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Alternative donor hematopoietic stem cell transplantation for mature lymphoid malignancies after reduced-intensity conditioning regimen: similar outcomes with umbilical cord blood and unrelated donor peripheral blood

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ABSTRACT

We have reported encouraging results of unrelated cord blood transplantation for patients with lymphoid malignancies. Whether those outcomes are comparable to matched unrelated donor transplants remains to be defined. We studied 645 adult patients with mature lymphoid malignancies who received an allogeneic unrelated donor transplant using umbilical cord blood (n=104) or mobilized peripheral blood stem cells (n=541) after a reduced-intensity conditioning regimen. Unrelated cord blood recipients had more refractory disease. Median follow-up time was 30 months. Neutrophil engraftment (81% *vs.* 97%, respectively; $P<0.0001$) and chronic graft-*versus*-host disease (26% *vs.* 52%; $P=0.0005$) were less frequent after unrelated cord blood than after matched unrelated donor, whereas no differences were observed in grade II-IV acute graft-*versus*-host disease (29% *vs.* 32%), non-relapse mortality (29% *vs.* 28%), and relapse or progression (28% *vs.* 35%) at 36 months. There were also no significant differences in 2-year progression-free survival (43% *vs.* 58%, respectively) and overall survival (36% *vs.* 51%) at 36 months. In a multivariate analysis, no differences were observed in the outcomes between the two stem cell sources except for a higher risk of neutrophil engraftment (hazard ratio=2.12; $P<0.0001$) and chronic graft-*versus*-host disease (hazard ratio 2.10; $P=0.0002$) after matched unrelated donor transplant. In conclusion, there was no difference in final outcomes after transplantation between umbilical cord blood and matched unrelated donor transplant. Umbilical cord blood is a valuable alternative for patients with lymphoid malignancies lacking an HLA-matched donor, being associated with lower risk of chronic graft-*versus*-host disease.

Introduction

Patients with advanced relapsed or refractory Hodgkin lymphoma (HL), non-Hodgkin's lymphoma (NHL), and chronic lymphocytic leukemia (CLL) have been reported to have lower relapse rates after allogeneic hematopoietic stem cell transplantation (HSCT) as compared to autologous transplant or chemotherapy alone.[1-10] However, higher median patient age and associated comorbid conditions, and extensive prior therapy including autologous HSCT, common in patients with mature lymphoid malignancies, increase non-relapse mortality (NRM) and limit the applicability of conventional myeloablative allogeneic HSCT.[11-13] Thus, reduced intensity conditioning (RIC) regimens have been increasingly used for the treatment of this patient population, resulting in acceptable NRM (4-30%) and promising survival (39-83%).[8,14-22] Low relapse rates and a plateau in the survival curves of patients with CLL/NHL[18,22-27] and in HL[4,8,20] after RIC allogeneic HSCT support an effective graft-*versus*-lymphoma (GVL) effect in this context.

For patients who need a potentially curative allogeneic HSCT and lack a suitable human leukocyte antigen (HLA)-matched sibling donor, alternative donors such as a matched unrelated volunteer donor or an unrelated umbilical cord blood donor must be considered.

Transplantation from a matched unrelated donor is limited by a high risk of graft-*versus*-host disease (GVHD) and donor availability. While umbilical cord blood is rapidly available

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and has relatively lower risk of GVHD considering the degree of HLA-mismatch, it is associated with slower hematopoietic recovery and higher risk of graft failure.[28-34]

We reported encouraging outcomes in 104 patients with mature lymphoid malignancies receiving an umbilical cord blood transplant (UCB) after myeloablative or RIC conditioning regimens.[35] Progression-free survival (PFS) was improved in patients with chemosensitive disease, those who have received higher cell doses, or low-dose total body irradiation (TBI) in the preparative regimen.

However, there are no data published so far comparing outcomes between UCB and conventional matched unrelated donor transplants (MUD) after RIC for the treatment of mature lymphoid malignancies. Thus, we report here a retrospective analysis comparing outcomes of adults with mature lymphoid malignancies who received a MUD or a UCB reported to the EBMT and Eurocord registries

Methods

Data collection

Eurocord and EBMT databases provided data on both UCB and MUD. Centers not associated with EBMT were asked to complete reports if umbilical cord blood units were obtained from Netcord banks.

The local ethics committees approved the different trials onto which the patients were enrolled and all patients gave written informed consent to participate in the trials and to be included in the Eurocord and EBMT according to the Declaration of Helsinki.

Inclusion criteria

The study included patients with mature lymphoid malignancies defined as HL, NHL and CLL who received an RIC allogeneic HCT between January 2000 and December 2008. Patients received an allograft from either matched unrelated donor peripheral blood stem cells (PBSC) or unrelated unmanipulated single-unit or double-unit umbilical cord blood grafts after a reduced-intensity conditioning (RIC) regimen.

Patients were included if they were over 17 years of age at the time of transplantation and had received a first allogeneic transplantation or an allogeneic transplantation after a failed autologous transplantation. Patients receiving multiple grafts (e.g. bone marrow and umbilical cord blood simultaneously), *ex vivo* T-cell depleted grafts or tandem transplantations were not eligible.

In the MUD group, only patients receiving from 8/8 (matching for HLA-A, -B, -C, and -DRB1 alleles), 10/10 (HLA-A, -B, -C, -DRB1 and -DQ) or a 12/12 (HLA-A, -B, -C, -DR, -DQ and DP) allelic matched donors or patients receiving grafts with one mismatch in HLA-DQ or HLA-DP (9/10 or 11/12) were included.

In the UCB group, only patients receiving a minimum of $2x10^7$ total nucleated cells infused/kg and no more than two mismatches between recipient and donor (HLA compatibility 4 out of 6), considering HLA-A and B- at the antigen level and DRB1 at the allele level, were included. Fifty-four patients in the UCB group included in this study had been reported previously.[35]

Statistical analysis

Patient-, disease-, and transplant-related variables were compared between the two groups using the χ^2 or Fisher's exact test for categorical variables and the Mann-Whitney or t-test for continuous variables.

Probabilities of PFS and OS were calculated using the Kaplan-Meier estimator. Cumulative incidence rates were calculated for neutrophil engraftment, acute and chronic GVHD, NRM and relapse, with death considered a competing event. We calculated 95% Confidence Intervals (CI) using the Greenwood formula. Adjusted probabilities for outcomes after transplantation were estimated using the Cox proportional hazards method. The impact of graft type was investigated in the final multivariate models adjusting for patient-, disease-, and transplant-related variables with an impact in univariate analyses or clinically relevant. First-order interactions between graft type and each variable of interest were examined. Variables were tested using a time-varying covariate method to determine whether the proportional hazards assumption was met. If a deviation from the proportionality assumption was found, a stratified Cox model was used. Results are presented as relative risks of failure (adverse prognostic factors *vs.* good prognostic factors), with the 95% confidence interval and the *P* value. All *P* values are two-sided. SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) and S-PLUS (TIBCO Software Inc., Palo Alto, CA, USA) software were used for statistical analyses.

Results

Patients' and disease characteristics

A total of 645 patients from 149 centers were included in this analysis with 104 patients receiving UCB and 541 patients receiving MUD (Table 1). Three-hundred and seventy patients had NHL, 156 had HL, and 119 CLL. There were 357 patients (55%) who had failed a prior autologous transplantation. MUD and UCB cohorts were comparable in all characteristics, except for disease status at transplant: there were more resistant/relapsed diseases in the UCB group (41%) than in the MUD group (29%) (*P*=0.02).

Graft and transplant characteristics

Conditioning regimen characteristics are summarized in Table 1. In the MUD group, all patients were at least 8 out of 8 HLA-matched to their donor: 58 patients (12%) were reported as 12/12, 312 (67%) as 10/10, 72 (15%) as 11/12 (one difference in DP or DQ), and 28 (6%) as 9/10 (one difference in DQ). Seventy-one patients were reported as 'matched unrelated donor', and therefore were at least 8/8, but no further details on compatibility were provided by the transplant center.

In the UCB group, 38 patients (36%) received a single and 66 (64%) a double UCB. Most patients (66%) received at least one UCB unit with two mismatches to the recipient (4/6 HLA-matched). The median number of total nucleated cells infused was $2.9x10^7$/kg (range 2.20-6.40) in recipients of single UCB and $3.2x10^7$/kg (range 2.00-15.00) in recipients of double grafts. The median number of $CD34^+$ cells infused was $1.30x10^5$/kg (range 0.27-6.40) in single umbilical cord blood units and $1.20x10^5$/kg (range 0.20-6.63) in double umbilical cord blood units.

Conditioning regimens varied according to the transplant center and were classified under the RIC definition.[36-38] The most commonly used regimens in the MUD group were the combination of fludarabine and an alkylating agent (50%), and in the UCB group the combination of fludarabine, cyclophosphamide and low-dose TBI (74%).

There was also a difference in GVHD prophylaxis between both groups. The combination of cyclosporine and mycophenolate mofetil was more frequently used in the UCB group (85% *vs.* 33%; *P*<0.0001), while *in vivo* T-cell depletion with alemtuzumab or antithymocyte globulin was more frequently used in the MUD group (73% *vs.* 21%;*P*<0.0001).

Median follow up for survivors was 28 months (range 3-119 months) for MUD patients and 35 months (range 3-74) for UCB patients (*P*=0.32).

Hematopoietic engraftment

The cumulative incidence (CI) of neutrophil engraftment was higher after MUD as compared to UCB at 30 (95% *vs.* 67%, respectively) and 60 days after transplant (97% *vs.* 81%; *P*<0.0001) (Table 2 and Figure 1). In a multivariate analysis, the use of MUD remained favorably associated with neutrophil engraftment (hazard ratio (HR) 2.12; 95% confidence interval (95%CI: 1.63-2.77) (Table 3). Median time to neutrophil recovery was 14 days (range 3-31) after MUD and 18 days (range 7-59) after UCB (*P*=0.006). Among 35 patients who did not engraft, 23 (66%) died early (before Day +30), 7 had neutrophil recovery with autologous reconstitution, and 5 were transplanted again from a different donor. Chimerism studies were available for 269 patients (42%). Most patients had complete chimerism in both the MUD (78%) and UCB groups (73%).

The cumulative incidence (CI) of platelet engraftment was significantly higher after a MUD (95%CI: 91% *vs.* 69% for UCB; *P*<0.0001) (Table 2), and in a multivariate analysis, MUD remained significantly associated with better platelet engraftment (HR 2.77; 95%CI: 2.13-3.59) (Table 3). Median time to platelet recovery was 14 days (range 7-74) after MUD and 35 days (range 4-124) after UCB (*P*<0.0001).

Graft-versus-host disease

There was no statistical difference in the cumulative incidence of grades II to IV acute GVHD at Day -100 risk between MUD and UCB recipients (Table 2). In a multivariate analysis, after adjustment for differences, cell source remained not significantly associated with the risk of acute GVHD.

Chronic GVHD was reported in 195 cases: 51% had limited and 49% extensive chronic GVHD. Among those with chronic GVHD, 96 of 196 (51%) in the MUD group and 10 of 25 (40%) in the UCB group had extensive disease. Patients receiving MUD had a higher risk of developing cGVHD than UCB recipients (52% vs. 26% for UCB; *P*<0.0001) (Table 2 and Figure 2). In a multivariate analysis, the use of MUD remained statistically associated with cGVHD (HR 2.22; 95%CI: 1.45-3.03) (Table 3).

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Table 1. Patients', disease, and transplant characteristics.

Characteristics	Total	MUD	UCB	*P*
Patients n.	645	541	104	
Age at transplantation, years, median (range)	50 (18-70)	50 (18-70)	48 (18-67)	NS
Male, n. (%)	424 (66)	362 (67)	62 (60)	NS
Recipient CMV-positive, n. (%)	289 (56)	235 (56)	54 (54)	NS
Histology at diagnosis (WHO classification), n. (%)				NS
Hodgkin lymphoma	156 (24)	127 (23)	29 (28)	
Chronic lymphocytic leukemia	119 (18)	97 (18)	22 (21)	
Non-Hodgkin lymphoma	370 (58)	317 (59)	53 (51)	
Follicular lymphoma	133 (21)	117 (22)	16 (15)	
Mantle cell lymphoma	82 (13)	74 (14)	8 (8)	
Diffuse large B-cell lymphoma	69 (11)	58 (11)	11 (10)	
Peripheral T-cell lymphoma	21 (3)	12 (2)	9 (9)	
Other	65 (10)	56 (10)	9 (9)	
Interval between diagnosis and transplant, median (months)	52 (3-372)	52 (3-372)	47 (6-258)	NS
Prior autologous transplant, n. (%)	357 (55)	302 (56)	55 (53)	NS
Disease status at HSCT, no. (%)				0.02
Complete remission 1 or 2 (CR1 or CR2)	134 (21)	105 (19)	29 (29)	
Sensitive relapse/progression, PR or CR>2	313 (49)	283 (52)	30 (30)	
Refractory disease or relapse	193 (30)	153 (29)	40 (41)	
Follow-up time for survivors, median (range)	28 (3-119)	25 (3-119)	35 (3-74)	NS
Conditioning regimen, no. (%)				
Fludarabine and melphalan	176 (28)	170 (32)	6 (6)*	<0.0001
Fludarabine and busulfan	123 (19)	120 (22)	3 (3)	
Fludarabine and TBI	100 (16)	98 (18)	2 (2)	
Cyclophosphamide, fludarabine and TBI 2 Gy	89 (14)	18 (3)	71 (74)*	
Cyclophosphamide, fludarabine and thiotepa	65 (10)	56 (11)	9 (10)	
Others	84 (13)	79 (14)	5 (5)	
Graft-*versus*-host disease prophylaxis, n. (%)				
Cyclosporine and mycophenolate mofetil	262 (41)	178 (33)	84 (85)*	<0.0001
Cyclosporine	166 (26)	163 (30)	3 (3)	
Cyclosporine and methotrexate	137 (21)	136 (25)	1 (1)	
Others	75 (12)	64 (12)	11 (11)	
Use of antithymocyte or antilymphocyte globulin (ATG/ALG), n. (%)	237 (38)	220 (41)	17 (21)*	<0.0001
Use of alemtuzumab, n. (%)	175 (27)	175 (32)	0 (0)*	<0.0001

NS: not significant; CMV: cytomegalovirus; WHO: World Health Organization; MUD: matched unrelated donor transplant; UCB: umbilical cord blood transplant; TBI: total body irradiation.

Non-relapse mortality

Overall, 171 patients died from non-relapse-related causes: 139 in the MUD group and 32 in the UCB group. The 36-month cumulative incidence of NRM was not statistically different between UCB and MUD (Table 2 and Figure 3), even after statistical adjustments for the differences between the groups (Table 3).

Relapse or progression

Overall, 195 patients relapsed or progressed after the transplant, 166 in the MUD group and 29 in the UCB group. Of note, overall 30% in the whole series were transplanted in relapse or with a refractory disease (29% in the MUD group and 41% in the UCB group; *P*=0.02) (Table 1). The cumulative incidence of relapse or progression was 34% at 36 months, without significant difference between MUD or UCB recipients (Table 2). In a multivariate analysis, stem cell source remained not associated with relapse or progression, but diagnoses other than indolent lymphoma (including CLL) and refractory/relapsed disease remained significantly associated with increased risk (Table 3).

Progression-free survival and overall survival

There was no significant difference in PFS between the UCB group and MUD transplants (41% *vs.* 36%, respectively) (Table 2 and Figure 4). Factors associated with decreased PFS in a multivariate analysis were age greater than 50 years, diagnoses other than indolent lymphoma, and refractory/relapsed disease (Table 3). Besides, there was a protective effect of chronic GVHD in preventing progression or relapse and in improving PFS rates: PFS was 57% in patients presenting *versus* 29% in those not presenting chronic GVHD (*P*<0.0001).

The probability of OS was 49% after a MUD transplant and 56% after a UCB (Table 2 and Figure 5). Factors associated with decreased OS were the same as for PFS, i.e. older age, diagnoses other than indolent lymphoma, and refractory/relapsed disease (Table 3).

Concerning the different malignancies analyzed, there were no significant differences in PFS or OS in patients with CLL, aggressive and indolent NHL, or HL according to stem cell source.

Discussion

Our study compared outcomes of patients with advanced mature lymphoid malignancies after either a UCB or a MUD RIC HSCT. Our main observations were: 1) higher incidence of graft failure after UCB; 2) lower incidence of chronic GVHD after UCB; and 3) similar risk of acute GVHD, NRM, relapse or progression; resulting in 4) similar PFS and OS between the two different stem cell sources.

To the best of our knowledge, this is the first study comparing outcomes of allogeneic HSCT using UCB or PBSC in patients with lymphoma or CLL. These results corroborate previously reported smaller series of patients[35,39,40] on the use of UCB in patients with advanced lymphoid malignancies. In the series published by our group, 104 patients from the EBMT and Eurocord databases were included.[35] NRM was 28%, relapse or progression 31%, and PFS was 40% at one year, after a median follow up of 18 months.

In the present study, cumulative incidence of neutrophil and platelet engraftment were decreased in UCB as compared to MUD and engraftment was delayed in UCB recipients (14 days *vs.* 18 days). However, the decreased engraftment rate did not impact on the risks of NRM, relapse or on PFS. Notably, most of the cases of graft failure were due to very early mortality, attributable to excessive toxicity in this heavily treated group of patients. As observed in previous studies comparing UCB with BM or PBSC in other indications[28,29] despite the larger risk of graft failure, there was no impact on survival, as some of these patients were either transplanted again or had autologous

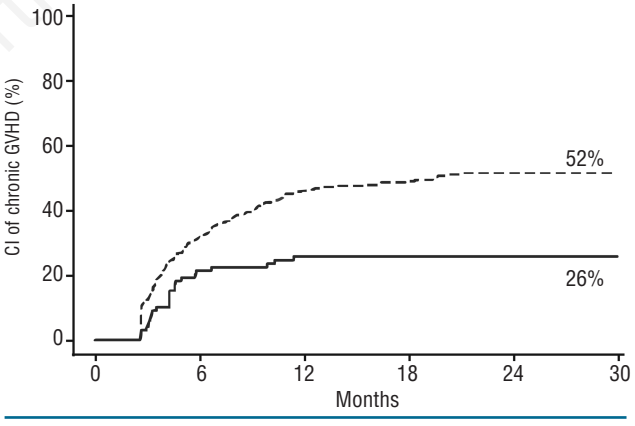

Figure 1. Cumulative incidence of neutrophil engraftment after UCB (solid line) and MUD allogeneic transplants (dotted line) for lymphoid malignancies.

Table 2. Point estimates of outcomes after MUD and UCB.

	MUD N=541		UCB N=104		*P*
	Events	%	Events	%	
Neutrophil engraftment at Day 60 (%)	483	97*	84	81*	<0.0001*
Acute GVHD at Day 100 (%)	175	32*	30	29*	NS*
Chronic GVHD at 3 years (%)	170	52*	25	26*	<0.0001*
Non-relapse-related mortality at 3 years (%)	139	28*	32	29*	NS*
Relapse or progression at 3 years (%)	166	35*	29	28*	NS*
Progression-free survival at 3 years (%)	305	36**	61	41**	NS**
Overall survival at 3 years (%)	245	49**	47	56**	NS**

** Cumulative incidence and P value Gray test, **Kaplan-Meier estimation P value log rank test. NS: not significant.*

reconstitution. In a series of 65 patients with lymphoma receiving a UCB after a RIC preparative regimen,[41] a shorter median time to neutrophil recovery (7.5 days) was observed, represented by a short period of mixed chimerism and transient autologous reconstitution in many cases.

NRM in allogeneic HSCT has decreased considerably over time, probably due to better patient selection and better supportive care.[42] Patients with lymphoma and CLL are usually referred to an allogeneic HSCT in very advanced phases of disease, as the last possibility of potentially curative treatment. In the present study, 95%CI of NRM was less than 30%, and PFS around 40% both after UCB and MUD, which are similar to previously reported values in RIC allogeneic HSCT for lymphoid malignancies using sibling donors/MUD[8,16-18,22-27,43] or UCB.[35,41]

The preparative regimen seems to have a strong influence on the risk of NRM. In a recently published retrospective registry-based analysis,[44] 120 patients receiving a double UCB had similar NRM rate after receiving a RIC regimen consisting of fludarabine, cyclophosphamide and low-dose TBI as compared to 424 MUD from a 7/8 or an 8/8 HLA-matched donor, but higher risk of NRM after other RIC conditioning regimens. No center effect was observed. In the present study, we were unable to analyze the association of center effect with outcomes due to the small number of patients included per center and the changes over time of the conditioning regimens, even in the same center.

Table 3. Multivariate analysis for main outcomes.

	Hazard ratio	95% confidence interval	*P*
Neutrophil engraftment			
Source of stem cells – MUD	2.12	1.63-2.77	<0.0001
Use of TBI	1.09	0.66-1.81	NS
Use of ATG	1.29	1.11-1.51	0.001
Chronic GVHD			
Source of stem cells – MUD	2.22	1.45-3.03	0.0002
Age > 50 years	1.18	0.89-1.57	NS
Non-relapse-related mortality			
Source of stem cells – MUD	1.22	0.79-1.88	NS
Age > 50 years	1.55	1.13-2.13	0.007
Relapse or progression			
Source of stem cells – MUD	1.23	0.82-1.89	NS
Diagnosis – other than indolent lymphoma*	3.03	1.59-5.88	<0.0001
Disease status – chemoresistant	1.40	1.05-1.88	0.02
Progression-free survival			
Source of stem cells – MUD	1.06	0.80-1.41	NS
Age > 50 years	1.25	1.01-1.55	0.04
Diagnosis – other than indolent lymphoma*	1.96	1.56-2.46	<0.0001
Disease status – chemoresistant	1.40	1.13-1.75	0.002
Overall survival			
Source of stem cells – MUD	1.14	0.82-1.57	NS
Age > 50 years	1.34	1.05-1.70	0.02
Diagnosis – other than indolent lymphoma	1.69	1.31-2.17	<0.0001
Disease status – chemoresistant	1.33	1.04-1.70	0.02

*Multivariate Fine and Gray for neutrophil engraftment, chronic GVHD, NRM, relapse or progression and Cox regression for PFS and OS. MUD: matched unrelated donor; NS: not significant. * The term "indolent lymphoma" is applied here both for indolent non-Hodgkin lymphoma and CLL. OBS: no variable remained significantly associated with the risk of acute GVHD.*

An intriguing aspect of our analysis is a considerably increased incidence of chronic GVHD in MUD using PBSC (HR 2.22; 95%CI: 1.45-3.03; *P*=0.0002), as previously described in acute leukemias.45 Whether the decreased incidence of chronic GVHD after UCB is a benefit in the long term and results in a better quality of life after HSCT remains to be determined.

One could argue that patients receiving a RIC regimen may present late onset of acute GVHD. Unfortunately, since our study is a registry-based analysis we were not able to analyze late-onset acute GVHD in both groups, since data on acute GVHD were collected considering those presenting before 100 days after graft infusion, according to the defined criteria.[46]

One could also argue that T-cell depletion would be expected to decrease the incidence of GVHD using MUD or UCB, which was not observed in our series. However, our objective was to compare graft sources in patients with lymphoma or CLL. Factors associated with outcomes were used for adjustments in the multivariate models. Therefore, our analysis does not allow us to address the

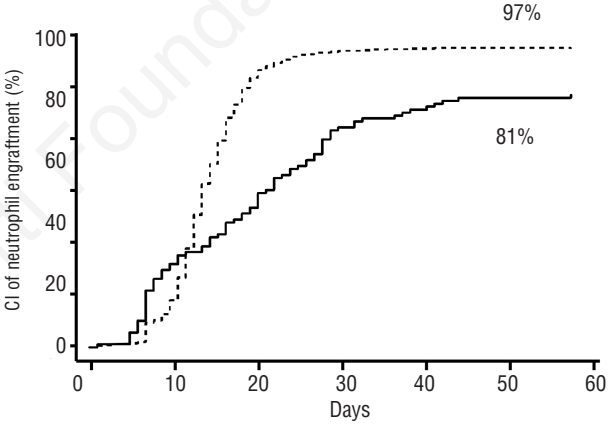

Figure 2. Cumulative incidence of chronic GVHD after UCB (solid line) and MUD allogeneic transplants (dotted line) for lymphoid malignancies.

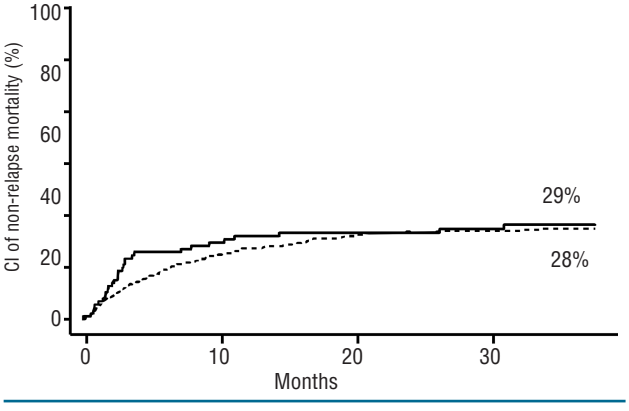

Figure 3. Cumulative incidence of non-relapse mortality (NRM) after UCB (solid line) and MUD allogeneic transplants (dotted line) for lymphoid malignancies.

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impact of T-cell depletion on the incidence of GVHD.

Interestingly, notwithstanding the decreased incidence of chronic GVHD after UCB as compared to MUD, we observed no differences in the incidence of relapse between the stem cell sources. Besides, consistent with others,[45] there was a significant association between chronic GVHD and a lower incidence of progression or relapse and better PFS. Other comparative studies in acute leukemia have observed both decreased incidence of chronic GVHD and decreased incidence of relapse rates after double UCB as compared to MUD.[44,47] The mechanism responsible for similar or decreased relapse incidence rates after UCB with less chronic GVHD remains to be determined. One could speculate whether these observations might possibly reflect a stronger GVL effect of UCB or simply a more frequent use of mismatched grafts and double grafts. Indeed, in our series, double cords were used in most cases of UCB and the majority of umbilical cord blood units were 4/6 HLA-matched, possibly leading to a more potent graft-*versus*-lymphoma effect.

In the previous analysis by our group[35] including both myeloablative and RIC UCB, as well as in a comparative series of patients receiving double or single UCB,[47] the use of double cord blood was associated with a decreased incidence of relapse. In the present study, since there were no differences in the risk of relapse or any of the analyzed outcomes between single or double UCB, we analyzed them together.

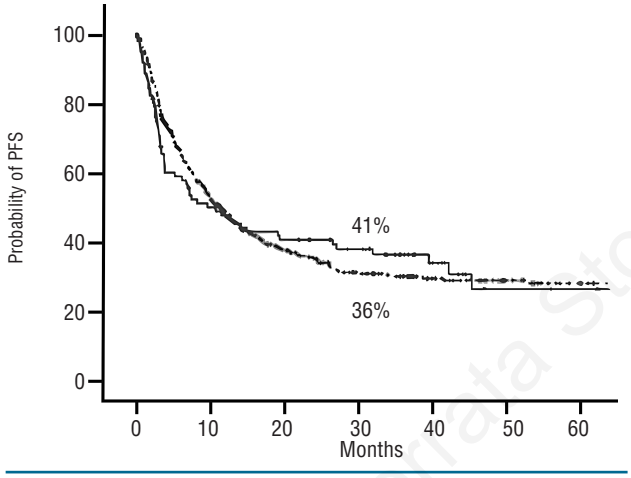

Figure 4. Estimated PFS after UCB (solid line) and MUD allogeneic transplants (dotted line) for lymphoid malignancies.

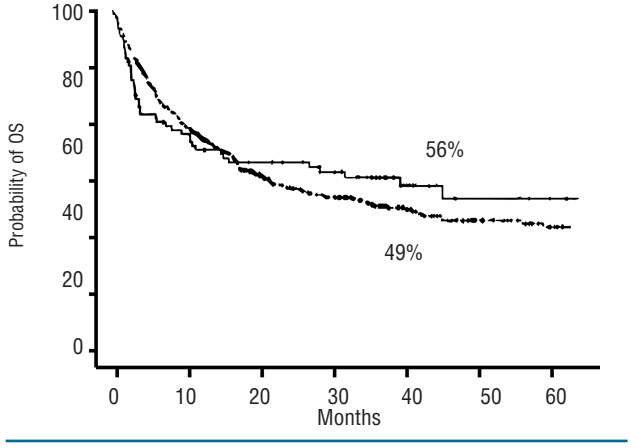

Figure 5. Estimated OS after UCB (solid line) and MUD allogeneic transplants (dotted line) for lymphoid malignancies.

As observed in other comparative studies,[28,29] a significantly higher proportion of patients were transplanted for refractory/relapsed disease in the UCB group than in the MUD group, and, despite that difference, relapse and PFS were comparable between the groups. This initial difference in patients' characteristics may be explained by the fact that UCB was, until recently, (and still is, in many clinical settings) considered an experimental approach. In many transplant centers, patients were probably offered this option only in very advanced phases of their disease, when no other options were available.

A major limitation to the use of umbilical cord blood is the paucity of progenitor cells in the graft, and lower doses are associated with lower rates of engraftment and worse survival.[28-35] Therefore, in the present study, only patients receiving a minimum of $2x10^7$ total nucleated cells infused/kg in the UCB group were included in order to compare outcomes using 'good' umbilical cord blood grafts (according to the current recommendations) or mobilized peripheral blood from a matched donor. Currently, the choice of cord blood unit is mainly based on the total nucleated cell (TNC) dose content in a cord blood unit that is superior to $2.5x10^7$ TNC/kg at freezing or more than $2x10^7$ TNC/kg at infusion. In order to reflect clinical practice, we selected only patients given a cell dose over $2x10^7$ TNC/kg. Our conclusions are, therefore, limited to patients receiving the minimum required cell dose and do not apply to any patient receiving a UCB graft.

The present study has several limitations, like all registry-based retrospective analyses. As expected, there was a significant difference in HSCT procedures, conditioning regimens and GVHD prophylaxis between the two stem cell sources. Although we adjusted for differences and known risk factors, only a randomized clinical trial could confirm these findings and reliably exclude selection bias. However, such a trial would be extremely complex to carry out, given the heterogeneity of clinical settings and difficulties in accrual, as only a few patients have both matched unrelated donors and umbilical cord blood available for transplant. In the context of advanced lymphoid malignancies with an indication for allogeneic transplant, the choice of intervention (in this case the stem cell source) should be established by the treating physician, based on the availability of a donor, and all complex criteria for donor selection. However, considering all the abovementioned limitations, our study supports the recommendation of the use of allogeneic UCB for the treatment of patients with advanced mature lymphoid malignancies lacking a suitable matched donor.

In summary, limiting HLA-disparity to two antigens and selecting umbilical cord blood grafts with adequate total nucleated cell doses, results in transplantation outcomes are not inferior to those of matched unrelated donors. UCB is associated with slower engraftment but lower risk of chronic GVHD. Prospective studies and longer follow up are needed to confirm this finding and to address the potential benefit of a lower risk of chronic GVHD in long-term survivors.

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