

ORIGINAL ARTICLE

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

C Ustun¹, F Giannotti^{2,3}, M-J Zhang^{4,5}, H-L Wang⁴, C Brunstein⁶, M Labopin^{7,8}, V Rocha⁹, M de Lima¹⁰, F Baron¹¹, BM Sandmaier¹², M Eapen⁴, E Gluckman^{3,13}, A Nagler^{14,15}, DJ Weisdorf¹⁶ and A Ruggeri^{2,3}

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

¹Division of Hematology, Oncology and Transplantation, Department of Medicine, University of Minnesota Medical Center, Minneapolis, MN, USA; ²Service d'Hématologie et Thérapie Cellulaire, Hôpital Saint Antoine, AP-HP, Paris, France; ³Eurocord, APHP, University Paris Diderot, Hôpital Saint Louis, Paris, France; ⁴CIBMTR (Center for International Blood and Marrow Transplantation), Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA; ⁵Division of Biostatistics, Institute for Health and Society, Medical College of Wisconsin, Milwaukee, WI, USA; ⁶University of Minnesota Medical Center Fairview, Minneapolis, MN, USA; ⁷European Group for Blood and Marrow Transplantation, Leiden, The Netherlands; ⁸Sorbonne Universités, Centre de Recherche (CDR), Saint Antoine, Paris, France; ⁹Churchill Hospital, Oxford, UK; ¹⁰Department of Medicine, Seidman Cancer Center, University Hospitals Case Medical Center, Cleveland, OH, USA; ¹¹Centre Hospitalier Universitaire de Liège, Domaine Universitaire du Sart Tilman, Leige, Belgium; ¹²Division of Medical Oncology, University of Washington and Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; ¹³Monacord, Centre Scientifique de Monaco, Monaco; ¹⁴The Bone Marrow Transplantation Department, Division of Internal Medicine, The Chaim Sheba Medical Center, Ramat-Gan, Israel; ¹⁵Sheba Cord Blood Bank, Rama-Gan, Israel and ¹⁶Division of Hematology, Oncology and Transplantation, Department of Medicine, University of Minnesota Medical Center, Minneapolis, MN, USA. Correspondence: Dr C Ustun, Department of Medicine, Division of Hematology, Oncology and Transplantation, University of Minnesota, Mayo mail code 480, 420 Delaware Street SE, Minneapolis, MN 55455, USA.

E-mail: custun@umn.edu

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 ≥ 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 $\geq 0.5 \times 10^9/l$ for the first of three measurements. Platelet recovery was defined as achieving platelets $\geq 20 \times 10^9/l$, 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 $11–50 \times 10^9/l$ vs $> 50 \times 10^9/l$), 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 ≤ 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 $> 50 \times 10^9/l$ at diagnosis compared with $\leq 10 \times 10^9/l$ (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 $> 50 \times 10^9/l$ 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
≤ 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
≤ 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)	
≥ 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. ^aMAC other: Flu+Mel+Thio+ATG, n = 3 and RIC other: Bu+Clo, n = 1; Flu+Mel, n = 1; TLI+ATG, n = 3. ^bOther 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									
<i>Graft source/donor</i>				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
<i>Time from diagnosis to CR1</i>							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						
<i>WBC count at diagnosis</i>				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			
<i>Disease status before HCT</i>													
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.

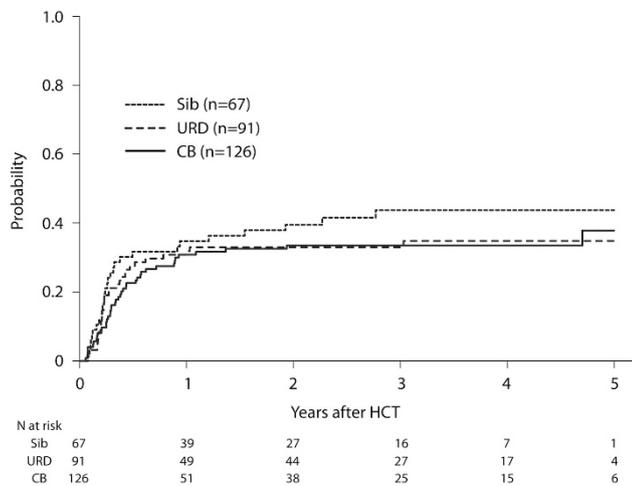


Figure 1. Adjusted cumulative incidence of relapse by donor type. The 3-year probabilities of relapse, adjusted for WBC count and remission status, were 44% (95% CI: 31–55), 33% (95% CI: 25–42) and 33% (95% CI: 24–42) after HLA-matched sibling, UCB and URD HCTs, respectively ($P=0.72$).

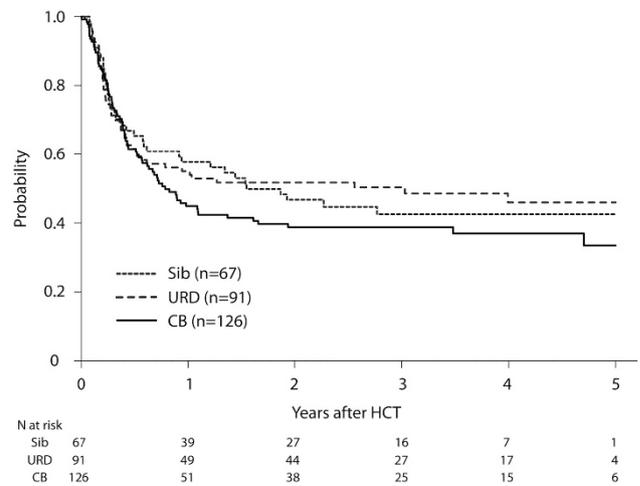


Figure 2. Adjusted LFS by donor type. The 3-year probabilities of LFS, after adjusting for WBC and disease status were 43% (95% CI: 30–54), 39% (95% CI: 30–47) and 50% (95% CI: 40–60) after HLA-matched sibling, UCB and URD HCTs, respectively ($P=0.42$).

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:

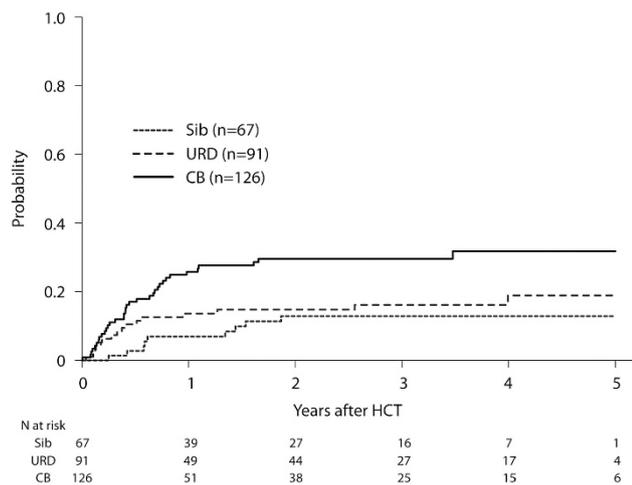


Figure 3. Adjusted cumulative incidence of NRM by graft source. The 3-year probabilities of NRM, after adjusting for time from diagnosis to CR1 were 14% (95% CI: 7–23), 28% (95% CI: 20–36) and 17% (95% CI: 10–25) after HLA-matched sibling, UCB and URD HCTs, respectively. Pairwise comparisons: UCB vs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

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

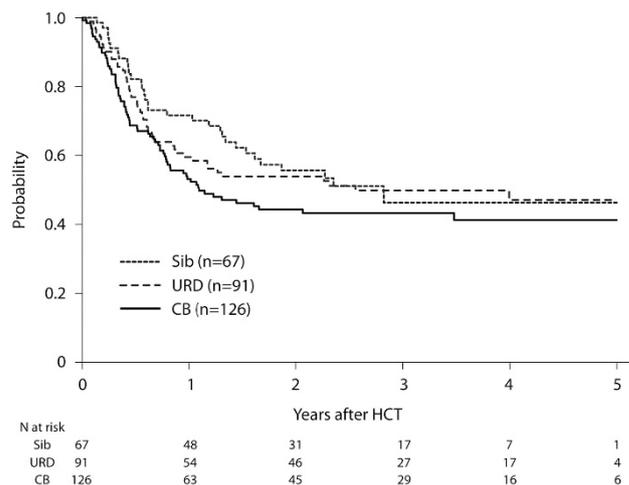


Figure 4. Adjusted OS by donor type. The 3-year probabilities of OS, adjusted for disease status were 46% (95% CI: 33–59), 43% (95% CI: 34–52) and 50% (95% CI: 39–60) after HLA-matched sibling, UCB and URD HCTs, respectively ($P=0.26$).

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 FLT3/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 allogeneic HCT.⁵⁶ In our study, we were unable to address this controversial issue. Interestingly, we observed that high WBC ($>50 \times 10^9/l$) at

diagnosis was found to be associated with a higher relapse risk⁵⁷ 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 HHS250201200016C 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.

*Corporate Members.

AUTHOR CONTRIBUTIONS

Additional contributing coauthors: Ravi Vij, Bipin N Savani, James Foran, Ulrike Bacher, Ann Jakubowski, Betty Hamilton, Michael Grunwald, Saar Gill, Mark Hertzberg, Samer Al-Homsi, Ghada Abusin, Bruce Camitta, Mitchell Cairo, Richard Olsson, Ran Reshef, Ayman Saad, Sahara Chhabra, David Rizzieri, Miguel A Diaz, Mohammed Mir, Cesar Freytes, Rammurti Kamble, Zachariah Deflipp, Taiga Nishihori, Marlise Luskin Sachiko Seo, Mona Wirk, Patrick Stiff, Gary Schiller, Muthalagu Ramanathan, Mahmoud Aljurf, Sid Ganguly, Veronika Bachanova, Nelson Chao, Peter Wiernik, Selina Luger, Mary Laughin, Jean Khoury, Saber Wael, Robert P Gale, Mark Litzow and Hillard Lazarus.

REFERENCES

- Thiede C, Steudel C, Mohr B, Schaich M, Schakel U, Platzbecker U *et al*. Analysis of FLT3-activating mutations in 979 patients with acute myelogenous leukemia: association with FAB subtypes and identification of subgroups with poor prognosis. *Blood* 2002; **99**: 4326–4335.
- Yamamoto Y, Kiyoi H, Nakano Y, Suzuki R, Kodera Y, Miyawaki S *et al*. Activating mutation of D835 within the activation loop of FLT3 in human hematologic malignancies. *Blood* 2001; **97**: 2434–2439.
- Gilliland DG, Griffin JD. The roles of FLT3 in hematopoiesis and leukemia. *Blood* 2002; **100**: 1532–1542.
- Kottaridis PD, Gale RE, Frew ME, Harrison G, Langabeer SE, Belton AA *et al*. The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials. *Blood* 2001; **98**: 1752–1759.
- Gale RE, Green C, Allen C, Mead AJ, Burnett AK, Hills RK *et al*. The impact of FLT3 internal tandem duplication mutant level, number, size, and interaction with NPM1 mutations in a large cohort of young adult patients with acute myeloid leukemia. *Blood* 2008; **111**: 2776–2784.
- Meshinchi S, Alonzo TA, Stirewalt DL, Zwaan M, Zimmerman M, Reinhardt D *et al*. Clinical implications of FLT3 mutations in pediatric AML. *Blood* 2006; **108**: 3654–3661.
- Whitman SP, Ruppert AS, Radmacher MD, Mrozek K, Paschka P, Langer C *et al*. FLT3 D835/836 mutations are associated with poor disease-free survival and a distinct gene-expression signature among younger adults with de novo cytogenetically normal acute myeloid leukemia lacking FLT3 internal tandem duplications. *Blood* 2008; **111**: 1552–1559.
- Brunet S, Labopin M, Esteve J, Cornelissen J, Socie G, Iori AP *et al*. Impact of FLT3 internal tandem duplication on the outcome of related and unrelated hematopoietic transplantation for adult acute myeloid leukemia in first remission: a retrospective analysis. *J Clin Oncol* 2012; **30**: 735–741.
- Linch DC, Hills RK, Burnett AK, Khwaja A, Gale RE. Impact of FLT3(ITD) mutant allele level on relapse risk in intermediate-risk acute myeloid leukemia. *Blood* 2014; **124**: 273–276.
- Whitman SP, Maharry K, Radmacher MD, Becker H, Mrozek K, Margeson D *et al*. FLT3 internal tandem duplication associates with adverse outcome and gene- and microRNA-expression signatures in patients 60 years of age or older with primary cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. *Blood* 2010; **116**: 3622–3626.
- Gale RE, Hills R, Kottaridis PD, Srirangan S, Wheatley K, Burnett AK *et al*. No evidence that FLT3 status should be considered as an indicator for transplantation in acute myeloid leukemia (AML): an analysis of 1135 patients, excluding acute promyelocytic leukemia, from the UK MRC AML 10 and 12 trials. *Blood* 2005; **106**: 3658–3665.
- Meshinchi S, Arcenci RJ, Sanders JE, Smith FO, Woods WB, Radich JR *et al*. Role of allogeneic stem cell transplantation in FLT3/ITD-positive AML. *Blood* 2006; **108**: 400.
- Bornhauser M, Illmer T, Schaich M, Soucek S, Ehninger G, Thiede C. Improved outcome after stem-cell transplantation in FLT3/ITD-positive AML. *Blood* 2007; **109**: 2264–2265.
- DeZern AE, Sung A, Kim S, Tsai HL, Kowalski J, Smith BD *et al*. Patients with FLT3/ITD AML may benefit from allogeneic transplant in first remission: outcomes from a consecutive series of patients at a single institution. *Blood* 2010; **116**: 896–897.
- Sengsayadeth SM, Jagasia M, Engelhardt BG, Kassim A, Strickland SA, Goodman S *et al*. Allogeneic stem cell transplantation for FLT3/ITD positive acute myeloid leukemia in CR1 implication for personalized therapy to prevent early relapses. *Biol Blood Marrow Transplant* 2012; **18**: S332–S333.
- Kayser S, Dohner K, Krauter J, Kohne C, Horst HA, Held G *et al*. Allogeneic transplantation from matched related and unrelated donors in first complete remission in younger adult AML patients with FLT3 internal tandem duplications. *Bone Marrow Transplant* 2011; **46**: S40–S41.
- Hemmati P, Terwey TH, Vuong LG, le Coutre PD, Dorken B, Arnold R. Allogeneic Stem. Cell transplantation for cytogenetically normal acute myeloid leukemia: impact of FLT3 and NPM1 mutational status. *Blood* 2013; **122**: 2104.
- Liegel J, Courville E, Sachs Z, Ustun C. Use of sorafenib for post-transplant relapse in FLT3/ITD-positive acute myelogenous leukemia: maturation induction and cytotoxic effect. *Haematologica* 2014; **99**: e222–e224.
- Deol A, Sengsayadeth S, Ahn K, Wang H, Aljurf M, Antin J *et al*. A Does FLT3 mutation impact survival after hematopoietic cell transplant for AML? *CIBMTR Anal Cancer* 2016; **122**: 3005–3014.
- Laboure G, Dulucq S, Vigouroux S, Lippert E, Pigneux A, Tabrizi R *et al*. Potent graft-versus-leukemia effect after reduced intensity (RIC) allogeneic stem-cell transplantation (asct) as post-remission therapy for intermediate-risk *de-novo* acute myeloid leukemia (AML) with FLT3-ITD genotype or wild-type (WT) NPM1 and CEBPA without FLT3-ITD. *Blood* 2011; **118**: 1766.

- 21 Schmid C, Labopin M, Socie G, Daguindau E, Volin L, Huynh A et al. Outcome of patients with distinct molecular genotypes and cytogenetically normal AML after allogeneic transplantation. *Blood* 2015; **126**: 2062–2069.
- 22 DeZern AE, Sung A, Kim S, Smith BD, Karp JE, Gore SD et al. Role of allogeneic transplantation for FLT3/ITD acute myeloid leukemia: outcomes from 133 consecutive newly diagnosed patients from a single institution. *Biol Blood Marrow Transplant* 2011; **17**: 1404–1409.
- 23 Bejanyan N, Oran B, Shanley R, Warlick E, Ustun C, Vercellotti G et al. Clinical outcomes of AML patients relapsing after matched-related donor and umbilical cord blood transplantation. *Bone Marrow Transplant* 2014; **49**: 1029–1035.
- 24 Brunstein CG, Gutman JA, Weisdorf DJ, Woolfrey AE, Defor TE, Gooley TA et al. Allogeneic hematopoietic cell transplantation for hematologic malignancy: relative risks and benefits of double umbilical cord blood. *Blood* 2010; **116**: 4693–4699.
- 25 Ruggeri A, Labopin M, Sormani MP, Sanz G, Sanz J, Volt F et al. Engraftment kinetics and graft failure after single umbilical cord blood transplantation using a myeloablative conditioning regimen. *Haematologica* 2014; **99**: 1509–1515.
- 26 Rocha V, Cornish J, Sievers EL, Filipovich A, Locatelli F, Peters C et al. Comparison of outcomes of unrelated bone marrow and umbilical cord blood transplants in children with acute leukemia. *Blood* 2001; **97**: 2962–2971.
- 27 Eapen M, Klein JP, Ruggeri A, Spellman S, Lee SJ, Anasetti C et al. Impact of allele-level HLA matching on outcomes after myeloablative single unit umbilical cord blood transplantation for hematologic malignancy. *Blood* 2014; **123**: 133–140.
- 28 Barker JN, Weisdorf DJ, Wagner JE. Creation of a double chimera after the transplantation of umbilical-cord blood from two partially matched unrelated donors. *N Engl J Med* 2001; **344**: 1870–1871.
- 29 Sandhu KS, Brunstein C, DeFor T, Bejanyan N, Arora M, Warlick E et al. Umbilical cord blood transplantation outcomes in acute myelogenous leukemia/myelodysplastic syndrome patients aged ≥ 70 years. *Biol Blood Marrow Transplant* 2015; **22**: 390–393.
- 30 Weisdorf D, Eapen M, Ruggeri A, Zhang MJ, Zhong X, Brunstein C et al. Alternative donor transplantation for older patients with acute myeloid leukemia in first complete remission: a center for International Blood and Marrow Transplant Research-Eurocord Analysis. *Biol Blood Marrow Transplant* 2014; **20**: 816–822.
- 31 de Latour RP, Brunstein CG, Porcher R, Chevallier P, Robin M, Warlick E et al. Similar overall survival using sibling, unrelated donor, and cord blood grafts after reduced-intensity conditioning for older patients with acute myelogenous leukemia. *Biol Blood Marrow Transplant* 2013; **19**: 1355–1360.
- 32 Eckfeldt CE, Randall N, Shanley RM, Yohe S, Bejanyan N, Dolan M et al. Umbilical cord blood transplantation is a suitable option for consolidation of acute myeloid leukemia with FLT3-ITD. *Haematologica* 2016; **101**: e348–e351.
- 33 Slovak ML, Kopecky KJ, Cassileth PA, Harrington DH, Theil KS, Mohamed A et al. Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group Study. *Blood* 2000; **96**: 4075–4083.
- 34 Mrozek K, Marcucci G, Nicolet D, Mahary KS, Becker H, Whitman SP et al. Prognostic significance of the European LeukemiaNet standardized system for reporting cytogenetic and molecular alterations in adults with acute myeloid leukemia. *J Clin Oncol* 2012; **30**: 4515–4523.
- 35 Cheson BD, Bennett JM, Kopecky KJ, Buchner T, Willman CL, Estey EH et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol* 2003; **21**: 4642–4649.
- 36 Bacigalupo A, Ballen K, Rizzo D, Giralt S, Lazarus H, Ho V et al. Defining the intensity of conditioning regimens: working definitions. *Biol Blood Marrow Transplant* 2009; **15**: 1628–1633.
- 37 Przepiorcka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant* 1995; **15**: 825–828.
- 38 Flowers ME, Kansu E, Sullivan KM. Pathophysiology and treatment of graft-versus-host disease. *Hematol Oncol Clin N Am* 1999; **13**: 1091–1112, viii–ix.
- 39 Zhang X, Zhang MJ. SAS macros for estimation of direct adjusted cumulative incidence curves under proportional subdistribution hazards models. *Comput Methods Programs Biomed* 2011; **101**: 87–93.
- 40 Zhang X, Loberiza FR, Klein JP, Zhang MJ A. SAS macro for estimation of direct adjusted survival curves based on a stratified Cox regression model. *Comput Methods Programs Biomed* 2007; **88**: 95–101.
- 41 de Latour RP, Brunstein C, Porcher R, Chevallier P, Robin M, Warlick E et al. Equivalent outcome between siblings, unrelated donors and cord blood after reduced intensity allogeneic hematopoietic cell transplantation for patients older than 50 years with acute myeloid leukaemia in complete remission. *Bone Marrow Transplant* 2013; **48**: S379–S380.
- 42 Ustun C, Courville E, DeFor T, Dolan M, Randall N, Yohe S et al. Myeloablative, but not reduced-intensity, conditioning overcomes the negative effect of flow-cytometric evidence of leukemia in acute myeloid leukemia. *Biol Blood Marrow Transplant* 2015; **22**: 669–675.
- 43 Ponce DM, Hilden P, Devlin SM, Maloy M, Lubin M, Castro-Malaspina H et al. High disease-free survival with enhanced protection against relapse after double-unit cord blood transplantation when compared with t cell-depleted unrelated donor transplantation in patients with acute leukemia and chronic myelogenous leukemia. *Biol Blood Marrow Transplant* 2015; **21**: 1985–1993.
- 44 Sato T, Yang X, Knapper S, White P, Smith BD, Galkin S et al. FLT3 ligand impedes the efficacy of FLT3 inhibitors *in vitro* and *in vivo*. *Blood* 2011; **117**: 3286–3293.
- 45 Rocha V, Gluckman E, Eurocord-Netcord R, European B, Marrow Transplant G. Improving outcomes of cord blood transplantation: HLA matching, cell dose and other graft- and transplantation- related factors. *Br J Haematol* 2009; **147**: 262–274.
- 46 Eapen M, Rubinstein P, Zhang MJ, Stevens C, Kurtzberg J, Scaradavou A et al. Outcomes of transplantation of unrelated donor umbilical cord blood and bone marrow in children with acute leukaemia: a comparison study. *Lancet* 2007; **369**: 1947–1954.
- 47 Rocha V, Labopin M, Sanz G, Arcese W, Schwerdtfeger R, Bosi A et al. Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia. *N Engl J Med* 2004; **351**: 2276–2285.
- 48 Grewal SS, Barker JN, Davies SM, Wagner JE. Unrelated donor hematopoietic cell transplantation: marrow or umbilical cord blood? *Blood* 2003; **101**: 4233–4244.
- 49 Sugimoto K, Narimatsu H, Kawase T, Iida H, Watanabe M, Kohno A et al. Clinical characteristics of chronic graft-versus-host disease following umbilical cord blood transplantation for adults. *Bone Marrow Transplant* 2008; **41**: 729–736.
- 50 Lazaryan A, Weisdorf DJ, DeFor T, Brunstein CG, MacMillan ML, Bejanyan N et al. Risk factors for acute and chronic graft-versus-host disease after allogeneic hematopoietic cell transplantation with umbilical cord blood and matched sibling donors. *Biol Blood Marrow Transplant* 2015; **22**: 134–140.
- 51 Narimatsu H, Miyakoshi S, Yamaguchi T, Kami M, Matsumura T, Yuji K et al. Chronic graft-versus-host disease following umbilical cord blood transplantation: retrospective survey involving 1072 patients in Japan. *Blood* 2008; **112**: 2579–2582.
- 52 Pratz KW, Sato T, Murphy KM, Stine A, Rajkhowa T, Levis M. FLT3-mutant allelic burden and clinical status are predictive of response to FLT3 inhibitors in AML. *Blood* 2010; **115**: 1425–1432.
- 53 Schlenk RF, Kayser S, Bullinger L, Kobbe G, Casper J, Ringhoffer M et al. Differential impact of allelic ratio and insertion site in FLT3-ITD-positive AML with respect to allogeneic transplantation. *Blood* 2014; **124**: 3441–3449.
- 54 Pratorcorona M, Brunet S, Nomdedeu J, Ribera JM, Tormo M, Duarte R et al. Favorable outcome of patients with acute myeloid leukemia harboring a low-allelic burden FLT3-ITD mutation and concomitant NPM1 mutation: relevance to post-remission therapy. *Blood* 2013; **121**: 2734–2738.
- 55 Oran B, Cortes J, Beitinjaneh A, Chen HC, de Lima M, Patel K et al. Allogeneic transplantation in first remission improves outcomes irrespective of FLT3-ITD allelic ratio in FLT3-ITD-positive acute myelogenous leukemia. *Biol Blood Marrow Transplant* 2016; **22**: 1218–1226.
- 56 Versluis J, In 't Hout FE, Devillier R, van Putten WL, Manz MG, Vekemans MC et al. Comparative value of post-remission treatment in cytogenetically normal AML subclassified by NPM1 and FLT3-ITD allelic ratio. *Leukemia* 2016; **31**: 26–33.
- 57 de Jonge HJ, Valk PJ, de Bont ES, Schuringa JJ, Ossenkoppele G, Vellenga E et al. Prognostic impact of white blood cell count in intermediate risk acute myeloid leukemia: relevance of mutated NPM1 and FLT3-ITD. *Haematologica* 2011; **96**: 1310–1317.
- 58 Whitman SP, Archer KJ, Feng L, Baldus C, Becknell B, Carlson BD et al. Absence of the wild-type allele predicts poor prognosis in adult de novo acute myeloid leukemia with normal cytogenetics and the internal tandem duplication of FLT3: a cancer and leukemia group B study. *Cancer Res* 2001; **61**: 7233–7239.
- 59 Sorrow ML, Giralt S, Sandmaier BM, De Lima M, Shahjahan M, Maloney DG et al. Hematopoietic cell transplantation specific comorbidity index as an outcome predictor for patients with acute myeloid leukemia in first remission: combined FHCRC and MDACC experiences. *Blood* 2007; **110**: 4606–4613.
- 60 Chen YB, Li S, Lane AA, Connolly C, Del Rio C, Valles B et al. Phase I trial of maintenance sorafenib after allogeneic hematopoietic stem cell transplantation for fms-like tyrosine kinase 3 internal tandem duplication acute myeloid leukemia. *Biol Blood Marrow Transplant* 2014; **20**: 2042–2048.

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