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GVHD after umbilical cord blood transplantation for acute leukemia: an analysis of risk factors and effect on outcomes

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Abstract

Using the Center for International Blood and Marrow Transplant Research (CIBMTR) registry, we analyzed 1,404 UCBT patients [single (< 18 years) = 810, double (≥ 18 years) = 594] with acute leukemia to define the incidence of acute and chronic graft-vs.-host disease (GVHD), analyze clinical risk factors and investigate outcomes. After single UCBT, 100-day incidence of grades II–IV aGVHD was 39% (95% CI, 36–43%), grades III–IV aGVHD was 18% (95% CI, 15–20%), and 1-year cGVHD was 27% (95% CI, 24–30%). After double UCBT, 100-day incidence of grades II–IV aGVHD was 45% (95% CI, 41%–49%), grades III–IV aGVHD was 22% (95% CI, 19–26%), and 1-year cGVHD was 26% (95% CI, 22–29%). For single UCBT, multivariate analysis showed that absence of anti-thymocyte globulin (ATG) was associated with aGVHD, whereas prior aGVHD was associated with cGVHD. For double UCBT, absence of ATG and myeloablative conditioning were associated with aGVHD, while prior aGVHD predicted for cGVHD. Grades III–IV aGVHD led to worse survival whereas cGVHD had no significant effect on disease-free or overall survival. GVHD is prevalent after UCBT with severe aGVHD leading to higher mortality. Future research in UCBT should prioritize prevention of GVHD.

Keywords

GVHD; umbilical cord blood; allogeneic transplantation

INTRODUCTION

Acute and chronic graft-vs.-host disease (GVHD) are significant complications after allogeneic hematopoietic stem cell transplantation (HSCT). Many recent changes in practice have led to changing patterns of GVHD. These include the introduction of alternative donor sources, reduced intensity conditioning and novel prophylaxis for GVHD. Risk factors for and effects on outcomes from GVHD have been described for conventional adult donor HSCT.[1]

Umbilical cord blood (UCB) has emerged as an alternative donor source with the development of new protocols which have significantly improved outcomes.[2] It is unclear if acute and chronic GVHD after UCBT has similar risk factors and effects on outcomes compared to conventional donor sources. In this study, we proposed to establish the incidence of clinically significant acute and chronic GVHD after UCBT, analyze the risk factors which are associated with its development and investigate the influence of acute and chronic GVHD on patient outcomes after UCBT.

METHODS

Data Source

The Center for International Blood and Marrow Transplant Research (CIBMTR) registry includes a voluntary working group of more than 450 centers worldwide that contribute detailed data on consecutive allogeneic and autologous hematopoietic cell transplantations to a statistical center at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program (NMDP) Coordinating Center in Minneapolis. Participating centers are required to report all transplants consecutively; patients are followed longitudinally and compliance is monitored by on-site audits. Computerized checks for discrepancies, physicians' review of submitted data and on-site audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected Health Information used in the performance of such research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the HIPAA Privacy Rule.[3]

Patient Selection

All patients who underwent UCBT for acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) between 2003 and 2012 and reported to CIBMTR were included initially (n=2,663). Cases were then excluded for several reasons including: related UCB units (n=51), ex vivo expanded units (n=84), ex vivo TCD (n=7), lack of research consent (n=24), lack of conditioning (n=4), lack of GVHD prophylaxis (n=49), use of non-myeloablative conditioning (n=4), use of ≤ 3/6 HLA-matched UCB units (n=40), lack of calcineurin inhibitor (n=68), missing HLA-matching data (n=18) and use of alemtuzumab (n=8). Based on numbers of cases and standard practice, only recipients of double UCBT ≥ 18 years old (excluded 206 recipients < 18 years of age) who received myeloablative or reduced intensity conditioning, and only recipients of single UCBT < 18 years old (excluded 247 recipients ≥ 18 years of age) who received myeloablative conditioning were included. HLA-match status was based on intermediate resolution for HLA-A and B and high resolution for HLA-DRB1. In the context of double UCBT, data on specific cord unit dominance was not available. For purposes of analysis of double UCBT, HLA-matching (relative to the recipient) was analyzed using the following categories of double cord blood combinations: 1) 4/6 + 4/6, 2) 4/6 + ≥ 5/6, and 3) ≥ 5/6 + ≥ 5/6. Disease status at transplant was defined as early (first complete remission), intermediate (second, or greater, complete remission) and advanced (presence of active disease).

Study Endpoints

The diagnoses of acute and chronic GVHD were reported by the treating center. Acute GVHD was diagnosed and graded per previously published consensus guidelines.[4] Chronic GVHD was diagnosed according to Seattle criteria[5] as the National Institutes of Health (NIH) consensus criteria[6] had not yet been implemented on CIBMTR forms during this time period. Overall survival considered death from any cause as the event, and surviving patients were censored at the date of last contact. Disease free survival was defined as survival without relapse or death from any cause, with patients who were alive and in complete remission censored at the time of last follow-up. Non-relapse mortality (NRM) was defined as death during a continuous complete remission. Relapse was defined as recurrence of the primary disease.

Statistical Analysis

Chi-square or Fisher's exact tests were used to compare frequencies for categorical variables, and ANOVA (analysis of variance) was used to compare means for continuous variables in different subsets. Univariate probabilities for overall survival were calculated using the Kaplan-Meier estimator.[7] Comparison of survival curves was made by the log-rank test. The cumulative incidences of acute GVHD and chronic GVHD were calculated by treating death as a competing risk.[8] Multivariate analysis was performed using Cox proportional hazards models for OS, progression-free survival (PFS), relapse, NRM, acute GVHD and chronic GVHD. All the clinical variables were first tested for affirmation of the proportional hazards assumption. Factors that violate the proportional hazards assumption were adjusted through stratification. Then a stepwise model building procedure was used to develop models for each outcome with a threshold of 0.05 for both entry and retention in the model. We also assessed the effects of acute GVHD II–IV, acute GVHD III–IV and chronic GVHD on OS, progression-free survival, relapse and NRM by forcing acute GVHD II–IV, acute GVHD III–IV or chronic GVHD into the multivariable models as a time-dependent variable. Center effect was also adjusted in all of the multivariable models. SAS version9.3 (SAS Institute, Cary, NC) was used for all the analyses.

RESULTS

Clinical Characteristics

A total of 810 recipients of single UCBT and 594 recipients of double UCBT were included. Patient and clinical characteristics are summarized in Table 1a. For the 810 recipients of single UCBT, median age was 6 (range, <1–18). 44% of patients had AML, 56% had ALL and all received myeloablative conditioning. 21% of patients received a 6/6 HLA-matched UCBT, 47% received a 5/6 HLA-matched UCBT and 32% received a 4/6 HLA-matched UCBT. All patients received calcineurin inhibitor-based GVHD prophylaxis. Anti-thymocyte globulin (ATG) was used in 64% of patients. Table 1a shows differences between patients who received ATG compared to those who did not.

For the 594 recipients of double UCBT, median age was 42 (range, 18–79). 72% of recipients had AML and 28% had ALL. 59% of patients received myeloablative conditioning while 41% received reduced intensity conditioning. 26% received a 5/6 + 5/6-

matched combination, 21% received a 5/6 + 4/6 combination, 42% of recipients received a 4/6 + 4/6 combination, and 10% received combinations including a 6/6 UCB unit. All patients received calcineurin inhibitor-based GVHD prophylaxis. ATG was employed in 21% of patients. Table 1b shows differences between patients who received ATG compared to those who did not.

Single UCBT - GVHD

After single UCBT, the cumulative incidence at of grades II–IV and grades III–IV acute GVHD at 100 days was 39% (95% CI, 36%–43%) and 18% (95% CI, 15%–20%), respectively (Table 2). Median time to acute GVHD was 25 days (range, 3–211). Multivariate analysis showed that absence of ATG was the only significant factor associated with grades II–IV (HR 1.56, 95% CI 1.21–2.01, p = 0.0006) (Figure 1). No significant factors were associated with grades III–IV acute GVHD. Notably, the following were not associated with acute GVHD: age, race, gender, CMV serostatus, HLA-matching, TNC dose, year of transplant, underlying disease, total body irradiation (TBI) and GVHD prophylaxis regimen. Given the clinical differences between recipients of ATG and those who did not, we performed this analysis in patients who did not receive ATG. In this subset, no factors were significantly associated with the development of acute GVHD.

After single UCBT, the cumulative incidence of chronic GVHD was 27% (95% CI, 24%–30%) at one year and median time to chronic GVHD was 5.3 months. Multivariate analysis showed that prior acute GVHD (HR 2.02, 95% CI, 1.51–2.70, p<0.0001) was the only significant factor associated with chronic GVHD. Notably, absence of ATG was not significantly associated with the development of chronic GVHD (HR 1.05, 95% CI, 0.76–1.44, p=0.78).

Double UCBT – GVHD

For recipients of double UCBT, the cumulative incidence at day 100 of grades II–IV and grades III–IV acute GVHD was 45% and 22%, respectively. Median onset to acute GVHD was 26 days (range 6–380). Multivariate analysis demonstrated that absence of ATG was associated with grades II–IV acute GVHD (HR 2.33, 95% CI 1.54–3.52, p = 0.0001) (Figure 2), but not with grades III–IV acute GVHD (HR 1.28, 0.89–1.84, p = 0.17). In addition, reduced intensity conditioning protected from both II–IV (HR 0.73, 95% CI 0.56–0.95, p = 0.019) and III–IV (HR 0.63, 95% CI 0.44–0.92, p = 0.016) acute GVHD. Notably, the following factors were not associated with acute GVHD: age, gender, CMV serostatus, HLA-matching, TNC dose, underlying disease, TBI, year of transplant and GVHD prophylaxis regimen. In patients who did not receive ATG, no factors were shown to be significantly associated with acute GVHD.

For all recipients of double UCBT, the cumulative incidence of chronic GVHD was 26% (95% CI, 22%–29%) at one year. Median time to chronic GVHD was 5.3 months. Multivariate analysis showed that prior acute GVHD (HR 2.12, 95% CI, 1.52–2.95, p <0.0001) was associated with chronic GVHD, while ATG had no significant effect.

Single UCBT – Effect of GVHD on NRM, Relapse, DFS, OS

For all recipients of single UCBT, the development of grades II–IV acute GVHD (HR 2.06, 95% CI 1.47–2.88, p < 0.0001) and grades III–IV acute GVHD (HR 2.75, 95% CI 1.92–3.93, p < 0.0001) were associated with increased NRM. For disease relapse, grades II–IV acute GVHD was protective (HR 0.69, 95% CI 0.51–0.93, p = 0.014) while grades III–IV disease had no significant effect (HR 0.78, 95% CI 0.53–1.15, p = 0.22). For DFS, the development of grades II–IV acute GVHD has no effect (HR 1.06, 95% CI 0.86–1.32, p = 0.58) while grades III–IV disease was associated with shorter DFS (HR 1.38, 95% CI 1.07–1.79, p = 0.014). Similarly, for OS, grades II–IV acute GVHD had no effect (HR 1.08, 95% CI 0.87–1.34, p = 0.50) while grades III–IV disease was associated with shorter survival (HR 1.51, 95% CI 1.17–1.95, p = 0.0017) (see Table 3a). When analyzed independently, grade II acute GVHD did not have a significant effect on DFS or OS compared to those without acute GVHD (HR 0.74, 95% CI 0.55–0.99, P=0.045 for OS; HR 0.77, 95% CI 0.57–1.03, p=0.08 for DFS). Compared to patients with grade III–IV acute GVHD, patients with grade II disease had similar rates of relapse, but less NRM and improved DFS and OS (data not shown). After single UCBT, chronic GVHD led to a higher risk of NRM (HR 1.53, 95% CI 0.97–1.90, p = 0.022) but no effect on relapse (HR 1.10, 95% CI 0.74–1.63, p = 0.63), DFS (HR 1.23, 95% CI 0.91–1.65, p = 0.18) and OS (HR 0.96, 95% CI 0.72–1.29, p = 0.82) (see Table 3a). Table 3b shows full results of the multivariate modeling.

Double UCBT – Effect of GVHD on NRM, Relapse, PFS, OS

For all recipients of double UCBT, the development of grades II–IV acute GVHD (HR 1.41, 95% CI 1.05–1.90, p = 0.022) and grades III–IV acute GVHD (HR 2.24, 95% CI 1.66–3.04, p < 0.0001) were associated with increased NRM. In terms of disease relapse, neither grades II–IV acute GVHD (HR 0.87, 95% CI 0.63–1.20, p = 0.39) nor grades III–IV disease (HR 0.68, 95% CI 0.44–1.06, p = 0.084) had any significant impact. Concerning DFS, the development of grades II–IV acute GVHD had no effect (HR 1.11, 95% CI 0.90–1.37, p = 0.34) while grades III–IV disease was associated with shorter DFS (HR 1.41, 95% CI 1.11–1.79, p = 0.005). Similarly, for OS, grades II–IV acute GVHD had no effect (HR 1.05, 95% CI, 0.86–1.30, p = 0.60) while grades III–IV disease was associated with shorter survival (HR 1.48, 95% CI, 1.17–1.86, p = 0.001) (see Table 3a). When analyzed independently, grade II acute GVHD did not have a significant effect on DFS (HR 0.80, 95% CI, 0.60–1.06, p = 0.12) but did lead to improved OS (HR 0.69, 95% CI, 0.52–091, p = 0.0084) when compared to those without acute GVHD. Compared to patients with grades III–IV disease, patients with grade II acute GVHD had similar rates of relapse, but had significantly less NRM and improved DFS and OS (data not shown). For all recipients of double UCBT, chronic GVHD showed a borderline significant association with a higher risk of NRM (HR 1.49, 95% CI, 0.98–2.29, p = 0.065) and a significantly lower relapse (HR 0.59, 95% CI 0.36–0.96, p= 0.033), but had no significant effect on DFS (HR 0.98, 95% CI 0.71–1.33, p = 0.87) or OS (HR 0.95, 95% CI 0.71–1.27, p = 0.70) (see Table 3a). Table 3b shows full results of the multivariate modeling.

DISCUSSION

We performed a large registry analysis using the CIBMTR database to define the incidence of acute and chronic GVHD, the clinical factors associated with their development and the effect of GVHD on outcomes after pediatric single and adult double UCBT. Our results confirm that the incidence of acute GVHD after UCBT is comparable to that observed with conventional donor sources[7], but the incidence of chronic GVHD appears to be less, which has been reported previously.[8,9]

In our study, for pediatric recipients of single UCBT, the absence of ATG was significantly associated with the development of grades II–IV acute GVHD. Prior acute GVHD was associated with chronic GVHD. In the setting of adult double UCBT, the absence of ATG and myeloablative conditioning were associated with grades II–IV acute GVHD while prior acute GVHD was associated with chronic GVHD. As expected, severe acute GVHD resulted in increased NRM and decreased DFS and OS after both single and double UCBT. After single UCBT, the development of chronic GVHD appeared to increase NRM; whereas after double UCBT, chronic GVHD was associated with less disease relapse. Yet, chronic GVHD clearly had no significant effect on DFS and OS.

Several retrospective analyses have previously attempted to define risk factors for acute and chronic GVHD after UCBT and these are summarized in Tables 4a and 4b, respectively. Similar to our analysis, lack of ATG and myeloablative conditioning have been associated with acute GVHD in other studies,[10–12] yet unlike our study, degree of HLA-matching has also been shown to be influential.[10,12,13] For chronic GVHD, as observed in our analysis, prior acute GVHD has been shown to be the most important factor,[10–12,14] and several groups have also reported the association of higher HLA-mismatch with chronic GVHD.[10,12,14]

Our study represents the largest study of UCBT patients investigating risk factors for acute and chronic GVHD, as well as the effect that acute and chronic GVHD has on long-term outcomes. The use of ATG appeared to be the most significant factor associated with acute GVHD after both single UCBT and double UCBT. It is important to note that our analysis did not distinguish different types of ATG, incorporate information on the dose or schedule employed as well as accompanying systemic corticosteroids given or report the rationale behind why treating physicians chose to use ATG. It is interesting that use of ATG was not significantly associated with chronic GVHD after single or double UCBT and this may reflect a significant difference between UCBT and other donor sources. After multivariate analysis, ATG had no significant effect on PFS or OS after single or double UCBT. While the overall effect of ATG was not a primary objective of this study, we do believe that future analyses are warranted with a focus on other important endpoints not collected here such as graft failure, specific infections and post-transplant lymphoproliferative disease. The use of ATG in UCBT is controversial as recent studies have suggested a benefit in terms of protection from GVHD,[15,16] while other studies have shown that ATG is associated with an increase in overall mortality.[17–19]

Interestingly, the degree of HLA-mismatch was not a significant factor in our multivariate analysis for single UCBT, and we could not analyze this factor accurately in double UCBT due to missing information on specific cord unit dominance. Other limitations of our analysis include those inherent to any large registry analysis including heterogeneity of practice. Specifically, for studies involving GVHD, the diagnosis does not undergo rigorous central review. This point is emphasized by a recent analysis describing characteristics of chronic GVHD in 87 patients undergoing UCBT at a single center. After review of medical records for the 54 patients who were reported to have chronic GVHD, only 7 had classic chronic GVHD.[20] In our analysis, the severity of chronic GVHD was not able to be analyzed as the modern NIH classification and grading system for chronic GVHD was developed in the midst of the era of transplantation for this group.[6] We also did not review or analyze any information on treatment for GVHD or response, but this should certainly be studied, especially as GVHD after UCBT may respond differently compared to GVHD after transplantation from other donor sources.[21]

In conclusion, acute and chronic GVHD remain significant complications after UCBT with severe acute GVHD clearly impacting long-term survival. Rates of acute GVHD appear comparable to what is observed with conventional matched donor sources, yet the incidence of chronic GVHD appears to be significantly less. In our study, omission of ATG was the most important risk factor associated with the development of acute GVHD, and prior acute GVHD was the most significant risk factor for the development of chronic GVHD. Preventing acute GVHD for patients after UCBT should be a priority and possible avenues include formally defining the role of ATG, enhanced or novel GVHD prophylaxis regimens[22,23] and improving methods of UCB expansion or activation to use better HLA-matched units.[24] While chronic GVHD appears to be less prevalent after UCBT, a future analysis should be performed when a large number of patients have been classified according to a standard grading scheme where severity of disease can be taken into account to truly assess its impact.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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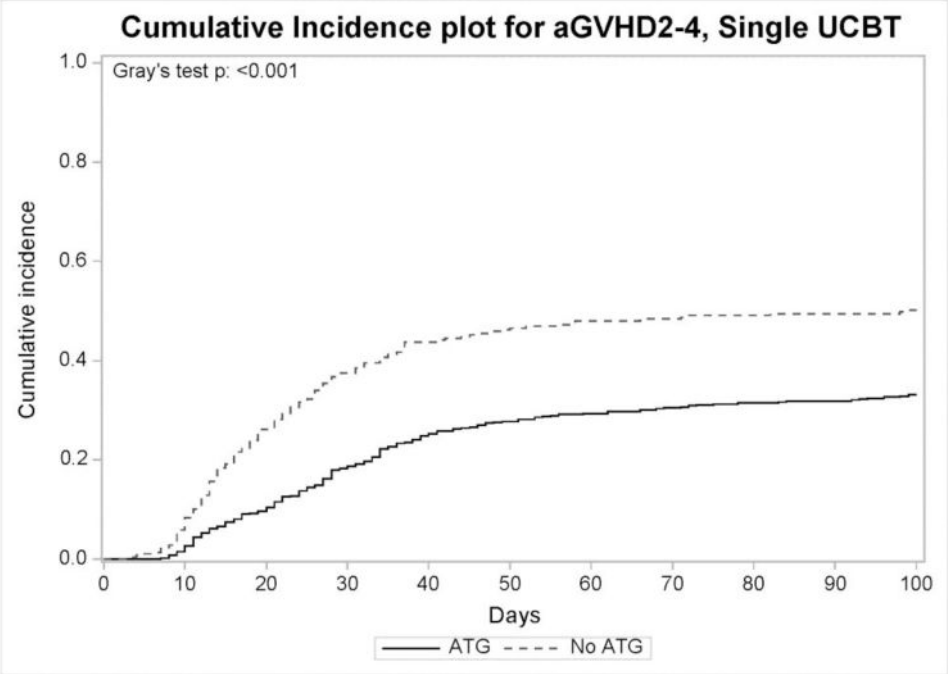

Figure 1.

Cumulative incidence of grades 2–4 acute GVHD in recipients of single UCBT who received ATG (n=521) and those who did not (n=289).

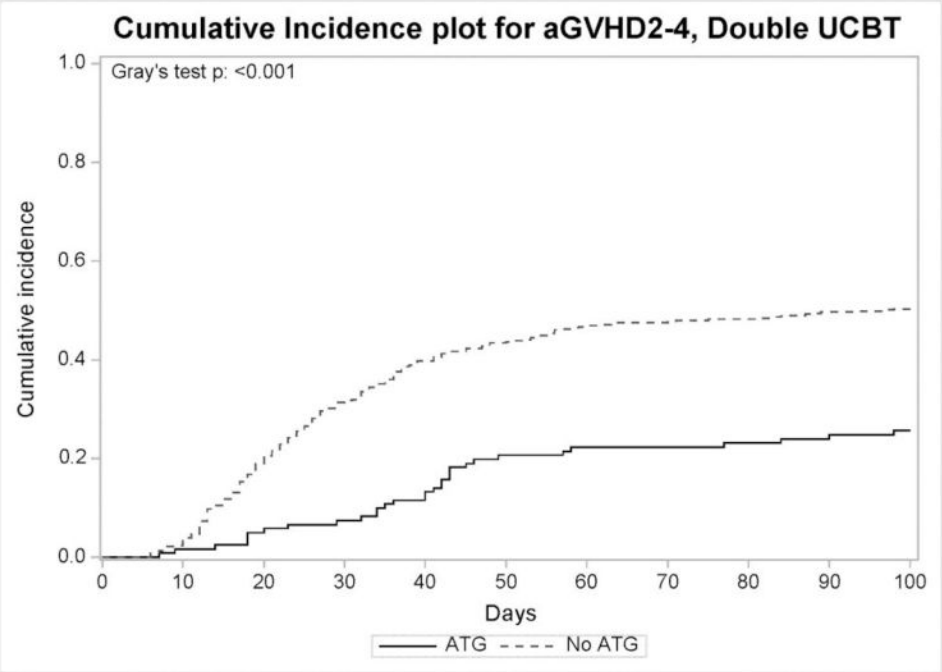

Figure 2.
Cumulative incidence of grades 2–4 acute GVHD in recipients of double UCBT who received ATG (n=122) and those who did not (n=472).

Table 1a

Clinical characteristics of patients undergoing single UCBT

Characteristic	All	With ATG	Without ATG	p
N	810	521	289	
Number of centers	105	88	68	
Age, median (range), years	6 (<1–18)	5 (<1–18)	7 (1–18)	<0.001
Age at UCBT, years				<0.001
0–4	346 (43%)	248 (48%)	98 (34%)	
5–9	275 (34%)	164 (31%)	111 (38%)	
10–14	148 (18%)	90 (17%)	58 (20%)	
15–17	41 (5%)	19 (4%)	22 (8%)	
Gender				0.37
Male	451 (56%)	284 (55%)	167 (58%)	
Female	359 (44%)	237 (45%)	122 (42%)	
Karnofsky/Lansky score				0.66
< 90	141 (17%)	93 (18%)	48 (17%)	
90–100	669 (83%)	428 (82%)	241 (83%)	
Race of recipient				0.03
Caucasian	469 (58%)	320 (61%)	149 (52%)	
African-American	77 (10%)	49 (9%)	28 (10%)	
Asian/Pacific Islander	45 (6%)	28 (5%)	17 (6%)	
Hispanic	176 (22%)	97 (19%)	79 (27%)	
Native American	11 (1%)	9 (2%)	2 (< 1%)	
Missing	32 (4%)	18 (3%)	14 (5%)	
CMV status of recipient				0.16
Negative	412 (51%)	278 (53%)	134 (46%)	
Positive	391 (48%)	239 (46%)	152 (53%)	
Missing	7 (< 1%)	4 (< 1%)	3 (1%)	
Disease				<0.001
AML	356 (44%)	255 (49%)	101 (35%)	
ALL	454 (56%)	266 (51%)	188 (65%)	
Disease status at UCBT				0.07
Early	282 (35%)	182 (35%)	100 (35%)	
Intermediate	412 (51%)	253 (49%)	159 (55%)	
Advanced	114 (14%)	84 (16%)	30 (10%)	
Missing	2 (<1%)	2 (<1%)	0	
Donor-Recipient sex match				0.71
F-M	215 (26%)	141 (27%)	74 (26%)	
F-F	175 (22%)	116 (22%)	59 (20%)	
M-M	234 (29%)	142 (27%)	92 (32%)	

Characteristic	All	With ATG	Without ATG	p
M-F	184 (23%)	121 (23%)	63 (22%)	
Missing	2 (<1%)	1 (<1%)	1 (<1%)	
HLA-matching				0.05
6/6	169 (21%)	111 (21%)	58 (20%)	
5/6	382 (47%)	230 (44%)	152 (53%)	
4/6	259 (32%)	180 (34%)	79 (27%)	
Total nucleated cell dose, pre-cryo, median (range) × 10^7/kg	7 (3–56)	7 (3–50)	6 (3–56)	0.03
Total nucleated cell dose, pre-cryo, × 10^7/kg				<0.001
3–5	195 (24%)	107 (21%)	88 (30%)	
5–8	223 (28%)	133 (26%)	90 (31%)	
≥ 8	289 (36%)	205 (39%)	82 (39%)	
Missing	103 (13%)	76 (15%)	27 (9%)	
Conditioning regimen				
Myeloablative	810 (100%)	521 (100%)	289 (100%)	–
Reduced Intensity	0	0	0	
TBI used	573 (71%)	314 (60%)	259 (90%)	<0.001
GVHD prophylaxis				<0.001
CNI + SIRO	34 (4%)	6 (1%)	28 (10%)	
CNI + MMF	327 (40%)	151 (29%)	176 (61%)	
CNI + MTX	102 (13%)	56 (11%)	46 (16%)	
CNI + COR	247 (30%)	220 (42%)	27 (9%)	
CNI ± other	100 (12%)	88 (17%)	12 (4%)	
Year of UCBT				<0.001
2003–2005	202 (25%)	184 (35%)	18 (6%)	
2006–2008	288 (36%)	182 (35%)	106 (37%)	
2009–2012	320 (39%)	155 (30%)	165 (57%)	

Abbreviations: UCBT = Umbilical Cord Blood Transplant; GVHD = graft-vs.-host disease; CNI = Calcineurin Inhibitor (either Cyclosporine or Tacrolimus); SIRO = Sirolimus; MMF = Mycophenolate mofetil; MTX = Methotrexate; COR = Corticosteroids (systemic).

Table 1b

Clinical characteristics of patients undergoing double UCBT

Characteristic	All	With ATG	Without ATG	p
N	594	122	472	
Number of centers	87	38	75	
Age, median (range), years	42 (18–79)	49 (18–74)	41 (18–79)	0.005
Gender				0.16
Male	297 (50%)	54 (44%)	253 (51%)	
Female	297 (50%)	68 (56%)	229 (49%)	
Karnofsky/Lansky score				<0.001
< 90	171 (29%)	50 (41%)	121 (26%)	
90–100	423 (71%)	72 (59%)	351 (74%)	
Race				0.02
Caucasian	371 (62%)	86 (70%)	285 (60%)	
African-American	69 (12%)	19 (16%)	50 (11%)	
Asian/Pacific Islander	49 (8%)	6 (5%)	43 (9%)	
Hispanic	84 (14%)	8 (7%)	76 (16%)	
Native American	4 (< 1%)	0	4 (< 1%)	
Missing	17 (3%)	3 (2%)	14 (3%)	
CMV status of recipient				0.01
Negative	183 (31%)	25 (20%)	158 (33%)	
Positive	397 (67%)	95 (78%)	302 (64%)	
Missing	17 (3%)	2 (2%)	12 (3%)	
Disease				0.006
AML	428 (72%)	100 (82%)	328 (69%)	
ALL	166 (28%)	22 (18%)	144 (31%)	
Disease status at UCBT				<0.001
Early	278 (47%)	46 (38%)	232 (49%)	
Intermediate	225 (38%)	43 (35%)	182 (39%)	
Advanced	91 (15%)	33 (27%)	58 (12%)	
Donor-Recipient gender				0.52
(F,F)-M or (F,M)-M	207 (35%)	38 (31%)	169 (36%)	
All other combinations	343 (58%)	76 (62%)	267 (57%)	
Missing	44 (7%)	8 (7%)	36 (8%)	
HLA-matching				0.77
4/6 + 4/6	251 (42%)	48 (39%)	203 (43%)	
One 4/6 UCB unit	134 (23%)	29 (24%)	105 (22%)	
No 4/6 UCB units	209 (35%)	45 (37%)	164 (35%)	
Total nucleated cell dose, pre-cryo, median (range) × 10^7/kg	5 (3–55)	4 (3–31)	5 (3–55)	0.02

Characteristic	All	With ATG	Without ATG	p
Total nucleated cell dose, pre-cryo, × 10^7/kg				0.17
3–5	268 (45)	64 (52%)	204 (43%)	
5–8	190 (32)	31 (25%)	159 (34%)	
≥ 8	47 (8)	7 (6%)	40 (8%)	
Missing	89 (15)	20 (16%)	69 (15%)	
Conditioning Regimen				0.002
Myeloablative	351 (59%)	57 (47%)	294 (62%)	
Reduced Intensity	243 (41%)	65 (53%)	178 (38%)	
TBI used	497 (83%)	60 (49%)	437 (93%)	<0.001
GVHD prophylaxis				<0.001
CNI + SIRO	27 (5%)	14 (11%)	13 (3%)	
CNI + MMF	535 (90%)	96 (79%)	439 (93%)	
CNI + MTX	15 (3%)	4 (3%)	11 (2%)	
CNI ± other	17 (4%)	8 (6%)	9 (2%)	
Year of UCBT				<0.001
2003–2008	188 (32%)	58 (48%)	130 (28%)	
2009–2012	406 (68%)	64 (52%)	342 (72%)	

Abbreviations: UCBT = Umbilical Cord Blood Transplant; GVHD = graft-vs.-host disease; CNI = Calcineurin Inhibitor (either Cyclosporine or Tacrolimus); SIRO = Sirolimus; MMF = Mycophenolate mofetil; MTX = Methotrexate; COR = Corticosteroids (systemic).

Table 2

Cumulative incidences of acute and chronic GVHD

	All (95% CI)	With ATG (95% CI)	Without ATG (95%CI)
Single UCBT	810	521 (64%)	289 (36%)
Cumulative incidence of grades II–IV acute GVHD[1]	39% (36%–43%)	33% (29%–37%)	50% (44%–56%)
Cumulative incidence of grades III–IV acute GVHD[1]	18% (15%–20%)	15% (12%–19%)	21% (17%–26%)
Cumulative incidence of chronic GVHD[2]	27% (24%–30%)	22% (19%–26%)	35% (29%–41%)
Double UCBT	594	122 (21%)	472 (79%)
Cumulative incidence of grades II–IV acute GVHD[1]	45% (41%–49%)	26% (18–34%)	50% (46%–55%)
Cumulative incidence of grades III–IV acute GVHD[1]	22% (19%–26%)	16% (10%–23%)	24% (20%–28%)
Cumulative incidence of chronic GVHD[2]	26% (22%–29%)	21% (15%–29%)	27% (23%–31%)

[1]Cumulative incidence of acute GVHD calculated through day +100 after UCBT

[2]Cumulative incidence of chronic GVHD calculated through 1 year after UCBT

Abbreviations: UCBT = umbilical cord blood transplant; GVHD = graft-versus-host disease; ATG = anti-thymocyte globulin

Table 3a

Effect of acute and chronic GVHD on outcomes after single and double UCBT

Single UCBT	**Relapse**	**Non-Relapse Mortality**	**Disease-Free Survival**	**Overall Survival**
Gr. 2–4 Acute GVHD	HR 0.69 (0.51–0.93) p = 0.014	HR 2.06 (1.47–2.88) p < 0.0001	HR 1.06 (0.86–1.32) p = 0.58	HR 1.08 (0.87–1.34) p = 0.50
Gr. 3–4 Acute GVHD	HR 0.78 (0.53–1.15) p = 0.22	HR 2.75 (1.92–3.93) p < 0.0001	HR 1.38 (1.07–1.79) p = 0.014	HR 1.51 (1.17–1.95) p = 0.0017
Chronic GVHD	HR 1.10 (0.74–1.63) p = 0.63	HR 1.53 (0.97–2.42) p = 0.068	HR 1.23 (0.91–1.65) p = 0.18	HR 0.96 (0.72–1.29) p = 0.82
Double UCBT	**Relapse**	**Non-Relapse Mortality**	**Disease-Free Survival**	**Overall Survival**
Gr. 2–4 Acute GVHD	HR 0.87 (0.63–1.20) p = 0.39	HR 1.41 (1.05–1.90) p = 0.022	HR 1.11 (0.90–1.37) p = 0.34	HR 1.05 (0.86–1.30) p = 0.60
Gr. 3–4 Acute GVHD	HR 0.68 (0.44–1.06) p = 0.084	HR 2.24 (1.66–3.04) p < 0.0001	HR 1.41 (1.11–1.79) p = 0.005	HR 1.48 (1.17–1.86) p = 0.001
Chronic GVHD	HR 0.59 (0.36–0.96) p = 0.033	HR 1.49 (0.98–2.29) p = 0.065	HR 0.98 (0.71–1.33) p = 0.87	HR 0.95 (0.71–1.27) p = 0.70

Abbreviations: UCBT=Umbilical Cord Blood Transplant; GVHD = Graft-vs.-Host Disease; Gr. = Grade

Table 3b

Hazard ratios for clinically significant predictors of major outcomes after single and double UCBT

Single UCBT					
	Overall Survival	**Disease-Free Survival**	**Relapse**	**Non-Relapse Mortality**	**Chronic GVHD**
Gr. II–IV Acute GVHD			0.69 (0.51–0.93) p=0.014	2.06 (1.47–2.88) p<0.0001	2.02 (1.51–2.70) p<0.0001
Primary Disease[1]	0.73 (0.58 – 0.91) p=0.0054	0.71 (0.57–0.89) p=0.0024			
Disease Status at Transplant[2]	1.37 (1.06 – 1.76) 2.89 (2.14–3.91) p<0.0001	1.32 (1.03–1.68) 2.58 (1.90–3.50) p<0.0001	1.57 (1.12–2.21) 4.88 (3.28–7.27) p<0.0001		
CMV Positivity	1.47 (1.19–1.82) p=0.0003	1.45 (1.17–1.79) p=0.0006		1.77 (1.27–2.46) p=0.0008	
Age[3]			0.77 (0.56–1.07) 0.61 (0.41–0.89) p=0.011	1.40 (0.95–2.07) 2.03 (1.37–3.01) p=0.0018	
Absence of ATG			1.49 (1.08–2.07) p=0.016	0.44 (0.30–0.66) p<0.0001	
TBI Use			0.59 (0.43–0.81) p=0.0013		
Double UCB					
	Overall Survival	**Disease-Free Survival**	**Relapse**	**Treatment-Related Mortality**	**Chronic GVHD**
Gr. II–IV Acute GVHD					2.12 (1.52–2.95) p<0.0001
Primary Disease[1]	1.02 (0.81–1.28) 1.86 (1.39–2.48) p<0.0001				
Disease Status at Transplant[2]		1.02 (0.81–1.28) 1.56 (1.12–2.18) p=0.022	1.42 (1.01–2.00) 3.56 (2.27–5.57) p<0.0001		
TBI Use		0.73 (0.55–0.97) p=0.032	0.67 (0.45–1.00) p=0.049		
Karnofsky Performance Status[4]	0.71 (0.57–0.89) p=0.0028	0.77 (0.61–0.97) p=0.024		0.66 (0.48–0.90) p=0.0095	
Conditioning Regimen[5]		1.36 (1.10–1.69) p=0.0048	2.53 (1.84–3.47) p<0.0001	0.59 (0.40–0.87) p=0.0083	

Single UCBT					
	Overall Survival	**Disease-Free Survival**	**Relapse**	**Non-Relapse Mortality**	**Chronic GVHD**
Age[3]				1.28 (0.88–1.87) 1.83 (1.17–2.86) p=0.029	

Hazards for each relationship presented, p values for entire trend presented

[1] ALL vs AML

[2] Intermediate vs. Early, Advanced vs. Early

[3] Age 5–9 vs. 0–4 and 10–17 vs. 0–4 for single UCBT; Age 18–29 vs. 30–49 vs. 50+ for double UCBT

[4] Karnofsky performance status < 90 vs 90–100

[5] Redcued Intensity vs. Myeloablative

Table 4a

Summary of studies analyzing risk factors for acute GVHD after UCBT

Study	Population	Incidence of grades II–IV acute GVHD	Incidence of grades III–IV acute GVHD	Risk Factors
Macmillan et al.[11]	Single UCBT (n=80)	39%	18%	Use of 2 UCB units NMA conditioning regimen No ATG
	Double UCBT (n=185)	58%	19%	
Lazaryan et al.[10]	Single UCBT (n=295)	26%	7%	Age ≥ 18 Higher HLA-mismatch[a]
	Double UCBT (n=416)	56%	21%	No ATG[a] Year of UCBT 2006 or later[a] Higher HLA-mismatch[b] Myeloablative conditioning[b]
Ponce et al.[13]	Double UCBT (n=115)	53%	23%	Higher HLA-mismatch[b]
Xavier et al.[12]	Double UCBT (n=921)	36%	15%	Myeloablative conditioning[a] Higher HLA-mismatch[a] No ATG Advanced disease stage[b]
Chen et al.	Single UCBT (n=810)	39%	18%	No ATG
	Double UCBT (n=594)	45%	22%	No ATG[a] Myeloablative conditioning

Abbreviations: GVHD = graft-vs.-host disease; UCBT = umbilical cord blood transplantation; UCB = umbilical cord blood; NMA = non-myeloablative; ATG = anti-thymocyte globulin; HLA = human leukocyte antigen; iv-TCD = in vivo T-cell depletion

[a]Only for grades II–IV acute GVHD

[b]Only for grades III–IV acute GVHD

Table 4b

Summary of studies analyzing risk factors for chronic GVHD after UCBT

Study	Population	Incidence of chronic GVHD	Risk Factors
Macmillan et al.[11]	Single UCBT (n=80)	18%	Prior grades II–IV acute GVHD
	Double UCBT (n=185)	17%	
Lazaryan et al.[10]	Single UCBT (n=295)	7%	Age ≥ 18 Non-use of cyclosporine/MMF for GVHD prophylaxis
	Double UCBT (n=416)	26%	Higher HLA-mismatch Myeloablative conditioning Prior grades II–IV acute GVHD
Ponce et al.[13]	Double UCBT (n=115)	23%	Not reported
Narimatsu et al.[14]	Single UCBT (n=1072)	28%	Higher recipient body weight Higher HLA-mismatch Myeloablative conditioning Use of mycophenolate mofetil Prior grades II–IV acute GVHD
Xavier et al.[12]	Double UCBT (n=921)	25%	Higher HLA-mismatch Prior grades II–IV acute GVHD
Chen et al.	Single UCBT (n=810)	27%	Prior grades II–IV acute GVHD
	Double UCBT (n=594)	26%	

Abbreviations: GVHD = graft-vs.-host disease; UCBT = umbilical cord blood transplantation; UCB = umbilical cord blood; MMF = mycophenolate mofetil; ATG = anti-thymocyte globulin; HLA = human leukocyte antigen; iv-TCD = in vivo T-cell depletion