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Cord Blood

Myeloablative Unrelated Cord Blood Transplantation in Adolescents and Young Adults with Acute Leukemia

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A B S T R A C T

Outcomes for adolescents and young adults (AYAs) with leukemia differ from other age groups and are still underrepresented in clinical research. The aim of this study was to analyze outcomes of umbilical cord blood transplant (UCBT) in AYAs with acute leukemia reported to Eurocord/European Society for Blood and Marrow Transplantation. Patients (N = 504) had acute lymphoblastic (59%) or myeloid leukemia (41%), were aged 15 to 25 years, and received UCBT after myeloablative conditioning regimens between 2004 and 2016. The primary endpoint was 3-year overall survival (OS). Median follow-up was 3.9 years. Transplant was single in 58% and double UCBT in 42%. Three-year OS was 45% and leukemia free survival (LFS) was 41%. Cumulative incidence functions (CIFs) of nonrelapse mortality (NRM) and relapse were 31% and 28%, respectively. CIF of acute graft-versus-host disease (GVHD) grades II to IV at day 100 was 28%. Three-year CIF of chronic GVHD was 25%. In adjusted analysis, better disease status at UCBT (hazard ratio [HR], 2.74; $P < .001$) and more recent UCBT (HR, 1.43; $P = .01$) were associated with increased OS, and a similar effect of these factors was observed on LFS. Contrastingly, the use of antithymocyte globulin had a negative effect in LFS. The risk of acute GVHD grades II to IV increased with the use of double UCBT (HR, 1.65; $P = .02$) and decreased with more recent transplant period (HR, .65; $P = .02$) and antithymocyte globulin use (HR, .55; $P = .01$). Outcomes of AYA UCBT improved in more recent years, becoming comparable with pediatric results. Demonstrating the feasibility of UCBT in AYAs facilitates stem cell source selection and provides the basis for future prospective studies.

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INTRODUCTION

Adolescents and young adults (AYAs) form a unique group of patients with biologic, clinical, social, and psychological features that differ from other age groups. These differences may have an important effect on treatment outcomes; therefore, research focused on this specific population is warranted. However, the participation rate of AYA patients in clinical trials is lower than the rates of children and older adults [1-3].

Another difficulty surrounding research on the AYA population is the lack of an exact definition for the age range considered for this group [4,5]. Depending on the aim of the study or reporting organization, the defined age range varies considerably, making the interpretation of the limited available data a difficult task [4].

EUROCARE-5 reported poorer survival in AYAs compared with children for several prevalent cancers including acute leukemia [6]. For patients with acute lymphoblastic leukemia (ALL), there is clear evidence that clinical outcomes after chemotherapy are markedly better in children than in older patients, including AYAs [7]. The difference may be related to tumor biology [6] but may also reflect increased toxicity, the lack of specific research on AYAs, and poor compliance with clinical protocols [1,7].

Acute leukemia represents about 6% of the neoplastic disease in AYAs, with similar incidences of acute myeloid leukemia (AML) and ALL [8]. Hematopoietic stem cell transplant (HSCT) is a potentially curative treatment for acute leukemia and other hematologic diseases. However, HSCT involves intensive treatment protocols with a non-negligible risk of possible life-threatening complications and lifelong side effects [7,9]. Most studies on AYAs with hematologic malignancies are focused on new medications or chemotherapy protocols but not on HSCT results [7,10-12]. In fact, AYAs are often included as a subset of pediatric or adult patients on HSCT research but are usually not considered as a main group of interest [7,13-15].

Umbilical cord blood (UCB) is 1 alternative donor source for HSCT for AYA patients whose leukemia often presents high-risk biologic features and who could benefit from an immediate transplant. UCB is readily available for use in contrast to other unrelated grafts in which search and recruitment of adult donors with an acceptable HLA compatibility with the recipient may delay transplantation [16]. Other alternative graft sources, such as haploidentical donors, must also be considered; however, for patients with comorbidities such as cardiomyopathy or renal failure, haploidentical protocols with post-HSCT cyclophosphamide that require intense hydration might be problematic [9,17], making UCB a desirable choice in these situations.

There is a lack of research studies on AYAs, especially on UCB transplant (UCBT). The aim of the current study is to fill this gap by providing comprehensive information on unrelated UCBT outcomes after myeloablative conditioning (MAC) regimens in a homogeneous cohort of AYA patients, aged 15 to 25, with acute leukemia.

METHODS

Data Collection

This is a registry-based retrospective study using Eurocord, the Paediatric Disease Working Party, and the Cellular Therapy & Immunobiology Working Party of the European Society for Blood and Marrow Transplantation (EBMT). All patients or legal guardians provided informed consent for research. This study was conducted according to the Declaration of Helsinki and approved by the Paediatric Disease Working Party and Cellular Therapy & Immunobiology Working Party of the EBMT and the institutional review board of Eurocord.

Inclusion and Exclusion Criteria

Inclusion criteria for the study were age between 15 and 25 years, diagnosis of ALL or AML, single or double UCBT as first allogeneic transplants between 2004 and 2016 in an EBMT center, and MAC regimen. Patients who received a related UCB, a manipulated graft, or a UCB co-infused with another stem cell source were excluded.

Definitions

Overall survival (OS) was defined as time from transplant to last follow-up or death. Leukemia-free survival (LFS) was defined as time from transplant to relapse, death, or date of last follow-up. Refined graft-versus-host disease (GVHD) free-/relapse free- survival (rGRFS) was defined as being alive with neither grades III to IV acute GVHD nor extensive chronic GVHD, relapse, or death [18]. Nonrelapse mortality (NRM) was defined as time to death without relapse. Relapse was defined as morphologic or clinical evidence of disease after a period of complete remission (CR).

Neutrophil engraftment was defined as the first day of 3 consecutive days with a neutrophil count $\geq .5 \times 10^9$/L without autologous reconstitution or graft rejection within the first 100 days of UCBT. Acute and chronic GVHD were diagnosed and defined according to standard criteria [19,20]. MAC was defined as regimens containing total body irradiation (TBI) $\geq$ 6 Gy fractionated or $\geq$8 Gy in a total dose, thiotepa $\geq$ 10 mg/kg, intravenous busulfan $>$ 6.4 mg/kg or equivalent dose in oral busulfan ($>$8.0 mg/kg), and melphalan $>$ 140 mg/m^2.

HLA compatibility between donor and recipient was defined considering low resolution for HLA-A and HLA-B and high-resolution typing for HLA-DRB1. Donor–recipient HLA match assignment for double UCBT was based on the unit with the higher number of mismatches with the recipient. Total nucleated cell doses reported for double UCBT grafts represent the combined information of the 2 UCB units.

Endpoints

The primary endpoint of the study was OS at 3 years. Secondary endpoints were probability of LFS, rGRFS, cumulative incidence of relapse, NRM, neutrophil engraftment, and acute and chronic GVHD.

Statistical Methods

The Kaplan-Meier estimator was used to calculate the probabilities of OS, LFS, and rGRFS. Cumulative incidence functions (CIFs) were used to calculate the cumulative incidences of relapse, NRM, neutrophil and platelet engraftment, and acute and chronic GVHD. Competitive events were considered as follows: for engraftment, death without engraftment; for relapse, death without disease recurrence or progression; for NRM, relapse after UCBT; for GVHD, relapse or death without GVHD (acute or chronic as applicable). All tests performed were 2-sided. Type I error was fixed at $P = .05$. Covariates reaching a significance level of .1 in the univariate analyses (UVAs) were included in the multivariate analysis (MVA) models. Age at UCBT was modeled as a continuous variable. Variables frequently associated with transplant outcomes were also included in the final models regardless of the statistical significance in UVAs. Cox and Fine-Gray proportional hazards models were used for the MVA [21]. Statistical analyses were performed with IBM SPSS statistics for Windows, version 25 (IBM Corp., Armonk, NY) and R for Windows 3.5.1 (R development Core Team, Vienna, Austria).

RESULTS

Patient and Transplant Characteristics

Five hundred four patients from the Eurocord/EBMT database met the criteria for the study. Patient and transplant characteristics are shown in Tables 1 and 2, respectively. Median age at diagnosis was 17.5 years (range, 4.5 to 25.4; first to third interquartile range [IQR], 15.2 to 20.7). Median age at UCBT was 19.4 years (range, 15 to 25.9; IQR, 16.7 to 22.2). Male patients comprised 63.9% of all patients. Median time from diagnosis to transplant was 11 months (range, 1 month to 16.7 years; IQR, 5 to 29 months). More than half of the patients received UCBT within a year from the diagnosis of acute leukemia (52.0%). ALL (n = 297, 58.9%) was more frequently

Table 1
Patient Characteristics

	Total (N = 504)		ALL (n = 297)		AML (n = 207)	
Characteristics	Median	IQR	Median	IQR	Median	IQR
Age at diagnosis, yr	17.5	15.2-20.7	17.2	14.9-20.0	18.0	15.8-21.5
Age at UCBT, yr	19.4	16.7-22.2	19.4	16.8-21.9	19.3	16.6-23.0
Time from diagnosis to UCBT, mo	11.0	5.0-29.0	16.0	6.0-39.0	7.0	4.0-19.0
Weight at UCBT, kg	63.0	55.0-73.0	64.0	55.0-73.5	61.0	55.0-72.5
	No. of Cases	Percent	No. of Cases	Percent	No. of Cases	Percent
Gender						
Male	322	63.9	203	68.4	119	57.5
Female	182	36.1	94	31.6	88	42.5
CMV serology						
Positive	270	57.1	162	57.7	108	56.2
Negative	203	42.9	119	42.3	84	43.8
Missing	31		16		15	
Disease status						
CR1	207	42.6	113	39.0	94	48.0
CR2	183	37.7	118	40.7	65	33.2
Advanced	96	19.8	59	20.3	37	18.9
Missing	18		7		11	
Year of UCBT						
2004-2009	246	48.8	147	49.5	99	47.8
2010-2016	258	51.2	150	50.5	108	52.2
Graft type						
Single UCBT	293	58.1	177	59.6	116	56.0
Double UCBT	211	41.9	120	40.4	91	44.0

Table 2
Transplant Characteristics

	Single UCBT		Double UCBT (n = 211)	
TNC dose, $\times 10^7$/kg (range) [IQR]	3.6 (.9-9.0) [3.0-4.4]		5.3 (2.3-10.6) [4.4-6.2]	
MAC regimens				
Non-TBI	167	(57.6)	42	(20.3)
TBI regimen	123	(42.4)	165	(79.7)
Missing	3		4	
	Total (N = 504)		Single UCBT		Double UCBT	
Gender compatibility						
Male to Female	195	(40.3)	188	(66.0)	101	(50.8)
Other	289	(59.7)	97	(34.0)	98	(49.2)
Missing	20		8		12	
No. of HLA mismatches						
0-1	161	(38.1)	89	(35.9)	72	(41.1)
2 or >2*	262	(61.9)	159	(64.1)	103	(58.9)
Missing	81		45		36	
GVHD prophylaxis						
CsA+MMF	223	(46.8)	102	(37.6)	121	(59.6)
CsA+Pred	122	(25.6)	98	(36.2)	24	(11.8)
CsA	46	(9.7)	22	(8.1)	24	(11.8)
Other(s)	85	(17.9)	49	(18.1)	36	(17.7)
Missing	28		22		6	
Use of ATG						
Yes	270	(57.9)	206	(75.7)	64	(33.0)
No	196	(42.1)	66	(24.3)	130	(67.0)
Missing	38		25		17	

Values are n (%) unless otherwise defined. TNC indicates total nucleated cells; CsA, cyclosporine; MMF, mycophenolate mofetil; Pred, corticosteroid.
* Only 25 patients with more than 2 HLA mismatches.

observed than AML (n = 207, 41.1%). Twenty patients were reported as having a secondary acute leukemia (4.0%), mostly due to other type of hematologic malignancy and/or history of chemotherapy and/or radiotherapy.

Positive cytomegalovirus (CMV) serology was observed in 57.1% of patients (n = 270). Median total nucleated cell dose was 3.6×10^7 for single (range, .9 to 9.0; IQR, 3.0 to 4.4) and 5.3×10^7 for double UCBT (range, 2.3 to 10.6; IQR, 4.4 to 6.2). A conditioning regimen containing TBI was used in 57.9% of patients (n = 288). The most frequently used conditioning regimens were cyclophosphamide + fludarabine + TBI (n = 139, 27.6%) and thiotepa + busulfan + fludarabine (n = 110, 21.8%). For GVHD prophylaxis, cyclosporine A + mycophenolate mofetil was used for 46.8 % of patients (n = 223).

Neutrophil and Platelet Engraftment

The CIF of neutrophil engraftment at day 60 was 87.7% (95% confidence interval [CI], 84.5% to 90.3%) with a median time to engraftment of 24 days. In UVA, patient-negative CMV serology, non-TBI regimen, better disease status, and recent transplant were associated with improved neutrophil engraftment. In the adjusted analysis (MVA), better disease status (advanced diseases versus first CR [CR1]; hazard ratio [HR], 1.67; 95% CI, 1.25 to 2.27;$P < .001$] and recent year of UCBT (HR, 1.41; 95% CI, 1.15 to 1.72;$P < .001$) were confirmed to be independently associated with a higher neutrophil engraftment, whereas the association with the use of non-TBI regimen was no longer observed. The CIF of platelet engraftment at day 100 was 59.6% (95% CI, .55 to .64). Platelet engraftment occurred at a median of 61 days. Recent year of UCBT and better disease status were similarly identified as significant factors associated with platelet engraftment in MVA. AML diagnosis compared with ALL showed significant impact on platelet engraftment in UVA (55.6% [95% CI, 49.7 to 61.0] versus 65.5 [95% CI, 58.5 to 71.6], respectively; $P = .04$); however, it was not significant after adjustment.

Survival

The UVA of OS, LFS, and rGRFS are provided in Table 3. Three-year OS was 44.9% (± 2.4%), and median follow-up for survivors was 3.9 years. In UVA, better disease status at UCBT and recent year of transplant were associated with a higher OS. Negative CMV serology and the absence of antithymocyte globulin (ATG) in the protocols were also significantly associated with a higher probability of OS, whereas the type of acute leukemia (ALL versus AML) and graft (single versus double UCBT) had no significant impact. In MVA, recent year of transplant and better disease status remained significantly associated with a favorable OS, and the use of ATG showed a borderline negative effect on OS (HR, 1.36; 95% CI, 1.00 to 1.85; $P = .05$) (Table 4).

Three-year LFS was 40.9% ± 2.3%, and LFS according to disease status is shown in Figure 1. The MVA showed that advanced disease status compared with CR1 (HR, 2.51; $P < .001$) and the use of ATG (HR, 1.43; $P = .02$) had a detrimental effect on LFS, whereas being transplanted in more recent years (HR, .74; $P = .02$) had a favorable effect.

Three-year rGRFS was 31.5% ± 2%. In UVA, rGRFS was lower in boys, in those with ALL (29.0% in ALL versus 35.1% in AML, $P = .045$), and in patients with positive CMV serology (28.0% versus 37.7%, $P < .01$). In MVA for rGRFS, negative CMV serology and better disease status (CR1 versus advanced disease) were observed to have a significant favorable impact on rGRFS, whereas the impact of gender was no longer significant in the adjusted model. There was a tendency for higher rGRFS in patients undergoing transplant in more recent years, but the results were not statistically significant (Table 4).

During the follow-up period 265 patients died. The reported causes of death were relapse (n = 109, 41.0%), infection (n = 75, 28.2%), GVHD (n = 34, 12.8%), other transplant-related causes (n = 44, 16.6%), and unknown or other (n = 3, 1.4%).

Acute and Chronic GVHD

One hundred fifty-five patients developed grades II to IV acute GVHD (73/155 had grades III to IV) during the observation period. The CIF of acute GVHD at day 100 was 27.8% (95% CI, 23.8% to 31.9%). Use of double UCBT, non-ATG protocols, and TBI-containing regimens were associated with a higher incidence of grades II to IV acute GVHD in UVA (Table 3). In MVA, recent year of transplantation, use of ATG, and use of single UCB decreased the risk of grades II to IV acute GVHD (Table 4).

One hundred twenty-four patients developed chronic GVHD during the follow-up period, with the extensive form reported in 52. The 3-year CIF of chronic GVHD was 25.3% (95% CI, 21.4% to 29.3%). Onset of chronic GVHD mostly occurred within 1 year of UCBT (1-year incidence of chronic GVHD was 22.0%). A higher risk of cGVHD was observed in patients with advanced disease (Table 4).

NRM and Relapse Incidence

The 3-year NRM was 31.1%, and the results of the UVA are provided in Table 3. In the MVA, recent transplant and better disease status remained strong factors for lower NRM, whereas CMV serology had a borderline effect on it (Table 4). CIF of relapse at 3 years was 27.9% (95% CI, 23.9% to 32.1%). Disease status was the only factor identified as having a significant impact in relapse in the adjusted analysis.

DISCUSSION

The unique characteristics of AYA patients and the lack of specific studies on this group limit knowledge on treatment outcomes and, consequently, hinder improvement in survival for this population. Our study reporting outcomes of AYA patients undergoing myeloablative UCBT for acute leukemia provides important novel data and, to our knowledge, represents the largest series in this setting.

AYAs have specific needs and complications and should be studied separately from children and older adults. Some patients are treated in pediatric units with high-intensity protocols, whereas others are treated in adult transplant units [3,14,22]. The transition from pediatric to adult transplant units involves changes in chemotherapy, conditioning, supportive care, and psychosocial support [3].

The classification of AYAs is very controversial [3-5]. In the available definitions the lower age limit varies from 10 to 21 years old, whereas the upper limit can fluctuate from 25 to 39 and even beyond in some rarer occasions [3,5]. This absence of consensus of the age definition of AYAs makes the available results difficult to compare and interpret.

In the present study AYA was defined as patients aged between 15 and 25 years because there is some consensus that this narrower group is truly representative of this developmental stage of life [5]. Moreover, according to a population-based study in the United States, after age 25 patients are seldom treated by pediatricians; consequently, only a fraction of AYAs with ALL receive a pediatric protocol [22] despite evidence of improved results with intensified chemotherapies of pediatric or pediatric-inspired regimens [10]. Keeping the

Table 3
Univariate Analysis of UCBT

	OS (mean ± SD)	*P*	LFS (mean ± SD)	*P*	rGRFS (mean ± SD)	*P*
Patient gender						
Male	42.8 ± 3.0	.22	38.3 ± 2.9	.13	28.0 ± 2.7	.006
Female	48.5 ± 3.9		45.2 ± 3.9		37.7 ± 3.8	
Body weight at UCBT*						
<63.0 kg	48.5 ± 3.5	.51	45.0 ± 3.5	.19	35.8 ± 3.4	.25
≥63.0 kg	41.2 ± 3.5		38.4 ± 3.4		29.9 ± 3.2	
CMV serology						
Negative	51.9 ± 3.7	.005	47.8 ± 3.7	.005	37.9 ± 3.6	.002
Positive	40.0 ± 3.3		35.6 ± 3.2		25.9 ± 2.9	
Type of acute leukemia						
ALL	44.8 ± 3.1	.69	38.5 ± 3.0	.15	29.0 ± 2.8	.045
AML	45.2 ± 3.7		44.4 ± 3.7		35.1 ± 3.5	
Disease status						
CR1	54.0 ± 3.7	<.001	48.5 ± 3.7	<.001	36.8 ± 3.6	<.001
CR2	48.1 ± 4.0		48.1 ± 3.9		33.6 ± 3.7	
Advanced disease	20.4 ± 4.3		19.8 ± 4.3		16.3 ± 3.9	
Year of UCBT						
2004-2009	36.8 ± 3.2	.001	33.4 ± 3.1	.001	27.2 ± 2.9	.03
2010-2016	53.8 ± 3.5		48.4 ± 3.5		35.4 ± 3.3	
Graft type						
Single UCBT	41.4 ± 3.2	.21	37.1 ± 3.1	.18	28.8 ± 2.9	.63
Double UCBT	49.5 ± 3.6		46.2 ± 3.6		35.1 ± 3.4	
No. of HLA mismatches						
0-1	47.9 ± 4.2	.25	46.6 ± 4.2	.10	34.7 ± 4.0	.27
≥2	45.3 ± 3.2		39.9 ± 3.2		31.2 ± 3.0	
TBI						
Non-TBI regimen	39.5 ± 3.9	.32	33.9 ± 3.7	.19	27.1 ± 3.5	.73
TBI regimen	47.2 ± 3.1		44.3 ± 3.0		33.4 ± 2.9	
Use of ATG						
No	52.2 ± 3.7	.03	48.0 ± 3.7	.01	34.9 ± 3.5	.80
Yes	38.7 ± 3.2		34.3 ± 3.1		28.2 ± 3.0	

	Grades II-IV Acute GVHD at Day 100		Chronic GVHD at 3 Years		NRM in 3 Years		Relapse Incidence	
	CIF (95% CI)	*P*	CIF (95% CI)	*P*	CIF (95% CI)	*P*	HR (95% CIF)	*P*
Patient gender								
Male	30 (25-35)	.20	28 (23-34)	.07	31 (25-36)	.90	31 (26-37)	.07
Female	24 (18-31)		20 (15-27)		32 (25-39)		23 (17-29)	
CMV serology								
Negative	28 (22-35)	.72	25 (19-32)	.97	25 (19-32)	.01	27 (21-34)	.72
Positive	30 (24-35)		26 (21-32)		36 (30-42)		29 (23-34)	
Number of HLA mismatches								
0-1 HLA mismatch	27 (20-34)	.07	25 (18-32)	.07	29 (22-37)	.51	24 (18-32)	.23
2 or >2 mismatches	31 (26-37)		28 (23-34)		32 (26-38)		28 (23-34)	
Type of acute leukemia								
ALL	31 (26-37)	.06	27 (21-32)	.49	33 (28-39)	.16	28 (23-34)	.99
AML	23 (18-30)		24 (18-30)		28 (22-35)		27 (21-34)	
Disease status								
CR 1	29 (23-35)	.92	30 (19-33)	.04	24 (18-30)	<.001	28 (21-34)	.05
CR 2	27 (21-34)		26 (20-33)		33 (26-40)		24 (18-31)	
Advanced disease	28 (19-37)		25 (17-33)		43 (33-53)		37 (27-47)	
Year of UCBT								
2004-2009	29 (24-35)	.47	25 (20-31)	.70	38 (19-29)	.001	29 (23-35)	.75
2010-2016	26 (21-32)		26 (20-31)		24 (19-30)		27 (22-34)	
Graft type								
Single UCBT	22 (17-27)	<.001	23 (18-28)	.13	32 (27-38)	.74	24 (18-30)	.16

(*continued*)

Table 3 (*Continued*)

	Grades II-IV Acute GVHD at Day 100		Chronic GVHD at 3 Years		NRM in 3 Years		Relapse Incidence	
	CIF (95% CI)	*P*	CIF (95% CI)	*P*	CIF (95% CI)	*P*	HR (95% CIF)	*P*
Double UCBT	36 (29-43)		28 (22-35)		30 (24-36)		31 (25-37)	
TBI used regimen								
Non TBI regimen	20 (14-25)	.001	23 (17-30)	.25	31 (25-38)	.95	35 (28-42)	.06
TBI regimen	34 (28-39)		27 (22-33)		31 (26-37)		24 (19-30)	
Use of ATG								
No	39 (31-46)	< .001	28 (22-35)	.34	28 (22-35)	.29	24 (18-30)	.08
Yes	21 (16-26)		24 (19-30)		33 (28-39)		32 (27-38)	

Values are percents.

* Median body weight was 63.0 kg.

Table 4
Multivariate Analysis

	OS		LFS		rGRFS*		NRM	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Type of acute leukemia								
AML (vs. ALL)	1.01 (.78-1.32)	.92	.89 (.69-1.16)	.40	.85 (.66-1.08)	.18	.89 (.62-1.28)	.54
Year of transplant								
2010-2016 (vs. 2004-2009)	.70 (.53-.92)	.01	.74 (.57-.96)	.02	.79 (.62-1.01)	.06	.62 (.43-.91)	.01
Graft type								
Double (vs. single)	1.16 (.85-1.58)	.34	1.15 (.85-1.54)	.36	1.07 (.81-1.40)	.65	1.14 (.76-1.72)	.53
Disease status								
CR2 (vs. CR1)	1.33 (.98-1.81)	.07	1.31 (.98-1.76)	.07	1.14 (.87-1.49)	.35	1.53 (1.03-2.28)	.04
Advanced (vs. CR1)	2.74 (1.97-3.81)	<.001	2.51 (1.82-3.46)	<.001	1.79 (1.32-2.42)	.00	2.13 (1.34-3.39)	.001
Age at UCBT								
Continuous	.98 (.94-1.02)	.28	.98 (.94-1.03)	.45	.99 (.96-1.03)	.76	.99 (.94-1.05)	.84
CMV serology								
Positive (vs. negative)	1.28 (.97-1.69)	.08	1.25 (.96-1.64)	.10	1.3 (1.01-1.66)	.04	1.45 (.99-2.12)	.05
Use of ATG								
Yes (vs. no)	1.36 (1.00-1.85)	.05	1.43 (1.06-1.93)	.02	.99 (.75-1.30)	.94	1.18 (.79-1.76)	.43
	Neutrophil Engraftment		Grades II-IV Acute GVHD		Chronic GVHD		Relapse	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Type of acute leukemia								
AML (vs. ALL)	.99 (.81-1.22)	.96	.68 (.46-1.01)	.06	.91 (.62-1.34)	.63	.97 (.65-1.44)	.88
Year of transplant								
2010-2016 (vs. 2004-2009)	1.41 (1.15-1.72)	< .001	.65 (.45-.94)	.02	.87 (.59-1.27)	.47	1.02 (.7-1.49)	.90
Graft type								
Double (vs. single)	.90 (.72-1.13)	.35	1.65 (1.07-2.53)	.02	1.26 (.85-1.87)	.25	1.03 (.67- 1.6)	.89
Disease status								
CR2 (vs. CR1)	.97 (.78-1.19)	.75	.90 (.60-1.35)	.61	.89 (.6-1.32)	.56	.88 (.57-1.36)	.57
Advanced (vs. CR1)	.60 (.44- .80)	<.001	.92 (.56-1.53)	.76	.44 (.24-.81)	.01	1.62 (1.02-2.56)	.04
Age at UCBT								
Continuous	1.00 (.97-1.03)	.92	.99 (.93-1.06)	.84	1.08 (1.02-1.14)	.01	.98 (.92-1.03)	.41
CMV serology								
Positive (vs. negative)	.83 (.68-1.02)	.071	1.28 (.88-1.87)	.20	N/A		.89 (.61-1.29)	.54
Use of ATG								
Yes (vs. no)	1.08 (.84- 1.40)	.55	.55 (.34-.87)	.01	.86 (.59-1.26)	.44	1.21 (.71-2.08)	.49

* rGRFS was also adjusted for gender.

upper age limit in our studies at 25 years potentially increases the proportion of patients treated with intensified protocols and makes the cohort more homogeneous for studying.

In our analyses, disease status and UCBT period were constantly observed to have an effect in outcomes, especially in OS and LFS as observed in previous studies [13,14]. In the adjusted analysis, the risk of death of patients with advanced disease was almost 3-fold the risk in of patients in CR1, and an improvement of over 40% in OS was observed for UCBT performed in more recent years. On the other hand, relapse incidence barely changed across transplant periods, and this was also reflected in a stable rGRFS.

In a review Mehta et al. [23] compared OS of AYAs with other age groups receiving either a matched sibling or an unrelated transplant for acute leukemia. They showed that overall results for patients with ALL and AML improved over time;

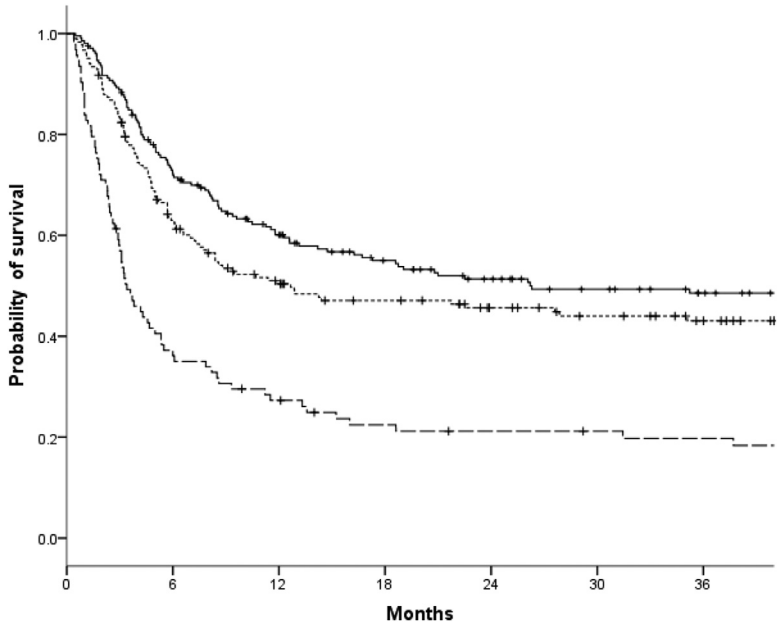

Figure 1. Three-year LFS according to disease status at UCBT. Solid line represents patients in CR1; dotted line represents patients in CR2; dashed line represents patients with advanced disease.

however, survival for AYA patients was inferior to children and superior to older adults [23]. In an exploratory analysis (results not shown) using the same selection criteria of the current study but considering a different population of patients (in addition to the study population) from other age groups, Eurocord database showed a 3-year OS in children (0 to 14 years) of 52.1% and 30.2% in adults (26 to 55 years). In the same database, restricting the results to UCBT performed in year 2010 or later, the 3-year OS was 53.8% and 39.6% in children and adults, respectively (unpublished data from Eurocord database). Interestingly, the results of the current study for AYA patients showed a 3- year OS of 36.8% for UCBT performed before 2010 and 53.8% for transplants performed thereafter, suggesting that in more recent years outcomes in AYAs have improved to comparable levels of results observed for pediatric patients (Supplementary Figures 1.1 and 1.2). The relatively stable incidence of relapse over the years may indicate that some of the improvement in outcomes observed in our study is the result of a reduction in NRM related to better UCB unit selection algorithms, lower toxicity of conditioning regimens, improved patient management and supportive care, and possibly a less frequent use of ATG in the recent era. Nevertheless, these recent changes were likely to have benefited patients for all generations confounded and a reduction of NRM alone may not explain the drastic advances observed in AYAs. In part, the improvement in outcomes demonstrated in this group is probably a reflection of the modification of pretransplant chemotherapy toward more frequent use of high-intensity pediatric protocols [7,12]. A meta-analysis evaluating the association of minimal residual disease with clinical outcome in children and adults with ALL showed that achieving minimal residual disease negativity is important regardless of the age group [24]. The intensification of treatment protocols for AYAs in more recent years might have contributed to achievement of a deeper CR, with no minimal residual disease, in a larger number of patients, improving UCBT outcomes over the years as demonstrated in our AYA cohort. However, testing this hypothesis or performing a formal comparative analysis was out of the scope of this study. Moreover, to perform a comparative study, it would be essential to have comprehensive data on pretransplant chemotherapy, biologic characteristics at diagnosis (cytogenetics, molecular, etc.), and minimal residual disease status at transplant [7,12,15,25], which is usually lacking from retrospective data registries. Nevertheless, the results presented in this report will help to establish recommendations for transplant for this particular population and serve as the basis for designing prospective protocols.

GVHD is a main concern for patients undergoing HSCT because it is associated with higher incidence of NRM and may have an impact on quality of life [19,26,27]. The specific incidence of GVHD in AYAs has been seldom addressed. One European analysis of patients (aged 5 to 35 years) with acute leukemia, undergoing HSCT with bone marrow or peripheral blood stem cell grafts, showed a significantly higher risk of grades II to IV acute GVHD for patients aged between 15 and 24 years [26] compared with other age groups. In our study, the incidence of acute GVHD grades II to IV was 27.8% and the incidence of chronic GVHD 25.3%. Of note, our study included only UCB, which has been generally associated with a lower incidence of GVHD compared with other unrelated donor graft sources [16]. A prospective study in children and AYAs receiving UCBT reported higher incidences of grades II to IV acute GVHD (41% in single UCBT and 45% in double UCBT) than our study [28]. The contrasting results observed might be related to differences in the age range of the cohort (0 to 34 years) and distribution of patients receiving ATG in each study (40% in the previous study compared with 60% in our cohort) Our adjusted results (MVA) showed that the use of single UCBT and ATG significantly reduced grades II to IV acute GVHD. Neither of these factors had an impact on the incidence of chronic GVHD.

It is important to emphasize the potential benefits of the low rates of chronic GVHD, which is an inherent characteristic of UCB. Chronic GVHD is not only a major cause of NRM but also has been shown to have an important detrimental impact on patients' quality of life and psychological and functional status [29,30], which is particularly worrisome for AYAs. These

patients are often not emotionally or socially established as adult patients and have to manage their educational and/or professional responsibilities along with the burden of their disease and comorbidities [2,4].

Relapse rate was 27.9%, and the only factor having a significant effect on the relapse incidence was disease status at UCBT. Patients in CR1 and CR2 had a risk of relapse of 27.6% and 24.5%, respectively, whereas patients with advanced disease had a risk of relapse of 36.8%. There was no difference in relapse according to the type of leukemia (AML or ALL), the use of single or double UCBT, or the use of ATG. A previous study showed that the use of ATG decreased OS and increase NRM for UCBT compared with other stem cell sources in patients in CR1/CR2 [25]. Our adjusted findings revealed a 30% lower LFS with the use of ATG. In a subgroup analysis of a prospective study of children and young adults undergoing either single or double UCBT, the authors reported a significantly lower relapse risk for patients who received double UCBT with TBI-based conditioning and no ATG [28]. In our cohort, patients who received ATG had a 21% increase in the risk of relapse, but the result was not statistically significant (HR, 1.21; 95% CI, .71 to 2.08; $P = .49$). Despite the positive effect of ATG in preventing GVHD, ATG had a detrimental effect on survival. Therefore, because our results together with the plethora of previous reports indicate that ATG use in UCBT has deleterious effect on treatment-related mortality, survival, immune reconstitution, and infectious mortality [31,32], we suggest that ATG should be omitted in UCBT for AYA patients. However, alternative non-lymphodepleting strategies to abrogate severe acute GVHD should be investigated.

A limitation of the current study was the unavailability of data on long-term complications, which prevented us from studying the incidence of secondary neoplastic diseases, endocrine abnormalities, and infertility, among other complications. Reproductive concerns in AYA patients after cancer treatments have been shown to have a negative psychological and social repercussion in this group of patients [2,33]. However, because treatment timing is usually prioritized to future complications, preservation of infertility is sometimes not thoroughly discussed despite having major consequences in the life of AYA HSCT survivors.

Further studies focused on AYAs are required, including prospective research considering pre-HSCT information and comparison with other stem cell sources. To facilitate research in AYAs, a group effort among pediatrician, adult hematologists, and other healthcare providers is needed.

In conclusion, this study showing large comprehensive MAC-UCBT outcomes in AYAs contributes to a better understanding of HSCT for an age group that is not thoroughly described in most publications. Demonstrating the feasibility of UCBT in AYA patients is important to facilitate the decision of stem cell source selection.

DECLARATION OF COMPETING INTEREST

There are no conflicts of interest to report.

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SUPPLEMENTARY MATERIALS

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2019.07.031.

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