)	
CsA/Tac+MTX	42 (63)	69 (76)	1 (<1)	
CsA/Tac+other	15 (22)	2 (2)	21 (17)	
Other[b]	0	3 (3)	7 (6)	
Transplant period				0.68
2007–2009	33 (49)	47 (52)	57 (45)	
2010–2012	34 (51)	44 (48)	69 (55)	
Follow-up, median (range), months	37 (13–61)	37 (12–65)	37 (6–84)	

Abbreviations: ATG, antithymocyte globulin; Bu, busulfan; Clo, clofarabine; CMV, cytomegalovirus; CR, complete remission; CsA, cyclosporine; Cy, cyclophosphamide; Flu, fludarabine; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplant; Mel, melphalan; MMF, mycophenolate mofetil; MTX, methotrexate; RIC, reduced intensity conditioning; Tac, tacrolimus; TBI, total body irradiation; Thio, thiotepa; TLI, total lymphoid irradiation; WBC, white blood cell. [a]MAC other: Flu+Mel+Thio+ATG, $n=3$ and RIC other: Bu+Clo, $n=1$; Flu+Mel, $n=1$; TLI+ATG, $n=3$. [b]Other GVHD prophylaxis: MTX, $n=2$; unknown, $n=9$.

Table 2. Multivariate analysis using proportional hazards model for relapse, NRM, LFS and OS

Variables	*Relapse*				*NRM*			*LFS*			*OS*		
	N	*RR*	*95% CI*	P-*value*	*RR*	*95% CI*	P-*value*	*RR*	*95% CI*	P-*value*	*RR*	*95% CI*	P-*value*
Graft source/donor				0.72			0.01			0.42			0.26
BM/PB sibling	67	1			1			1			1		
BM/PB unrelated	91	0.81	0.49–1.36	0.43	1.49	0.65–3.38	0.34	0.94	0.61–1.45	0.78	1.09	0.69–1.70	0.72
UCB	126	0.86	0.52–1.42	0.54	2.83	1.33–6.04	0.007	1.19	0.79–1.80	0.40	1.36	0.9–2.06	0.14
Time from diagnosis to CR1							0.056						
< 5 weeks	117				1								
5–8 weeks	81				0.37	0.18–0.75	0.0063						
⩾8 weeks	60				0.74	0.38–1.41	0.36						
Missing	26				0.66	0.25–1.70	0.38						
WBC count at diagnosis				0.001						0.0031			
⩽10	61	1						1					
10–50	86	1.48	0.78–2.79	0.23				1.44	0.89–2.33	0.14			
>50	97	2.72	1.52–4.86	0.0007				2.16	1.37–3.40	0.0009			
Missing	40	1.18	0.52–2.66	0.69				1.22	0.67–2.21	0.52			
Disease status before HCT													
CR1	222	1						1			1		
CR2	62	1.83	1.17–2.84	0.0076				1.67	1.17–2.39	0.0052	1.55	1.08–2.22	0.019

Abbreviations: BM, bone marrow; CI, confidence interval; CR, complete remission; HCT, hematopoietic cell transplantation; LFS, leukemia-free survival; NRM, non-relapse mortality; OS, overall survival; PB, peripheral blood; RR, relative risk; UCB, umbilical cord blood; WBC, white blood cell.

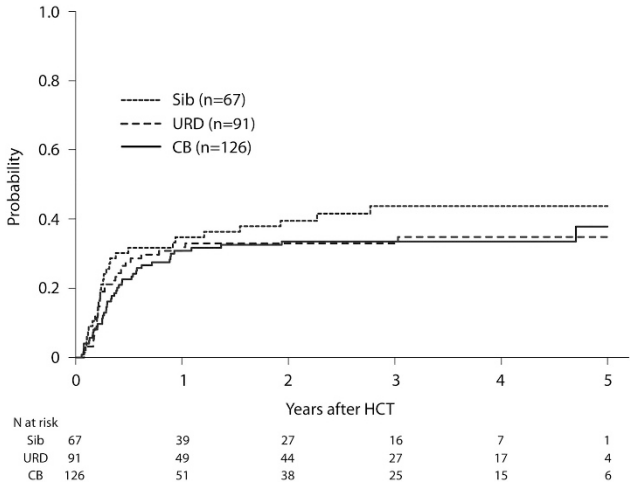

Figure 1. Adjusted cumulative incidence of relapse by donor type. The 3-year probabilities of relapse, adjusted for WBC count and remission status, were 44% (95% CI: 31–55), 33% (95% CI: 25–42) and 33% (95% CI: 24–42) after HLA-matched sibling, UCB and URD HCTs, respectively ($P = 0.72$).

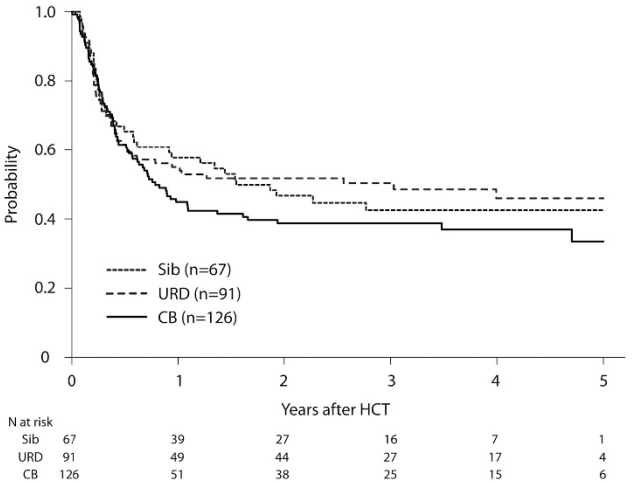

Figure 2. Adjusted LFS by donor type. The 3-year probabilities of LFS, after adjusting for WBC and disease status were 43% (95% CI: 30–54), 39% (95% CI: 30–47) and 50% (95% CI: 40–60) after HLA-matched sibling, UCB and URD HCTs, respectively ($P = 0.42$).

NRM and OS

Compared with HLA-matched sibling HCT, NRM risks were higher after UCB HCT, but not after URD HCT (Table 2). NRM risks were marginally, but not significantly, higher after UCB HCT compared with URD HCT (HR 1.72, 95% CI: 0.95–3.12, $P = 0.07$). The 3-year probabilities of NRM were 14% (95% CI: 7–23), 28% (95% CI: 20–36) and 17% (95% CI: 10–25) after HLA-matched sibling, UCB and URD HCTs, respectively (Figure 3 and Supplementary Table 1). However, there were no significant differences in risks of overall mortality between the three donor types (Table 2). The 3-year probabilities of OS, adjusted for disease status were 46% (95% CI: 33–59), 43% (95% CI: 34–52) and 50% (95% CI: 39–60) after HLA- matched sibling, UCB and URD HCTs, respectively ($P = 0.26$ (Figure 4). The most common cause of death was disease relapse for each treatment group (Supplementary Table 2). Overall mortality was higher for HCTs in CR2 (1.55, 95% CI: 1.08–2.22, $P = 0.02$) (Table 2).

Hematopoietic recovery and GVHD

The median time to reach neutrophil engraftment was longer for UCB HCT (day +22) compared with HLA-matched sibling and URD HCTs (day +14 for each) ($P < 0.001$). However, by day +60, there was no significant difference in engraftment among the three groups. Compared with HLA-matched sibling HCT, grade II–IV acute GVHD risks were higher after URD HCT (HR 1.85, 95% CI:

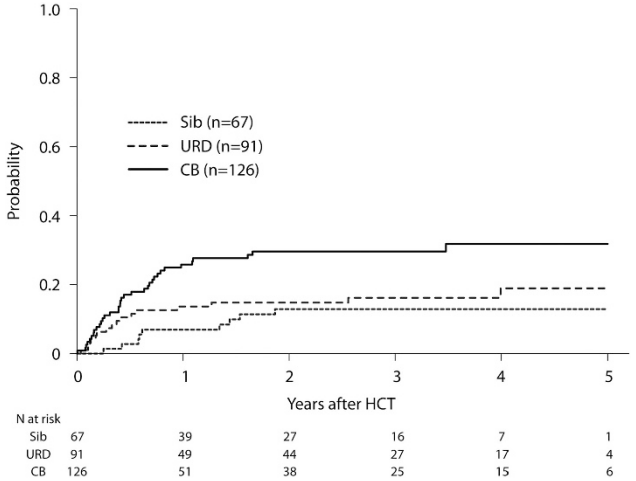

Figure 3. Adjusted cumulative incidence of NRM by graft source. The 3-year probabilities of NRM, after adjusting for time from diagnosis to CR1 were 14% (95% CI: 7–23), 28% (95% CI: 20–36) and 17% (95% CI: 10–25) after HLA-matched sibling, UCB and URD HCTs, respectively. Pairwise comparisons: UCB vs URD, $P = 0.07$; UCB vs sibling, $P = 0.02$; URD vs sibling, $P = 0.47$.

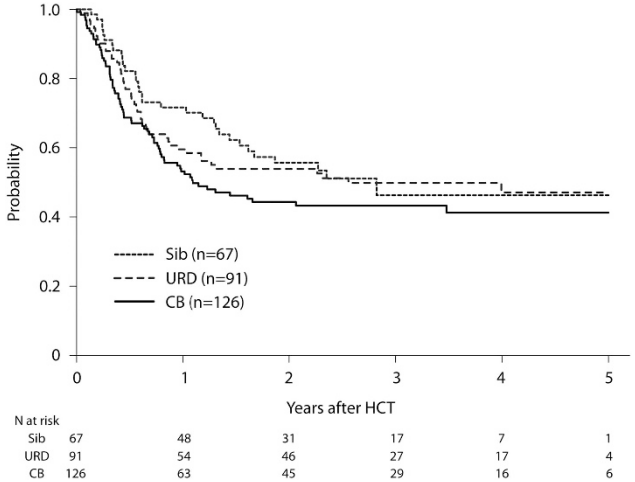

Figure 4. Adjusted OS by donor type. The 3-year probabilities of OS, adjusted for disease status were 46% (95% CI: 33–59), 43% (95% CI: 34–52) and 50% (95% CI: 39–60) after HLA-matched sibling, UCB and URD HCTs, respectively ($P = 0.26$).

1.08–3.15, $P = 0.02$), but were not statistically different after UCB HCT (HR 1.66, 95% CI: 0.99–2.78, $P = 0.06$). The day-100 probabilities of acute GVHD were 27% (95% CI: 17–38), 42% (95% CI: 33–50) and 45% (95% CI: 35–56) after HLA-matched sibling, UCB and URD HCTs, respectively. In contrast, chronic GVHD risks were significantly lower after UCB HCT compared with HLA-matched sibling (HR 0.59, 95% CI: 0.37–0.94, $P = 0.03$) or URD HCT (HR 0.50, 95% CI: 0.32–0.76, $P = 0.001$). Chronic GVHD risks were similar after HLA-matched sibling or URD HCT (HR 1.19, 95% CI: 0.77–1.83, $P = 0.44$). The 3-year probabilities of chronic GVHD were 62% (95% CI: 49–75), 32% (95% CI: 24–41) and 60% (95% CI: 49–70) after HLA-matched sibling, UCB and URD HCTs, respectively.

GVHD-free, relapse-free survival at year 1 and 3 years was slightly, but not significantly, higher in UCB HCT (26%, 95% CI: 18–34 and 20%, 95% CI: 14–28) vs sibling HCT (16%, 95% CI: 9–26 and 5%, 95% CI: 1–12) or URD HCT (16%, 95% CI: 10–25 and 8%, 95% CI: 3–15), $P = 0.12$.

Prognostic factors in UCB HCT

In the cohort of UCB HCTs, the 2-year relapse risk was significantly lower in patients receiving MAC compared with RIC (25%, 95% CI: 16–35% vs 45%, 95% CI: 30–61, $P = 0.03$). In contrast, NRM risk at 2 years was significantly higher in patients receiving MAC compared with RIC (37%, 95% CI: 16–35% vs 13%, 95% CI: 4–25, $P = 0.009$). This resulted in similar 2-year LFS for MAC (38%, 95% CI: 27–49) and RIC (42%, 95% CI: 27–58, $P = 0.65$) UCB HCTs and similar 2-year OS for MAC (40%, 95% CI: 30–51) and RIC (52%, 95% CI: 37–67, $P = 0.21$). The number of UCB units infused (i.e., single vs double) had no impact on any reported outcomes.

DISCUSSION

In this study, we found that FLT3+ AML patients receiving UCB HCT had no statistically significant difference in relapse and LFS rates compared with HLA-matched sibling or URD HCTs. This is concordant with prior studies comparing UCB with other graft sources.[24,30,41] In our study, despite a greater proportion of UCB recipients receiving RIC than MAC (32% vs sibling 9% and MUD 15%), which is associated with higher relapse rates in patients with AML, with or without *FLT3* mutation,[19,42] the adjusted risks of relapse and treatment failure were similar for the three groups. UCB HCT patients also had a longer duration to reach CR1. Therefore, our data support an inference that there is graft-versus-leukemia effect after single or double UCB HCT,[24,43] even for FLT3+ AML and its attendant high risk of relapse. Consistent with our large multicenter study, a single center study on 66 AML patients (22 FLT3+ and 44 FLT3 −) receiving UCB HCT showed that the negative effect of FLT3+ AML was overcome by UCB HCT.[32] Two-year relapse rate was for FLT3+ AML 29%, whereas 36% for FLT − AML, which led to LFS: 48% vs 37%, and OS: 47% vs 42% in FLT3+ AML vs FLT3 − AML, respectively). As the high-risk nature of FLT3+ AML and the need for aggressive consolidation with allogeneic HCT is well recognized, our observation has major clinical implications for FLT3+ AML patients in CR after initial therapy. Non-HCT consolidative chemotherapies may lead to increased FLT3 ligand plasma levels and thus resistance to further therapies.[44] Our data demonstrates that performing allogeneic HCT as consolidation in CR1 yields favorable outcomes given poorer survival for HCT during CR2.

The higher NRM after UCB HCT may be attributed to slower hematopoietic recovery and subsequent infections.[24,45,46] Some UCB reports suggest that acute GVHD risks are similar or lower than after HLA-matched sibling HCT or URD HCT.[24,47,48] The notably lower risks of chronic GVHD offset these early complications in UCB HCT.[24,49–51] In this study, while the incidence of acute GVHD after UCB was not significantly different than other graft types; however, chronic GVHD was significantly less frequent after UCB HCT. Although there was no statistically significant difference observed, OS was slightly lower and GRFS was slightly better for UCB HCT compared with other donor grafts.

We had insufficient data available to separately analyze FLT3/ITD+ or FLT3/TKD+ AML or the *FLT3*-mutant allelic burden[5,9,52,53] and had only incomplete data on NPM1 mutations. In the literature, *FLT3*/ITD mutation is frequently associated with poor prognosis; this is less certain for the *FLT3*/TKD mutation.[4,15] While the coexistence of *NPM1* mutations in patients with FL3/ITD+ AML may influence the risk of relapse,[21,54] a recent study from MD Anderson showed that allogeneic HCT remained statistically significant with improved RFS and OS independent of *FLT3*/ITD allelic ratio and *NPM1* mutation status in multivariate regression models.[55] This might not be true for RIC allogenic HCT.[56] In our study, we were unable address this controversial issue. Interestingly, we observed that high WBC ($>50\times10^9$/l) at

diagnosis was found to be associated with a higher relapse risk[57] and it may be correlated with the *FLT3*/ITD allelic ratio.[1,5,57,58] As expected, HCT during CR2 was also associated with significant increased relapse and with inferior LFS and OS. Another potential limitation of the study is that the available data from the three international registries had differing number of cases using each graft type. While referral patterns and graft choices and the resultant influence on outcomes might differ in the cases reported from each registry, we could not directly probe this possibility with available data. We could not evaluate HCT-comorbidity index, shown to be associated with NRM and OS,[59] because of insufficient data.

These data support the use of UCB as a donor graft for patients with FLT3+ AML who lack a readily available HLA-matched sibling donor. Our data also suggest that delay to HCT in these patients with an expectedly short CR1 adversely affects outcomes, possibly further favoring the more quickly available UCB. Studies on the use of partially matched related donors, as yet another rapidly available donor type are warranted. Additionally, following any donor HCT, post-transplant maintenance with FLT3 inhibitors seems promising because 30–40% of patients still relapse after allogeneic HCT regardless of graft type.[60]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

The CIBMTR is supported by Public Health Service Grant/Cooperative Agreement 5U24-CA076518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI) and the National Institute of Allergy and Infectious Diseases (NIAID); a Grant/Cooperative Agreement 5U10HL069294 from NHLBI and NCI; a contract HHSH250201200016C with Health Resources and Services Administration (HRSA/DHHS); two Grants N00014-15-1-0848 and N00014-16-1-2020 from the Office of Naval Research; and grants from Alexion; *Amgen Inc.; Anonymous donation to the Medical College of Wisconsin; Astellas Pharma US; AstraZeneca; Be the Match Foundation; *Bluebird Bio Inc.; *Bristol Myers Squibb Oncology; *Celgene Corporation; Cellular Dynamics International Inc.; *Chimerix Inc.; Fred Hutchinson Cancer Research Center; Gamida Cell Ltd; Genentech Inc.; Genzyme Corporation; *Gilead Sciences Inc.; Health Research Inc. Roswell Park Cancer Institute; HistoGenetics Inc.; Incyte Corporation; Janssen Scientific Affairs, LLC; *Jazz Pharmaceuticals Inc.; Jeff Gordon Children's Foundation; The Leukemia and Lymphoma Society; Medac GmbH; MedImmune; The Medical College of Wisconsin; *Merck & Co. Inc.; Mesoblast; MesoScale Diagnostics Inc.; *Miltenyi Biotec Inc.; National Marrow Donor Program; Neovii Biotech NA Inc.; Novartis Pharmaceuticals Corporation; Onyx Pharmaceuticals; Optum Healthcare Solutions Inc.; Otsuka America Pharmaceutical Inc.; Otsuka Pharmaceutical Co. Ltd, Japan; PCORI; Perkin-Elmer Inc.; Pfizer Inc.; *Sanofi US; *Seattle Genetics; *Spectrum Pharmaceuticals Inc.; St Baldrick's Foundation; *Sunesis Pharmaceuticals Inc.; Swedish Orphan Biovitrum Inc.; Takeda Oncology; Telomere Diagnostics Inc.; University of Minnesota; and *Wellpoint Inc. The views expressed in this article do not reflect the official policy or position of the National Institute of Health, the Department of the Navy, the Department of Defense, Health Resources and Services Administration (HRSA) or any other agency of the US Government.

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Supplementary Information accompanies this paper on the Leukemia website (http://www.nature.com/leu)