VOLUME 27 · NUMBER 2 · JANUARY 10 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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 Miletrie, Poitiers; Institut Paoli Calmettes, Marseille, France; Hospital Universitário La Fe, Valencia; BMT Unit, Hospital Clínic 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.

Submitted January 2, 2008; accepted July 24, 2008; published online ahead of print at www.jco.org on December 8, 2008.

Supported by Grant No. 357706/6 from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, Ministério da Educação (CAPES/MEC), Brazil (C.A.R.).

Presented in part at the 49th Annual Meeting of the American Society of Hematology, December 8-11, 2007, Atlanta, GA, and at the 34th Annual European Group of Blood and Marrow Transplantation Meeting, March 30-April 2, 2008, Florence, Italy.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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.

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

0732-183X/09/2702-256/$20.00

DOI: 10.1200/JCO.2007.15.8865

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 $CD34^+$ 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.

J Clin Oncol 27:256-263. © 2008 by American Society of Clinical Oncology

INTRODUCTION

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

Comparative studies have reported lower relapse rates after allogeneic transplant relative to autologous transplant.[10] However, conventional allogeneic HSCT is associated with high non–relapse-related mortality (NRM), which offsets the potential survival benefit of this procedure.[11-14]

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

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.[28,29] 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.[28-32] However, the low number of progenitor cells has been associated with delayed engraftment and increased risk of NRM.[31,32] Strategies to overcome this barrier include the use of two partially HLA-matched UCB units (double UCBT).[33,34]

There have been a few isolated reports for refractory NHL[35-37] and malignant lymphoma treated by RIC-UCBT.[38,39] 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.[40]

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 0.5×10^9/L, and the incidence of platelet recovery as the first of 7 consecutive days of an unsupported platelet count of at least 20×10^9/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,[41] 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[42] and the proportional subdistribution hazard

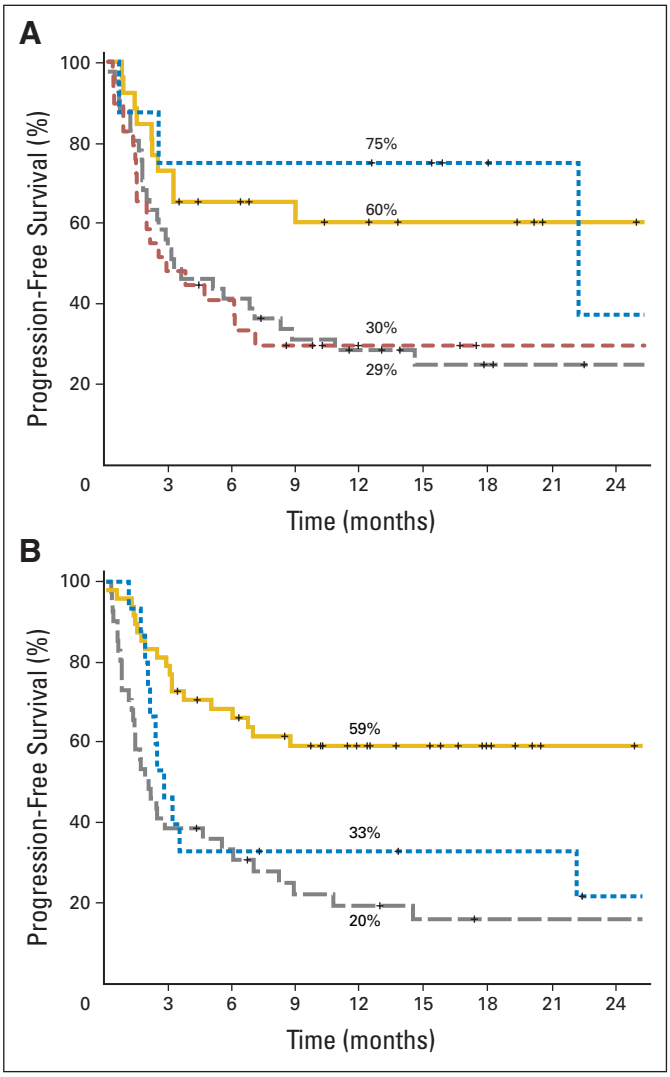

Fig 1. (A) Estimated progression-free survival (PFS) according to histologic subtype. Patients with indolent non-Hodgkin's lymphoma (NHL; yellow line), mantle-cell lymphoma (blue line), aggressive NHL (gray line), and Hodgkin's lymphoma (red line). (B) Estimated PFS according to the use of total-body 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.[43] 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, $\times 10^7$/kg		
1		
Median	2.41	
Range	0.88-10.20	
2		
Median	3.02	
Range	1.20-7.90	
No. of total CD34$^+$ cells infused, $\times 10^5$/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)
Age, years							
< 41	54	87	38	12	34	28	35
≥ 41	49	82	19	38	27	54	62
P		NS	.04	.002	NS	.02	.02
Lymphoma subtype							
Indolent NHL	26	85	20	36	19	60(1)	68
Mantle cell lymphoma	8	63	0	38	25	75(2)	75
Hodgkin's lymphoma	29	90	35	12	35	30(3)	41
Aggressive NHL	41	85	34	22	37	29(4)	36
P		NS	NS	NS	NS	.02*	.09*
Disease features							
Chemosensitive	42	93	28	23	22	49	54
Chemoresistant	62	77	29	26	38	34	44
P		.08	NS	NS	.06	.04	.09
No. of UCB units							
1	78	81	26	22	38	35	42
2	26	92	31	32	13	57	65
P		.06	NS	NS	.009	.06	.09
Conditioning regimen							
RIC	64	86	20	32	34	46	59
MAC	36	83	38	14	31	31	33
P		NS	NS	.04	NS	NS	.03
Use of TBI							
No	41	73	50	11	30	20(1x)	20
Low-dose	48	92	13	39	28	60(2x)	74
High-dose	15	87	20	13	47	33(3x)	39
P		.0007*	.0006*	.003*	NS	< .0001*	< .0001*
Use of ATG/ALG							
No	56	91	18	33	26	56	68
Yes	46	76	38	14	39	23	26
P		.004	.04	.02	NS	.001	< .0001
TNC $\times 10^7$/kg							
< 2	32	75	41	20	38	21	22
≥ 2	67	91	22	27	29	49	61
P		.05	.02	NS	NS	< .0001	< .0001
$CD34^+$ cells $\times 10^5$/kg							
< 1	47	78	33	25	30	37	41
≥ 1	45	93	23	27	32	45	59
P		< .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^x) *v* (3^x) is .30; (2^x) *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 $CD34^+$ cell dose greater than 1.0×10^5/kg (96% *v* 77%; $P < .0001$). In a multivariate analysis, the use of low-dose TBI ($P = .04$; Table 4), and a higher $CD34^+$ 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 1.0×10^5/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 2×10^7/kg (22% *v* 41%; $P = .02$). In a multivariate analysis, the use of low-dose TBI ($P = .03$), and a TNC dose higher than 2×10^7/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.

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

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

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 2×10^7/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 2×10^7/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 2×10^7/kg (61% *v* 22%; $P < .0001$). In multivariate analysis, use of low-dose TBI ($P < .0001$), and TNC dose higher than 2×10^7/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.

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.[38,39] And the use of conventional allogeneic HSCT in patients with lymphoma and CLL is still limited.[3,4] 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.[22,25,44-47] We observed an NRM incidence of 28% and PFS and OS rates of 40% and 48% at 1 year, respectively. Branson et al[25] 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.[22] 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%.[48-50]

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.[51,52] 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, Chistopher 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, Chistopher Dalley, Enric Carreras, Mohamad Mohty, Peter Dreger, Anna Sureda, Eliane Gluckman, Vanderson Rocha

REFERENCES

1. Chopra R, Goldstone AH, Pearce R, et al: Autologous versus allogeneic bone marrow transplantation for non-Hodgkin's lymphoma: A case-controlled analysis of the European Bone Marrow Transplant Group Registry data. J Clin Oncol 10: 1690-1695, 1992

2. Verdonck LF, Dekker AW, Lokhorst HM, et al: Allogeneic versus autologous bone marrow transplantation for refractory and recurrent low-grade non-Hodgkin's lymphoma. Blood 90:4201-4205, 1997

3. Buser AS, Stern M, Bucher C, et al: High-dose chemotherapy using BEAM without autologous rescue followed by reduced-intensity conditioning allogeneic stem-cell transplantation for refractory or relapsing lymphomas: A comparison of delayed versus immediate transplantation. Bone Marrow Transplant 39:335-340, 2007

4. Vigouroux S, Michallet M, Porcher R, et al: Long-term outcomes after reduced-intensity conditioning allogeneic stem cell transplantation for low-grade lymphoma: A survey by the French Society of Bone Marrow Graft Transplantation and Cellular Therapy (SFGM-TC). Haematologica 92:627-634, 2007

5. Anderlini P, Champlin RE: Reduced intensity conditioning for allogeneic stem cell transplantation in relapsed and refractory Hodgkin lymphoma: Where do we stand? Biol Blood Marrow Transplant 12:599-602, 2006

6. Jabbour E, Hosing C, Ayers G, et al: Pretransplant positive positron emission tomography/gallium scans predict poor outcome in patients with recurrent/refractory Hodgkin lymphoma. Cancer 109: 2481-2489, 2007

7. Brugiatelli M, Bandini G, Barosi G, et al: Management of chronic lymphocytic leukemia: Practice guidelines from the Italian Society of Hematology, the Italian Society of Experimental Hematology and the Italian Group for Bone Marrow Transplantation. Haematologica 91:1662-1673, 2006

8. Dreger P, Corradini P, Kimby E, et al: Indications for allogeneic stem cell transplantation in chronic lymphocytic leukemia: The EBMT transplant consensus. Leukemia 21:12-17, 2007

9. Kharfan-Dabaja MA, Anasetti C, Santos ES: Hematopoietic cell transplantation for chronic lymphocytic leukemia: An evolving concept. Biol Blood Marrow Transplant 13:373-385, 2007

10. Peniket AJ, Ruiz de Elvira MC, Taghipour G, et al: An EBMT registry matched study of allogeneic stem cell transplants for lymphoma: Allogeneic transplantation is associated with a lower relapse rate but a higher procedure-related mortality rate than autologous transplantation. Bone Marrow Transplant 31:667-678, 2003

11. Ringdén O, Labopin M, Frassoni F, et al: Allogeneic bone marrow transplant or second autograft in patients with acute leukemia who relapse after an autograft: Acute Leukaemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant 24:389-396, 1999

12. Aksentijevich I, Jones RJ, Ambinder RF, et al: Clinical outcome following autologous and allogeneic blood and marrow transplantation for relapsed diffuse large-cell non-Hodgkin's lymphoma. Biol Blood Marrow Transplant 12:965-972, 2006

13. Uzunel M, Remberger M, Sairafi D, et al: Unrelated versus related allogeneic stem cell transplantation after reduced intensity conditioning. Transplantation 82:913-919, 2006

14. Morris E, Thomson K, Craddock C, et al: Outcomes after alemtuzumab-containing reduced-intensity allogeneic transplantation regimen for relapsed and refractory non-Hodgkin lymphoma. Blood 104:3865-3871, 2004

15. Khouri I, Saliba R, Hosing C, et al: Autologous stem cell vs non-myeloablative allogeneic transplantation after high-dose rituximab containing conditioning regimens for relapsed chemosensitive lymphoma. Blood 106:48a, 2005

16. Maris MB, Sandmaier BM, Storer B, et al: Allogeneic hematopoietic cell transplantation (HCT) after nonmyeloablative conditioning for relapsed or refractory follicular lymphoma. Blood 106:329a, 2005

17. Khouri IF, Keating M, Korbling M, et al: Transplant-lite: Induction of graft-versus-malignancy using fludarabine-based nonablative chemotherapy and allogeneic blood progenitor-cell transplantation as treatment for lymphoid malignancies. J Clin Oncol 16:2817-2824, 1998

18. van Besien K, Loberiza FR Jr, Bajorunaite R, et al: Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. Blood 102:3521-3529, 2003

19. Van Besien K, Carreras J, Zhang MJ, et al: Reduced intensity vs myeloablative conditioning for HLA-matched sibling transplantation in follicular lymphoma. Blood 106:656a, 2005

20. Caballero D, García-Marco JA, Martino R, et al: Allogeneic transplant with reduced intensity conditioning regimens may overcome the poor prognosis of B-cell chronic lymphocytic leukemia with unmutated immunoglobulin variable heavy-chain gene and chromosomal abnormalities (11q- and 17p-). Clin Cancer Res 11:7757-7763, 2005

21. Khouri IF: Reduced-intensity regimens in allogeneic stem-cell transplantation for non-hodgkin lymphoma and chronic lymphocytic leukemia. Hematology Am Soc Hematol Educ Program 390-397, 2006

22. Robinson SP, Goldstone AH, Mackinnon S, et al: Chemoresistant or aggressive lymphoma predicts for a poor outcome following reduced-intensity allogeneic progenitor cell transplantation: An analysis from the Lymphoma Working Party of the European Group for Blood and Bone Marrow Transplantation. Blood 100:4310-4316, 2002

23. Khouri IF, Saliba RM, Giralt SA, et al: Nonablative allogeneic hematopoietic transplantation as adoptive immunotherapy for indolent lymphoma: Low incidence of toxicity, acute graft-versus-host disease, and treatment-related mortality. Blood 98: 3595-3599, 2001

24. Escalón MP, Champlin RE, Saliba RM, et al: Nonmyeloablative allogeneic hematopoietic transplantation: A promising salvage therapy for patients with non-Hodgkin's lymphoma whose disease has failed a prior autologous transplantation. J Clin Oncol 22:2419-2423, 2004

25. Branson K, Chopra R, Kottaridis PD, et al: Role of nonmyeloablative allogeneic stem-cell transplantation after failure of autologous transplantation in patients with lymphoproliferative malignancies. J Clin Oncol 20:4022-4031, 2002

26. Khouri IF, Lee MS, Saliba RM, et al: Nonablative allogeneic stem-cell transplantation for advanced/recurrent mantle-cell lymphoma. J Clin Oncol 21:4407-4412, 2003

27. Maris MB, Sandmaier BM, Storer BE, et al: Allogeneic hematopoietic cell transplantation after fludarabine and 2 Gy total body irradiation for relapsed and refractory mantle cell lymphoma. Blood 104:3535-3542, 2004

28. Rocha V, Labopin M, Sanz G, et al: Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia. N Engl J Med 351:2276-2285, 2004

29. Gluckman E, Rocha V, Arcese W, et al: Factors associated with outcomes of unrelated cord blood transplant: Guidelines for donor choice. Exp Hematol 32:397-407, 2004

30. Rocha V, Gluckman E: Clinical use of umbilical cord blood hematopoietic stem cells. Biol Blood Marrow Transplant 12:34-41, 2006 (suppl 1)

31. Laughlin MJ, Eapen M, Rubinstein P, et al: Outcomes after transplantation of cord blood or bone marrow from unrelated donors in adults with leukemia. N Engl J Med 351:2265-2275, 2004

32. Wagner JE, Barker JN, DeFor TE, et al: Transplantation of unrelated donor umbilical cord blood in 102 patients with malignant and nonmalignant diseases: Influence of CD34 cell dose and HLA disparity on treatment-related mortality and survival. Blood 100:1611-1618, 2002

33. Barker JN, Weisdorf DJ, DeFor TE, et al: Transplantation of 2 partially HLA-matched umbilical cord blood units to enhance engraftment in adults with hematologic malignancy. Blood 105:1343-1347, 2005

34. Ballen KK, Spitzer TR, Yeap BY, et al: Double unrelated reduced-intensity umbilical cord blood transplantation in adults. Biol Blood Marrow Transplant 13:82-89, 2007

35. Herbert KE, Spencer A, Grigg A, et al: Graft-versus-lymphoma effect in refractory cutaneous T-cell lymphoma after reduced-intensity HLA-matched sibling allogeneic stem cell transplantation. Bone Marrow Transplant 34:521-525, 2004

36. Ooi J, Iseki T, Ito K, Mori Y, et al: Successful unrelated cord blood transplantation for relapse after autologous transplantation in non-Hodgkin's lymphoma. Leuk Lymphoma 43:653-655, 2002

37. Yoshimasu T, Manabe A, Tanaka R, et al: Successful treatment of relapsed blastic natural killer cell lymphoma with unrelated cord blood transplantation. Bone Marrow Transplant 30:41-44, 2002

38. Yuji K, Miyakoshi S, Kato D, et al: Reduced-intensity unrelated cord blood transplantation for patients with advanced malignant lymphoma. Biol Blood Marrow Transplant 11:314-318, 2005

39. Majhail NS, Weisdorf DJ, Wagner JE, et al: Comparable results of umbilical cord blood and HLA-matched sibling donor hematopoietic stem cell transplantation after reduced-intensity preparative regimen for advanced Hodgkin lymphoma. Blood 107:3804-3807, 2006

40. Arcese W, Rocha V, Labopin M, et al: Eurocord-Netcord Transplant group. Unrelated cord blood transplants in adults with hematologic malignancies. Haematologica 91:223-230, 2006

41. Przepiorka D, Weisdorf D, Martin P, et al: 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant 15:825-828, 1995

42. Gooley TA, Leisenring W, Crowley J, et al: Estimation of failure probabilities in the presence of competing risks: New representations of old estimators. Stat Med 18:695-706, 1999

43. Gray RJ: A class K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 116:1141-1154, 1988

44. Schmitz N, Dreger P, Glass B, et al: Allogeneic transplantation in lymphoma: Current status. Haematologica 92:1533-1548, 2007

45. Rezvani AR, Storer B, Maris M, et al: Nonmyeloablative allogeneic hematopoietic cell transplantation in relapsed, refractory, and transformed indolent non-Hodgkin's lymphoma. J Clin Oncol 26:211-217, 2008

46. Khouri IF, Saliba RM, Korbling M, et al: Nonmyeloablative allogeneic transplantation (NMT) for relapsed follicular lymphoma (FL): Continuous Complete remission with longer follow-up. Blood 110: 485a, 2007

47. Shea TC, Johnston J, Walsh W, et al: Reduced intensity allogeneic transplantation provides high disease-free and overall survival in patients (Pts) with advanced indolent NHL and CLL: CALGB 109901. Blood 110: 486a, 2007

48. Delgado J, Thomson K, Russell N, et al: Results of alemtuzumab-based reduced-intensity allogeneic transplantation for chronic lymphocytic leukemia: A British Society of Blood and Marrow Transplantation Study. Blood 107:1724-1730, 2006

49. Sorror ML, Maris MB, Sandmaier BM, et al: Hematopoietic cell transplantation after nonmyeloablative conditioning for advanced chronic lymphocytic leukemia. J Clin Oncol 23:3819-3829, 2005

50. Brown JR, Kim HT, Li S, et al: Predictors of improved progression-free survival after nonmyeloablative allogeneic stem cell transplantation for advanced chronic lymphocytic leukemia. Biol Blood Marrow Transplant 12:1056-1064, 2006

51. Brunstein CG, Barker JN, Weisdorf DJ, et al: Umbilical cord blood transplantation after nonmyeloablative conditioning: Impact on transplantation outcomes in 110 adults with hematologic disease. Blood 110:3064-3070, 2007

52. Verneris MR, Brunstein C, DeFor TE, et al: Risk of relapse (REL) after umbilical cord blood transplantation (UCBT) in patients with acute leukemia: Marked reduction in recipients of two units. Blood 106:305a, 2005

Acknowledgment

We thank I. Ionescu, F. Garnier, A.L. Herr, W. Chaves, and K. Boudjedir for assistance with data retrieval, and R. Willemze and W. Chaves for assistance with manuscript preparation.

ERRATA

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 2×10^7/kg (49% *v* 21%; $P < .0001$)."

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

DOI: 10.1200/JCO.2009.22.9435

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

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.

DOI: 10.1200/JCO.2009.22.9419

