

# Analysis of Risk Factors for Outcomes After Unrelated Cord Blood Transplantation in Adults With Lymphoid Malignancies: A Study by the Eurocord-Netcord and Lymphoma Working Party of the European Group for Blood and Marrow Transplantation

Celso A. Rodrigues, Guillermo Sanz, Claudio G. Brunstein, Jaime Sanz, John E. Wagner, Marc Renaud, Marcos de Lima, Mitchell S. Cairo, Sabine Fürst, Bernard Rio, Christopher Dalley, Enric Carreras, Jean-Luc Harousseau, Mohamad Mohty, Denis Taveira, Peter Dreger, Anna Sureda, Eliane Gluckman, and Vanderson Rocha

From the Eurocord Office, Hôpital Saint Louis; Hôtel Dieu, Nantes; Hôtel Dieu, Paris; Hôpital La Milettrie, Poitiers; Institut Paoli Calmettes, Marseille, France; Hospital Universitário La Fe, Valencia; BMT Unit, Hospital Clinic Barcelona, IDIBAPS; Hospital Santa Creu i Sant Pau, Barcelona, Spain; University of Minnesota Medical School, Minneapolis, MN; The University of Texas M. D. Anderson Cancer Center, Houston, TX; Morgan Stanley Children's Hospital, New York Presbyterian, Columbia University, New York, NY; Royal Hallamshire Hospital, Sheffield, United Kingdom; and the University of Heidelberg, Heidelberg, Germany.

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Corresponding author: Celso A. Rodrigues, MD, Eurocord / ARTM-Hôpital Saint Louis, 1, Av Claude Vellefaux, 75475 Paris Cedex 10 France; e-mail: [celsoarrais@uol.com.br](mailto:celsoarrais@uol.com.br).

The Appendix is included in the full-text version of this article, available online at [www.jco.org](http://www.jco.org). It is not included in the PDF version (via Adobe® Reader®).

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## ABSTRACT

### Purpose

To determine risk factors of umbilical cord blood transplantation (UCBT) for patients with lymphoid malignancies.

### Patients and Methods

We evaluated 104 adult patients (median age, 41 years) who underwent unrelated donor UCBT for lymphoid malignancies. UCB grafts were two-antigen human leukocyte antigen-mismatched in 68%, and were composed of one ( $n = 78$ ) or two ( $n = 26$ ) units. Diagnoses were non-Hodgkin's lymphoma (NHL,  $n = 61$ ), Hodgkin's lymphoma (HL,  $n = 29$ ), and chronic lymphocytic leukemia (CLL,  $n = 14$ ), with 87% having advanced disease and 60% having experienced failure with a prior autologous transplant. Sixty-four percent of patients received a reduced-intensity conditioning regimen and 46% low-dose total-body irradiation (TBI). Median follow-up was 18 months.

### Results

Cumulative incidence of neutrophil engraftment was 84% by day 60, with greater engraftment in recipients of higher CD34<sup>+</sup> kg/cell dose ( $P = .0004$ ). CI of non-relapse-related mortality (NRM) was 28% at 1 year, with a lower risk in patients treated with low-dose total-body irradiation (TBI;  $P = .03$ ). Cumulative incidence of relapse or progression was 31% at 1 year, with a lower risk in recipients of double-unit UCBT ( $P = .03$ ). The probability of progression-free survival (PFS) was 40% at 1 year, with improved survival in those with chemosensitive disease (49% v 34%;  $P = .03$ ), who received conditioning regimens containing low-dose TBI (60% v 23%;  $P = .001$ ), and higher nucleated cell dose (49% v 21%;  $P = .009$ ).

### Conclusion

UCBT is a viable treatment for adults with advanced lymphoid malignancies. Chemosensitive disease, use of low-dose TBI, and higher cell dose were factors associated with significantly better outcome.

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## INTRODUCTION

Allogeneic hematopoietic stem-cell transplantation (HSCT) is a curative approach for patients with advanced, relapsed, or refractory non-Hodgkin's lymphoma (NHL),<sup>1-4</sup> Hodgkin's lymphoma (HL),<sup>5,6</sup> and chronic lymphocytic leukemia (CLL).<sup>7-9</sup>

Comparative studies have reported lower relapse rates after allogeneic transplant relative to autologous transplant.<sup>10</sup> However, conventional allogeneic HSCT is associated with high non-

relapse-related mortality (NRM), which offsets the potential survival benefit of this procedure.<sup>11-14</sup>

Reduced-intensity conditioning (RIC) regimens have been used with increasing frequency in such high-risk populations.<sup>14-21</sup> Low relapse rates after RIC transplant suggest that the graft-versus-lymphoma (GVL) effect of donor T cells is retained.<sup>5,17,20-27</sup>

Umbilical cord blood (UCB) is an alternative source of hematopoietic stem cells for the treatment of hematologic malignancies in patients lacking a

human leukocyte antigen (HLA)-matched donor.<sup>28,29</sup> Advantages of UCB include prompt availability and decreased risk of graft-versus-host disease (GVHD) despite HLA mismatch. These attributes make UCB applicable to nearly all patients, particularly those with less common tissue types, such as those in ethnic and racial minorities.<sup>28-32</sup> However, the low number of progenitor cells has been associated with delayed engraftment and increased risk of NRM.<sup>31,32</sup> Strategies to overcome this barrier include the use of two partially HLA-matched UCB units (double UCBT).<sup>33,34</sup>

There have been a few isolated reports for refractory NHL<sup>35-37</sup> and malignant lymphoma treated by RIC-UCBT.<sup>38,39</sup> This larger analysis has allowed us to report the general experience of unrelated UCBT in the treatment of advanced lymphoid malignancies in adults, and to identify treatment- and disease-based factors associated with better or poorer outcomes.

## PATIENTS AND METHODS

### Data Collection

Eurocord is a registry of related and unrelated UCBT that works in collaboration with the European Group of Blood and Marrow Transplantation (EBMT), and Netcord banks. Netcord is an international organization that encompasses cord blood banks all over the world, mostly in Europe (the Appendix, online only, contains a listing of banks). Eurocord and EBMT databases provided data on UCBT. Centers not associated with EBMT were asked to complete reports if UCB units were obtained from Netcord banks. All data were verified and updated by the institution's physicians and data managers. All patients or legal guardians provided informed consent for the UCBT according to the Declaration of Helsinki.

### Inclusion Criteria

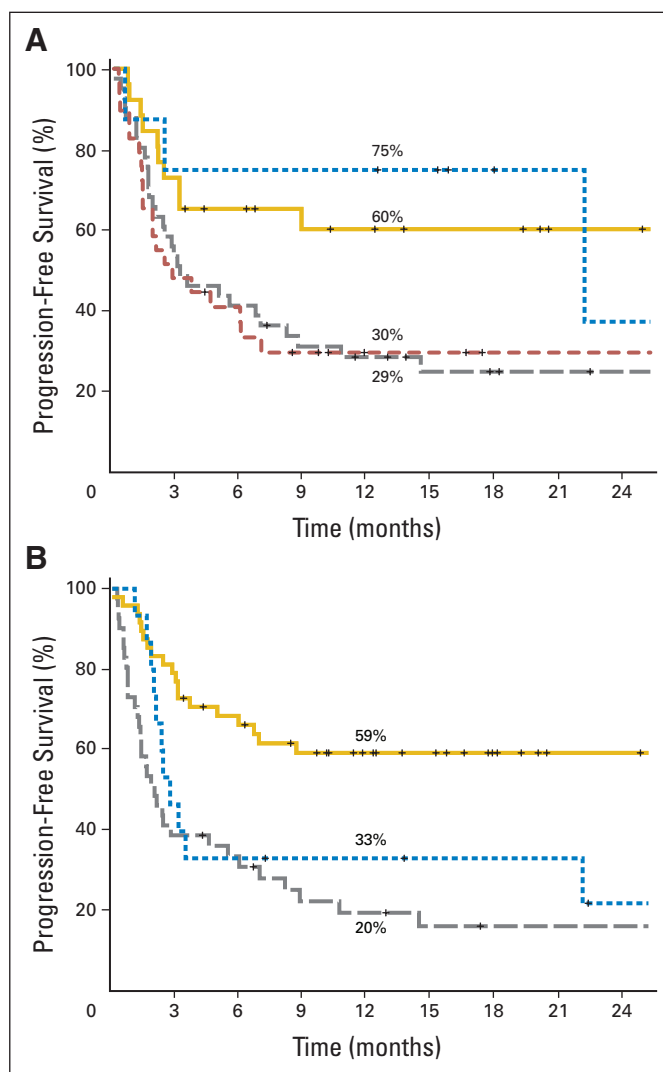
The study included patients with malignant lymphoma (both HL and NHL) or CLL (1) who received an unrelated and unmanipulated single-unit or double-unit UCBT; (2) who were older than 15 years at the time of transplantation; and (3) for whom there were adequate and sufficient data to perform the analysis. Twelve patients included in this study were previously reported.<sup>40</sup>

### End Point Definitions

The primary end point was progression-free survival (PFS) at 1 year, defined as the time from transplantation to relapse, disease progression, or death. Other end points included incidence of neutrophil recovery, defined as first of 3 consecutive days with a neutrophil count of at least  $0.5 \times 10^9/L$ , and the incidence of platelet recovery as the first of 7 consecutive days of an unspun platelet count of at least  $20 \times 10^9/L$ ; graft failure was defined as no sign of neutrophil recovery, as well as transient engraftment of donor cells 60 days after transplantation; acute GVHD at day 100 and chronic GVHD at 1 year, diagnosed and graded according to published criteria,<sup>41</sup> with histopathologic confirmation when possible; relapse or progression at 1 year, as defined by the centers on the basis of clinical, imaging or laboratory evidence; and NRM at 6 months and at 1 year, defined as deaths related to transplantation and not to relapse. Chimerism data was evaluated in the first 3 months after UCBT. Full donor chimerism was defined as the presence of more than 95% of the cells of donor origin, mixed chimerism if more than 5% and less than 95% of donor cells and autologous recovery if less than 5% of donor cells. Data on the method of chimerism detection were not collected.

### Statistical Analysis

Data were analyzed through March 2007. Cumulative incidence function (CIF) using death as a competing event was used to estimate neutrophil and platelet engraftment, acute and chronic GVHD, NRM, and relapse. The Kaplan-Meier method was used to estimate overall survival (OS) and PFS. For continuous variables, the median was used as the cutoff point. For assessment of prognostic factors using CIF, univariate and multivariate analyses were performed using the Gray's test<sup>42</sup> and the proportional subdistribution hazard



**Fig 1.** (A) Estimated progression-free survival (PFS) according to histologic subtype. Patients with indolent non-Hodgkin's lymphoma (NHL; yellow line), mantle-cell lymphoma (blue line), aggressive NHL (gray line), and Hodgkin's lymphoma (red line). (B) Estimated PFS according to the use of total-body irradiation (TBI). Patients who received low-dose TBI-containing regimens (yellow line), high-dose TBI (blue line), or no TBI (gray line), after umbilical cord blood transplantation for lymphoid malignancies.

regression model of Fine and Gray.<sup>43</sup> For OS and PFS, log-rank tests and Cox proportional-hazards model in univariate and multivariate analyses were used. Acute and chronic GVHD were assessed as time-dependent covariates for PFS. Each potential risk factor was tested independently. All factors that reached  $P \leq .05$  in the univariate analysis were included in the multivariate model. All models were built using a forward stepwise method. Only factors that reached a  $P \leq .05$  were held in the final model. Of note, the factors "lymphoma subtype" and "use of TBI" were initially classified into multiple categories. However, in an effort to minimize multiple comparisons, and as there were no statistical differences between the categories "no TBI" and "high-dose TBI" (Appendix Table A1, online only), these categories were collapsed and the variable "use of TBI" was analyzed as "low-dose TBI versus others." The variable "lymphoma subtype" was not included in the final multivariate analysis because the group of patients with mantle-cell lymphoma was too small, and clinically different from indolent lymphoma. The use of antithymocyte or antilymphocyte globulin (ATG/ALG) was also not included in the final model because of a strong correlation with myeloablative conditioning regimen (Appendix Table A2, online only). Statistical analyses were

performed with SPSS (SPSS Inc, Chicago, IL), and S-Plus (Insightful Corp, Seattle, WA) software packages.

## RESULTS

### Patient and Disease Characteristics

A total of 104 patients from 34 EBMT transplant centers and 14 non-EBMT centers, who underwent transplantation between January 1996 and June 2007, met the inclusion criteria: 15 patients received transplants from 1996 to 2001, 30 from 2002 to 2004, and 59 from 2005 to 2007. Sixty-one patients had NHL, 29 had HL, and 14 CLL. Patient and disease characteristics are summarized in Table 1. Forty-two patients with a response to the last therapy before the transplant (complete or partial remission) were considered chemosensitive, and 62 patients with primary refractory disease or refractory relapse before transplant were considered chemoresistant.

### Graft and Transplant Characteristics

Graft and conditioning regimen characteristics are summarized in Table 2. A total of 78 patients received a single UCBT, and 26 received a double UCBT.

**Table 1.** Patient and Disease Characteristics (N = 104)

Characteristic	No.	%
Age at transplantation, years		
Median	41	
Range	16-65	
Weight at transplantation, kg		
Median	68	
Range	39-130	
Male	55	53
Recipient CMV positive	52	50
Histology at diagnosis (WHO classification)		
Hodgkin's lymphoma	29	28
Chronic lymphocytic leukemia	14	13
Non-Hodgkin's lymphoma	61	59
Mature B-cell neoplasms	39	38
Diffuse large B-cell lymphoma	19	19
Follicular lymphoma	10	10
Mantle cell lymphoma	8	8
Small lymphocytic lymphoma	2	2
Mature T-cell neoplasms	22	21
Peripheral T-cell lymphoma	8	8
Anaplastic large cell lymphoma	6	6
Extranodal NK/T-cell lymphoma	3	3
Angioimmunoblastic T-cell lymphoma	2	2
Hepatosplenic T-cell lymphoma	2	2
Subcutaneous panniculitis-like T-cell lymphoma	1	1
Interval between diagnosis and transplant, months		
Median	36	
Range	6-248	
Prior autologous transplant	62	60
Disease status at UCBT		
Complete remission	24	23
Partial remission	18	17
Refractory disease or relapse	62	60

Abbreviations: CMV, cytomegalovirus; NK, natural killer; UCBT, umbilical cord blood transplantation.

**Table 2.** Graft and Transplant Characteristics

Characteristic	No.	%
No. of UCB units		
1	78	75
2	26	25
No. of HLA disparities*		
6/6 match	7	10
5/6 match	16	23
4/6 match	42	60
3/6 match	5	7
No. of HLA disparities†		
2 units 6/6 match	2	9
2 units 5/6 match	4	18
2 units 4/6 match	12	55
1 unit 5/6 and 1 unit 4/6 match	3	13
1 unit 4/6 and 1 unit 3/6 match	1	5
No. of total nucleated cells infused, ×10 <sup>7</sup> /kg		
1		
Median	2.41	
Range	0.88-10.20	
2		
Median	3.02	
Range	1.20-7.90	
No. of total CD34 <sup>+</sup> cells infused, ×10 <sup>5</sup> /kg		
1		
Median	1.07	
Range	0.06-14.30	
2		
Median	0.91	
Range	0.14-5.15	
Conditioning regimen (n = 100)		
Reduced-intensity	64	64
Cyclophosphamide + fludarabine + TBI 2 Gy	42	42
Busulfan + thiotepa + fludarabine	9	9
Cyclophosphamide + fludarabine ± thiotepa	4	4
Others	9	9
Myeloablative	36	36
Busulfan + thiotepa + fludarabine	9	9
Busulfan + cyclophosphamide ± thiotepa ± melphalan	9	9
Cyclophosphamide + TBI 12 Gy ± fludarabine	8	8
Others	10	10
Use of total body irradiation		
No	41	40
Low-dose	48	46
High-dose	14	14
Graft-versus-host disease prophylaxis (n = 100)		
Cyclosporin + mycophenolate mofetil	52	53
Cyclosporin + prednisone	26	26
Cyclosporin ± methotrexate	7	7
Others	15	15
Use ATG or ALG (n = 102)	46	45
Follow-up time for survivors, months		
Median	18	
Range	3-74	

Abbreviations: UCB, umbilical cord blood; HLA, human leukocyte antigen; TBI, total-body irradiation; ATG, antithymocyte globulin; ALG, antilymphocyte globulin.  
\*One unit, antigen-level HLA-A and B and allele-level HLA-DRB1 typing.  
†Two units, antigen-level HLA-A and B and allele-level HLA-DRB1 typing.

Conditioning regimen varied according to the transplant center. A total of 64 patients received an RIC regimen, and 36 received a myeloablative conditioning regimen. For four patients, detailed data on the conditioning regimen were not available. Median follow-up time for survivors was 18 months (range, 3 to 74 months).

### Engraftment and Chimerism Studies

The cumulative incidence of neutrophil recovery was 84% by day 60. Neutrophil recovery occurred in 86% of patients at a median of 17 days (range, 3 to 54 days) for patients who received RIC and in 83% at a median of 22 days (range, 11 to 48 days) for patients who received

myeloablative regimens. Eight patients died before day +30 without achieving neutrophil engraftment. Primary graft failure occurred in nine patients: five patients had autologous reconstitution and four engrafted after a second transplant (two patients received an autograft; one a UCBT and one a peripheral blood-stem-cell transplant).

In a univariate analysis, the following variables were associated with a higher incidence of neutrophil engraftment (Table 3): use of low-dose TBI in the conditioning regimen (92% v 73% for patients not receiving TBI and 87% for patients receiving high-dose TBI;  $P = .0007$ ), regimens not incorporating ATG/ALG (91% v 76%;

**Table 3.** Univariate Analysis for Outcomes After Umbilical Cord Blood Transplantation for Patients With Lymphoid Malignancies (N = 104)

Variable	No.	%					
		Neutrophil Engraftment at Day 60 (n = 84)	Non-Relapse-Related Mortality at 1 Year (n = 28)	Acute Graft-Versus-Host Disease at Day 100 (N = 24)	Relapse or Progression at 1 Year (n = 31)	Progression-Free Survival at 1 Year (n = 40)	Overall Survival at 1 Year (n = 48)
<b>Age, years</b>							
< 41	54	87	38	12	34	28	35
≥ 41	49	82	19	38	27	54	62
<i>P</i>		NS	.04	.002	NS	.02	.02
<b>Lymphoma subtype</b>							
Indolent NHL	26	85	20	36	19	60 <sup>(1)</sup>	68
Mantle cell lymphoma	8	63	0	38	25	75 <sup>(2)</sup>	75
Hodgkin's lymphoma	29	90	35	12	35	30 <sup>(3)</sup>	41
Aggressive NHL	41	85	34	22	37	29 <sup>(4)</sup>	36
<i>P</i>		NS	NS	NS	NS	.02*	.09*
<b>Disease features</b>							
Chemosensitive	42	93	28	23	22	49	54
Chemoresistant	62	77	29	26	38	34	44
<i>P</i>		.08	NS	NS	.06	.04	.09
<b>No. of UCB units</b>							
1	78	81	26	22	38	35	42
2	26	92	31	32	13	57	65
<i>P</i>		.06	NS	NS	.009	.06	.09
<b>Conditioning regimen</b>							
RIC	64	86	20	32	34	46	59
MAC	36	83	38	14	31	31	33
<i>P</i>		NS	NS	.04	NS	NS	.03
<b>Use of TBI</b>							
No	41	73	50	11	30	20 <sup>(1x)</sup>	20
Low-dose	48	92	13	39	28	60 <sup>(2x)</sup>	74
High-dose	15	87	20	13	47	33 <sup>(3x)</sup>	39
<i>P</i>		.0007*	.0006*	.003*	NS	< .0001*	< .0001*
<b>Use of ATG/ALG</b>							
No	56	91	18	33	26	56	68
Yes	46	76	38	14	39	23	26
<i>P</i>		.004	.04	.02	NS	.001	< .0001
<b>TNC × 10<sup>7</sup>/kg</b>							
< 2	32	75	41	20	38	21	22
≥ 2	67	91	22	27	29	49	61
<i>P</i>		.05	.02	NS	NS	< .0001	< .0001
<b>CD34<sup>+</sup> cells × 10<sup>5</sup>/kg</b>							
< 1	47	78	33	25	30	37	41
≥ 1	45	93	23	27	32	45	59
<i>P</i>		< .0001	NS	NS	NS	NS	NS

NOTE. Superscripted parentheticals refer to the *P* value for pairwise tests: (1) v (2) is .92; (3) v (4) is .83; (1 and 2) v (3 and 4) is .002; (1<sup>x</sup>) v (3<sup>x</sup>) is .30; (2<sup>x</sup>) v (1 and 3) is < .0001.

Abbreviations: NS, not significant; NHL, non-Hodgkin's lymphoma; UCB, umbilical cord blood; RIC, reduced-intensity conditioning; MAC, myeloablative conditioning; TBI, total-body irradiation; ATG, antithymocyte globulin; ALG, antilymphocyte globulin; TNC, total nucleated cells; NS, not significant.

\*3 df.

$P = .004$ ), and infused CD34<sup>+</sup> cell dose greater than  $1.0 \times 10^5/\text{kg}$  (96% v 77%;  $P < .0001$ ). In a multivariate analysis, the use of low-dose TBI ( $P = .04$ ; Table 4), and a higher CD34<sup>+</sup> cell dose ( $P = .0004$ ) remained favorably associated with engraftment. Number of HLA mismatches was not identified as a factor associated with neutrophil engraftment.

The cumulative incidence of platelet engraftment was 65% by day 180. In a univariate analysis, factors associated with higher incidence of platelet engraftment were use of low-dose TBI (88% v 53% in patients not receiving TBI and 47% in those receiving high-dose TBI;  $P < .0001$ ), regimens not incorporating ATG/ALG (71% v 57%;  $P = .04$ ), and infused CD34 cell dose greater than  $1.0 \times 10^5/\text{kg}$  (85% v 58%;  $P = .002$ ). In a multivariate analysis, only low-dose TBI remained associated with platelet engraftment ( $P = .003$ ).

In recipients of single UCBT, chimerism studies were available for 54 of 62 assessable patients. Forty patients (74%) had complete chimerism, and eight patients (15%) had mixed chimerism at first testing (before day +100). Of these, four patients became complete chimeras at the second or third evaluation.

In recipients of double UCBT, chimerism data were available in 17 out of 21 assessable patients. Sixteen patients (94%) had complete chimerism and one patient (6%) had a mixed chimerism. In 16 cases, engraftment was derived from one unit and in two cases, from both units.

## NRM

Twenty-nine patients died as a result of non-relapse-related causes. The principal causes of NRMs were infection (69%): bacterial ( $n = 9$ ), viral ( $n = 6$ ), or fungal ( $n = 5$ ). Cumulative incidence of NRM was 24% at 6 months and 28% at 1 year. Factors associated with a lower NRM were age at least 41 years (19% v 38%;  $P = .04$ ), use of low-dose TBI (13% v 50% in patients not receiving TBI and 20% in those receiving high-dose TBI;  $P = .0006$ ), regimens not incorporating ATG/ALG (18% v 38%;  $P = .04$ ), and total nucleated cell (TNC) dose higher than  $2 \times 10^7/\text{kg}$  (22% v 41%;  $P = .02$ ). In a multivariate

analysis, the use of low-dose TBI ( $P = .03$ ), and a TNC dose higher than  $2 \times 10^7/\text{kg}$  ( $P = .045$ ) were associated with lower NRM. Although patients who received an RIC also tended to have lower NRM compared with those receiving myeloablative regimens (20% v 38%), this beneficial effect was driven only by RIC regimens incorporating low-dose TBI, and not by the others.

## GVHD

The cumulative incidence of acute GVHD grades 2 to 4 and 3 to 4 was 24% and 8%, respectively. Factors associated with a higher risk of acute GVHD were age 41 years or older (38% v 12%;  $P = .002$ ), use of low-dose TBI (39% v 11% in patients not receiving and 13% in those receiving high-dose TBI;  $P = .003$ ), regimens not incorporating ATG/ALG (33% v 14%;  $P = .02$ ), and RIC-UCBT (32% v 14%;  $P = .04$ ). In a multivariate analysis, only older age remained significantly associated with the risk of acute GVHD ( $P = .02$ ).

Fifty-two patients were assessable for chronic GVHD; the cumulative incidence at 1 year was 18%. Eight patients (15%) developed limited and 10 (19%) extensive chronic GVHD.

## Relapse or Progression

The cumulative incidence of relapse or progression was 31% at 1 year and 35% at 2 years. Overall, 35 patients (33%) relapsed or progressed after the UCBT, with a median time to relapse or progression of 3 months (range, 1 to 33 months). Of these 35 patients, 29 (83%) were transplanted in relapse, partial remission, or had refractory disease at transplant.

Factors associated with lower relapse or progression rates were chemosensitive disease (22% v 38%;  $P = .05$ ) and use of double UCBT (13% v 38%;  $P = .009$ ). In a multivariate analysis, only the use of double UCBT ( $P = .02$ ) remained associated with lower relapse risk.

## PFS and OS

The probability of PFS was 40% at 1 year and 36% at 2 years. Factors associated with PFS were age at least 41 years (54% v 28%;  $P = .02$ ), presence of chemosensitive disease (49% v 34%;  $P = .04$ ), histologic subtype (60% in indolent NHL, 75% in mantle cell NHL, 29% in aggressive NHL, and 30% in HL;  $P = .02$ ; Fig 1A), use of low-dose TBI (59% v 20% in patients not receiving TBI and 33% in those receiving high-dose TBI;  $P < .0001$ ), use of regimens not incorporating ATG/ALG (56% v 23%;  $P = .001$ ; Fig 1B), and a TNC dose higher than  $2 \times 10^7/\text{kg}$  (49% v 21%;  $P < .0001$ ). In a multivariate analysis, use of low-dose TBI ( $P = .001$ ), chemosensitive disease ( $P = .03$ ), and a TNC dose higher than  $2 \times 10^7/\text{kg}$  ( $P = .009$ ) remained factors associated with a better PFS.

Acute or chronic GVHD, analyzed as time dependent covariates, were not statistically associated with PFS (for acute GVHD, relative risk [RR] = 0.56; 95% CI, 0.56 to 1.11;  $P = .10$ ; for chronic GVHD, RR = 0.39; 95% CI, 0.09 to 1.73;  $P = .22$ ).

OS at 1 year was 48%. Factors associated with OS were similar to those for PFS: older age (62% v 35%;  $P = .02$ ), use of low-dose TBI (74% v 20% in patients not receiving TBI and 39% in those receiving high-dose TBI;  $P < .0001$ ), use of regimens not incorporating ATG/ALG (68% v 26%;  $P < .0001$ ), and higher UCB graft TNC dose greater than  $2 \times 10^7/\text{kg}$  (61% v 22%;  $P < .0001$ ). In multivariate analysis, use of low-dose TBI ( $P < .0001$ ), and TNC dose higher than  $2 \times 10^7/\text{kg}$  ( $P = .01$ ) remained associated with better OS. In the subgroup of patients with indolent lymphoid disease, PFS was 75% in patients with follicular lymphoma and 43% in those with CLL.

**Table 4.** Multivariate Analysis for NRM, Relapse or Progression, PFS, and OS

Variable	Relative Risk	95% CI	P
<b>Neutrophil engraftment</b>			
Use of low-dose TBI	1.62	1.03 to 2.57	.04
CD34 <sup>+</sup> cells > $1 \times 10^5/\text{kg}$	2.67	1.55 to 4.61	.0004
<b>NRM</b>			
Use of low-dose TBI	0.30	0.10 to 0.89	.03
TNC > $2 \times 10^7/\text{kg}$	0.45	0.21 to 0.98	.045
<b>Acute GVHD</b>			
Age $\geq$ 41 years	2.92	1.20 to 7.13	.02
<b>Relapse or progression</b>			
2 UCB units	0.28	0.09 to 0.87	.03
<b>PFS</b>			
Chemosensitive disease	0.54	0.31 to 0.93	.03
Use of low-dose TBI	0.40	0.23 to 0.69	.001
TNC > $2 \times 10^7/\text{kg}$	0.49	0.29 to 0.84	.009
<b>OS</b>			
Use of low-dose TBI	0.30	0.16 to 0.58	.0003
TNC > $2 \times 10^7/\text{kg}$	0.47	0.26 to 0.83	.01

Abbreviations: NRM, non-relapse-related mortality; PFS, progression-free survival; OS, overall survival; TBI, total-body irradiation; TNC, total nucleated cell; GVHD, graft-versus-host disease; UCB, umbilical cord blood.

In the subgroup of patients who were not in complete remission at transplant ( $n = 80$ ), 30 (38%) remain in remission after UCBT with a median follow-up of 18 months (range, 4 to 57 months). PFS and OS at 1 year were 40% and 46%, respectively. PFS was 69% for patients who received low-dose TBI versus only 9% in those not receiving TBI and 36% in those who received high-dose TBI ( $P < .0001$ ).

## DISCUSSION

In the present study, we demonstrated that UCBT is a viable option for patients with lymphoma and CLL. Despite the fact that most patients received transplants in an advanced phase of their disease, relatively low NRM and good survival rates were observed. Especially favorable characteristics were chemosensitive disease, use of low-dose TBI, and higher cell doses.

To date, there have been only a few isolated reports on the use of UCBT in patients with advanced lymphoid malignancy.<sup>38,39</sup> And the use of conventional allogeneic HSCT in patients with lymphoma and CLL is still limited.<sup>3,4</sup> The reported studies are heterogeneous in terms of patient, transplant, and disease features, which make comparisons difficult.

Our results, using unrelated donor UCB, are comparable to those using HLA-matched donors.<sup>22,25,44-47</sup> We observed an NRM incidence of 28% and PFS and OS rates of 40% and 48% at 1 year, respectively. Branson et al<sup>25</sup> observed 20% of NRM of and a PFS of 50% at 14 months (median follow-up time) in 38 patients with advanced lymphoma who received an RIC HLA-matched sibling donor transplant. The Lymphoma Working Party of the EBMT reported a NRM of 26% and a PFS of 46% at 1 year with a median follow-up of 7 months, in 188 patients with lymphoma who received an RIC-HSCT.<sup>22</sup> Survival was significantly better in those with chemosensitive disease, HL, and indolent NHL.

In the present study, chemosensitivity also favorably influenced PFS (49% v 34%), and OS (54% v 44%). Besides, we also observed that patients with indolent NHL presented a significantly better outcome: NRM, PFS, and OS rates were 20%, 60%, and 68%, respectively. A better response rate in indolent disease is expected in this group of patients in which RIC regimens were the most frequently used. Besides, the observed worse prognosis of UCBT for both HL and aggressive NHL might also be related to the high toxicity of the conditioning regimen, yielding a high NRM rate, and a high relapse risk in a group of patients with advanced phases of disease because UCBT is usually the last possibility of treatment and is still considered experimental by many transplant centers.

To our knowledge, this is the first study to report patients with CLL who received a UCBT. We observed a 1-year PFS and OS of 43% and 51%, respectively. These results are comparable with those of allogeneic HSCT in the RIC setting, with PFS rates ranging from 34% to 52% and OS from 51% to 60%.<sup>48-50</sup>

We observed a significantly lower NRM and better PFS and OS rates in patients who received low-dose TBI. The assumption is that this regimen provides sufficient immunosuppression with lower risk of regimen-related toxicity, thus accounting for its overall beneficial effect. RIC regimens not incorporating low-dose TBI resulted in outcomes comparable to that of myeloablative therapies. The GVL effect appears to be sufficient after low-dose TBI, on the basis of the observed risks of relapse and progression in this series.

Immunosuppression with ATG/ALG was associated with poor outcomes in a univariate analysis. However, because of the correlation with myeloablative conditioning regimens in the majority of cases in our series, the role of ATG/ALG was not appropriately addressed and should be further evaluated in a more homogenous population.

In this multicentric based-registry analysis, we were not able to analyze the association of center effect with outcomes because of the small number of patients included per center and the changes over time of the conditioning regimens, even in a same center.

One of the intriguing findings of this study is the possible enhanced GVL effect associated with double UCBT. Such a finding has also been observed in adults with various hematologic malignancies.<sup>51,52</sup> Whether this apparent enhancement of GVL is simply the result of a greater state of allogeneic immune cell activation or the greater use of more HLA-disparate UCB units has yet to be determined.

Incidence of acute GVHD was higher in patients older than 41 years, but age was not associated with PFS. One could argue that this observation could be related to a stronger GVL effect. However, there was no statistical association between GVHD and PFS, despite a trend of improved PFS in patients presenting GVHD. The GVL effect after UCBT in patients with lymphoma needs to be analyzed in a larger series of patients and with a longer follow-up.

In conclusion, UCBT is a viable alternative in adult patients with advanced lymphoma and CLL who lack an HLA-matched donor, with particularly encouraging results for patients with chemosensitive disease receiving low-dose TBI-based conditioning regimens and adequate cell doses. On the basis of our findings, several important strategies should be considered: (1) greater use of less toxic RIC regimens, such as those containing low-dose TBI, (2) better selection of UCB units, and (3) broader use of double UCBT.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

## AUTHOR CONTRIBUTIONS

**Conception and design:** Celso A. Rodrigues, Eliane Gluckman, Vanderson Rocha

**Provision of study materials or patients:** Celso A. Rodrigues, Guillermo Sanz, Claudio G. Brunstein, Jaime Sanz, John E. Wagner, Marc Renaud, Marcos de Lima, Mitchell S. Cairo, Sabine Fürst, Bernard Rio, Christopher Dalley, Enric Carreras, Jean-Luc Harousseau, Mohamad Mohty, Anna Sureda, Eliane Gluckman, Vanderson Rocha

**Collection and assembly of data:** Celso A. Rodrigues, Guillermo Sanz, Jaime Sanz, Marc Renaud, Marcos de Lima, Mitchell S. Cairo, Enric Carreras, Mohamad Mohty, Denis Taveira, Eliane Gluckman, Vanderson Rocha

**Data analysis and interpretation:** Celso A. Rodrigues, Anna Sureda, Eliane Gluckman, Vanderson Rocha

**Manuscript writing:** Celso A. Rodrigues, Eliane Gluckman, Vanderson Rocha

**Final approval of manuscript:** Celso A. Rodrigues, Guillermo Sanz, Claudio G. Brunstein, John E. Wagner, Marcos de Lima, Mitchell S. Cairo, Sabine Fürst, Bernard Rio, Christopher Dalley, Enric Carreras, Mohamad Mohty, Peter Dreger, Anna Sureda, Eliane Gluckman, Vanderson Rocha

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## ERRATA

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The January 10, 2009, article by Rodrigues et al entitled, “Analysis of Risk Factors for Outcomes After Unrelated Cord Blood Transplantation in Adults With Lymphoid Malignancies: A Study by the Eurocord-Netcord and Lymphoma Working Party of the European Group for Blood and Marrow Transplantation” (J Clin Oncol 27:256-263, 2009) contained errors.

In the Results section, under PFS and OS, the second sentence referred to Figure 2 and Figure 3, whereas it should have been Figure 1A and Figure 1B, as follows:

“Factors associated with PFS were age at least 41 years (54% v 28%;  $P = .02$ ), presence of chemosensitive disease (49% v 34%;  $P = .04$ ), histologic subtype (60% in indolent NHL, 75% in mantle cell NHL, 29% in aggressive NHL, and 30% in HL;  $P = .02$ ; **Fig 1A**), use of low-dose TBI (59% v 20% in patients not receiving TBI and 33% in those receiving high-dose TBI;  $P < .0001$ ), use of regimens not incorporating ATG/ALG (56% v 23%;  $P = .001$ ; **Fig 1B**), and a TNC dose higher than  $2 \times 10^7/\text{kg}$  (49% v 21%;  $P < .0001$ ).”

The online version has been corrected in departure from the print.

DOI: 10.1200/JCO.2009.22.9435

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The July 1, 2008, article by Cohen et al entitled, “Relationship of Circulating Tumor Cells to Tumor Response, Progression-Free Survival, and Overall Survival in Patients With Metastatic Colorectal Cancer” (J Clin Oncol 26:3213-3221, 2008) contained an error.

In Figure 1F, the last column heading of the table comparing groups 1-4 was given as “Median PFS in Months (95% CI),” whereas it should have been “Median OS in Months (95% CI).”

DOI: 10.1200/JCO.2009.22.9393

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The December 1, 2008, article by Di Leo et al entitled, “Phase III, Double-Blind, Randomized Study Comparing Lapatinib Plus Paclitaxel With Placebo Plus Paclitaxel As First-Line Treatment for Metastatic Breast Cancer” (J Clin Oncol 26:5544-5552, 2008) contained an error. In Figure 3B, the hazard ratio was given as 0.35, whereas it should have been 0.53.

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