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Brief Articles

Changing Trends of Unrelated Umbilical Cord Blood Transplantation for Hematologic Diseases in Patients Older than Fifty Years: A Eurocord-Center for International Blood and Marrow Transplant Research Survey

Hanadi Rafii [1,2,*], Annalisa Ruggeri [1,3], Fernanda Volt [1,2], Claudio G. Brunstein [4], Jeanette Carreras [5], Mary Eapen [5], Eliane Gluckman [1,2], Daniel J. Weisdorf [4]

[1] Eurocord, APHP, University Paris Diderot, Hôpital Saint Louis, Paris, France
[2] Monacord, Centre Scientifique de Monaco, Monaco
[3] Service d'Hématologie et Thérapie Cellulaire, Hôpital Saint Antoine, AP-HP, Paris, France
[4] Blood and Marrow Transplant Program, University of Minnesota, Minneapolis, Minnesota
[5] Department of Medicine, Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, Wisconsin

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Over the last decade, there has been an increase in the use of umbilical cord blood (UCB) as an alternative source of stem cells both for children and adults. The development of double cord blood transplantation and the introduction of less toxic conditioning regimens helped to overcome the cell dose limitation and to decrease transplantation-related mortality, extending its use in adults. These advances in UCB transplantation (UCBT) techniques have resulted in acceptable outcomes for safety, engraftment, and survival, similar to those achieved with other graft sources [1,2].

Nevertheless, in the last few years, we witnessed slower growth in the numbers of UCBTs and unrelated donor transplantations, which is likely related to the increasing use of haploidentical donors after the development of post-transplantation cyclophosphamide for graft-versus-host disease (GVHD) prophylaxis and unmanipulated graft [3]. In 2014, 2% of the allogeneic transplantations performed in Europe used UCB compared with 10% haploidentical and other mismatch siblings, 35% identical siblings, and 52% unrelated donor transplantations [4]. Similar trends were reported by the Center for International Blood and Marrow Transplant Research (CIBMTR) [CIBMTR annual reports] with 8% UCBTs, 32% identical sibling, 11% haploidentical, and 50% unrelated donor transplantations.

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* Correspondence and reprint requests: Dr. Hanadi Rafii, University Paris Diderot, Hôpital Saint Louis, Eurocord, 1 Avenue Claude Vellefaux, 75010 Paris, France.
E-mail address: hanadi.rafii-elayoubi-ext@aphp.fr (H. Rafii).

However, apart from limited series [5-10], little is known about the use of UCBT in the elderly population, particularly in those over 60 years of age. The management of these patients usually presents significant challenges because of more aggressive disease and poor outcomes with non-transplantation therapy. These patients often do not receive intensive treatments because of their age and only a few are offered the curative potential of allogeneic hematopoietic transplantation. Beyond the common perception that older adults cannot tolerate aggressive therapy because of comorbidities, they may be less likely to have an available and clinically suitable matched related donor.

We evaluated the use of UCBT in patients older than 50 years who underwent transplantation between January 2005 and December 2014 in Europe and North America. The characteristics of these patients, their disease, and transplantation were assessed using data reported to the CIBMTR and Eurocord. Patients were grouped based on their age into 3 groups (50 to 59 years, 60 to 69 years, and $\geq$ 70 years).

Two thousand four hundred eighty-two patients, 50 years and older, underwent UCBT including 1406 patients (n = 768 [55%] ages 50 to 59 years and n = 638 [45%] ages $\geq$ 60 years) reported to the CIBMTR and 1076 patients (n = 433 [64%] ages 50 to 59 years and n = 248 [36%] ages $\geq$ 60 years) were reported to Eurocord. Seventy-four patients (3%) were $\geq$ 70 years; diagnoses were mainly acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS), mostly reported to the CIBMTR.

The indications for UCBT included primarily malignant conditions, with AML being the most common both in CIBMTR and Eurocord registries (52% versus 45%), followed by MDS and non-Hodgkin lymphoma. Most AML patients (>75%) underwent transplantation in complete remission, whereas 60% of patients with lymphoma were not in

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complete remission at time of transplantation. Plasma cell disorders, rarely an indication for transplantation in the United States outside of clinical trials, represented 1% of the indications for UCBT in CIBMTR compared with 6% of the cases in Eurocord. Only 14 patients (1%) with nonmalignant hematologic disorders were reported.

Reduced-intensity conditioning was used more frequently in Europe: it was used in 77% of patients reported to Eurocord and 54% reported to CIBMTR in the age group of 50 to 59 years, and in 93% in Eurocord and 76% in CIBMTR for older patients. The reduced-intensity conditioning combination of low-dose (200 to 400 cGy) total-body irradiation with cyclophosphamide and fludarabine was used for most of the patients in both registries [5]. Calcineurin inhibitor–based GVHD prophylaxis was used in nearly all patients. Cyclosporine (92%) was predominantly used in Europe whereas tacrolimus and mycophenolate mofetil were more often used in North America. Allografts in both cohorts were derived from unmanipulated single or double UCB units. Double UCBT accounted for 77% of cases reported to CIBMTR and 61% to Eurocord. Patient and transplantation characteristics are summarized in Table 1.

Although smaller studies have highlighted the feasibility of UCBT in older patients [6-8], the present survey presents a comprehensive population analysis of patients addressing the use of UCBT in North America and Europe. The number of transplantations increased dramatically over the years both in the CIBMTR cohort (average yearly increase of 15%) and in the Eurocord cohort (average yearly increase of 29%), the largest increase occurring from 2005 to 2009 (Figure 1).

This overall increase in the proportion of elderly patients undergoing UCBT from 2005 to 2013 appears largely to be driven by the reported successful experience in UCBT in many centers reflecting improvements in graft selection and post-transplantation care. After 2013, the number of transplantations started to decrease in both cohorts, a probable

Table 1
Characteristics of Allogeneic Cord Blood Transplant Recipients Fifty Years of Age and Older Registered with the CIBMTR and Eurocord between 2005 and 2014

Characteristic	50 to 59 Years		60 to 69 Years		70 + Years old	
	CIBMTR	Eurocord	CIBMTR	Eurocord	CIBMTR	Eurocord
No. of patients	768	635	575	430	63	11
Disease						
AML	352 (46)	293 (46)	339 (59)	187 (44)	40 (63)	5 (46)
ALL	80 (10)	59 (9)	27 (5)	22 (5)	0	3 (27)
CML	25 (3)	19 (3)	6 (1)	14 (3)	1 (2)	—
CLL	38 (5)	39 (6)	18 (3)	24 (6)	1 (1)	—
Other leukemias	28 (4)	6 (1)	13 (2)	1 (<1)	3 (5)	—
MDS/MPD	108 (14)	110 (17)	96 (17)	98 (23)	15 (24)	3 (27)
NHL	115 (15)	65 (10)	68 (12)	52 (12)	3 (5)	—
HL	12 (2)	4 (1)	2 (<1)	1 (<1)	—	—
PCD/MM	7 (1)	37 (6)	3 (1)	26 (6)	—	—
SAA/BMFS	2 (<1)	3 (1)	2 (<1)	5 (1)	—	—
Other	1 (<1)	—	1 (<1)	—	—	—
AML disease status						
CR1	169 (48)	129 (44)	194 (57)	89 (48)	34 (65)	3 (60)
CR2+	93 (26)	94 (32)	74 (22)	55 (29)	11 (21)	1 (20)
PIF/relapse	80 (23)	45 (15)	65 (19)	26 (14)	7 (14)	1 (20)
Missing	10 (3)	25 (9)	6 (2)	17 (9)	—	—
ALL disease status						
CR1	61 (76)	37 (62)	17 (63)	13 (59)	—	2 (67)
CR2+	14 (18)	12 (20)	7 (26)	5 (23)	—	1 (33)
Relapse	5 (6)	5 (9)	3 (11)	1 (4)	—	—
Missing	—	5 (9)	—	3 (14)	—	—
Previous autologous HCT						
NHL	48 (77)	39 (30)	29 (74)	28 (39)	1 (50)	—
HL	6 (10)	3 (2)	2 (5)	1 (2)	—	—
PCD/MM	5 (8)	33 (25)	2 (5)	24 (33)	—	—
AML	1 (2)	30 (23)	2 (5)	12 (17)	1 (50)	—
MDS/MPD	2 (3)	8 (6)	3 (8)	2 (3)	—	—
ALL	—	1 (1)	1 (3)	1 (1)	—	—
Other	—	18 (13)	—	4 (5)	—	—
Conditioning regimen intensity						
RIC	416 (54)	446 (70)	431 (75)	395 (92)	55 (87)	11 (100)
MAC	328 (43)	175 (28)	133 (23)	30 (7)	6 (10)	—
Missing	24 (3)	14 (2)	11 (2)	5 (1)	2 (3)	—
No. of UCB units infused						
Double	584 (76)	343 (54)	454 (79)	305 (71)	47 (75)	9 (82)
Single	182 (24)	292 (46)	119 (21)	125 (29)	12 (19)	2 (18)
GVHD prophylaxis						
Tac + MMF ± other	242 (32)	9 (2)	166 (29)	4 (1)	22 (35)	2 (18)
Tac ± other	108 (14)	5 (1)	83 (14)	6 (1)	7 (12)	—
CsA + MMF ± other	125 (16)	438 (69)	122 (21)	346 (80)	16 (25)	7 (64)
CsA ± other	278 (36)	148 (23)	198 (34)	48 (11)	16 (25)	1 (9)
Other	7 (1)	9 (1)	4 (1)	8 (2)	2 (3)	1 (9)
Missing	8 (1)	26 (4)	2 (<1)	18 (4)	—	—

ALL indicates acute lymphoblastic leukemia; CML, chronic myeloid leukemia; CLL, chronic lymphocytic leukemia; MPD, myeloproliferative disorders; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; PCD, plasma cell disorders; MM, multiple myeloma; SAA, severe aplastic anemia; BMFS, bone marrow failure syndromes; CR1, first complete remission; CR2+, second complete remission or more; PIF, primary induction failure; HCT, hematopoietic stem cell transplantation; RIC, reduced-intensity conditioning; MAC, myeloablative conditioning; Tac, tacrolimus; MMF, mycophenolate mofetil; CsA, cyclosporine A.