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Full Length Article

Cord Blood

Umbilical Cord Blood Transplantation for Fanconi Anemia With a Special Focus on Late Complications: a Study on Behalf of Eurocord and SAAWP-EBMT

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A B S T R A C T

Hematopoietic cell transplantation (HCT) remains the sole available curative treatment for Fanconi anemia (FA), with particularly favorable outcomes reported after matched sibling donor (MSD) HCT. This study aimed to describe outcomes, with a special focus on late complications, of FA patients who underwent umbilical cord blood transplantation (UCBT). In this retrospective analysis of allogeneic UCBT for FA performed between 1988 and 2021 in European Society for Blood and Marrow Transplantation (EBMT)-affiliated centers, a total of 205 FA patients underwent UCBT (55 related and 150 unrelated) across 77 transplant centers. Indications for UCBT were bone marrow failure in 190 patients and acute leukemia/myelodysplasia in 15 patients. The median age at transplantation was 9 years (range, 1.2 to 43 years), with only 20 patients aged >18 years. Among the donor-recipient pairs, 56% (n = 116) had a 0 to 1/6 HLA mismatch. Limited-field radiotherapy was administered to 28% (n = 58) and 78% (n = 160) received a fludarabine (Flu)-based conditioning regimen. Serotherapy consisted of antithymocyte globulin (n = 159; 78%) or alemtuzumab (n = 12; 6%). The median follow-up was 10 years for related UCBT and 7 years for unrelated UCBT. Excellent outcomes were observed in the setting of related UCBT, including a 60-day cumulative incidence (CuI) of neutrophil recovery of 98.1% (95% confidence interval [CI], 93.9% to 100%), a 100-day CuI of grade II-IV acute graft-versus-host disease (GVHD) of 17.3% (95% CI, 9.5% to 31.6%), and a 5-year CuI of chronic GVHD (cGVHD) of 22.7% (95% CI, 13.3% to 38.7%; 13% extensive). Five-year overall survival (OS) was 88%. In multivariate analysis, none of the factors included in the model predicted a better OS. In unrelated UCBT, the 60-day CuI of neutrophil recovery was 78.7% (95% CI, 71.9% to 86.3%), the 100-day CuI of grade II-IV aGVHD was 31.4% (95% CI, 24.6% to 40.2%), and the 5-year CuI of cGVHD was 24.3% (95% CI, 17.8% to 32.2%; 12% extensive). Five-year OS was 44%. In multivariate analysis, negative recipient cytomegalovirus serology, Flu-based conditioning, age <9 years at UCBT, and 0 to 1/6 HLA mismatch were associated with improved OS. A total of 106 patients, including 5 with acute leukemia/myelodysplasia, survived for >2 years after UCBT. Nine of these patients developed subsequent neoplasms (SNs), including 1 donor-derived acute myelogenous leukemia and 8 solid tumors, at a median of 9.7 years (range, 2.3 to 21.8 years) post-UCBT (1 related and 8 unrelated UCBT). In a subset of 49 patients with available data, late nonmalignant complications affecting various organ systems were observed at a median of 8.7 years (range, 2.7 to 28.8 years) post-UCBT. UCB is a valid source of stem cells for transplantation in patients with FA, with the best results observed after related UCBT. After unrelated UCBT, improved survival was observed in patients who underwent transplantation at a younger age, with Flu-based conditioning, and with better HLA parity. The incidence of organ-specific complications and SNs was relatively low. The incidence of SNs, mostly squamous cell carcinoma, increases with time. Rigorous follow-up and lifelong screening are crucial in survivors of UCBT for FA.

INTRODUCTION

Fanconi anemia (FA) is an inherited bone marrow failure (BMF) syndrome characterized by a broad spectrum of morphologic malformations, progressive trilineage cytopenia, multisystem defects, and increased predisposition to hematologic malignancies and solid tumors [1–3]. The Fanconi core complex and its associated protein complexes are required to ensure timely DNA repair. The risk for these major events is age-dependent. Approximately 75% of FA patients have birth defects. Severe BMF develops in 70% of patients by age 50 years, typically peaking during childhood at a median age of 7 years. Myeloid malignancies (eg, myelodysplasia [MDS], acute myeloid leukemia [AML]) are observed in approximately 30% to 40% of patients by age 40 years, with the usual onset after adolescence [4]. Additionally, solid tumors, mostly squamous cell carcinomas (SCCs), may develop at an unusually early age, and their incidence tends to increase over time [5,6].

Although conservative treatment with androgens and/or transfusions may be indicated for

mild cytopenia, allogeneic hematopoietic cell transplantation (HCT) remains the sole available curative therapy, able to correct the hematologic manifestations of FA and prolong survival [7]. Transplantation outcomes have improved in recent years due to changes in clinical practice, including the use of fludarabine (Flu)-based conditioning regimens [8–10]. The best results have been observed when HCT is performed at a younger age, prior to transfusion dependence and prior to clonal evolution and the development of MDS or acute leukemia [11–13].

Positive outcomes have been documented after HLA-matched sibling donor (MSD) HCT, with a 5-year overall survival (OS) exceeding 80% for optimal transplant indications [11,12,14-16]. Historically, the use of alternative donor transplants has posed challenges marked by significant toxicity and high incidence of graft failure (GF). Nonetheless, adjustments in treatment regimen intensity have resulted in reduced toxicity and greater control of graft-versus-host disease (GVHD) in this setting, with subsequent improved survival rates [12,17-22].

However, despite an overall improvement in HCT outcomes, the impact on long-term survival of patients with FA has been minimal, owing to a high rate of late mortality associated with a growing risk of subsequent neoplasms (SNs) and other disease-related complications in survivors [6,23-27]. A >15% increased risk of SN has been reported beyond 20 years post-HCT, with related mortality [4,5]. This highlights the critical importance of close monitoring for early detection of SNs in transplant recipients.

Studies focusing on umbilical cord blood transplantation (UCBT) for FA that include data on late post-transplantation complications are scarce. Usually, UCBT outcomes are reported together with outcomes from other graft sources. We analyzed all cases of related and unrelated UCBT for FA performed between 1988 and 2021 and reported to Eurocord and the European Society for Blood and Marrow Transplantation (EBMT) registries. Our aim was to evaluate outcomes after UCBT in a relatively large cohort, determine associated risk factors, and describe the development of late complications in the survivors.

METHODS

Study Design

We retrospectively reviewed the cases of all consecutive FA patients available in the EBMT/Eurocord databases who underwent a first related or unrelated allogeneic UCBT between October 1988 and December 2021. Eligible graft sources were single-unit UCB (sUCB), double-unit UCB (dUCB), and UCB coinfused with other grafts (related haploidentical or bone marrow [BM] from the same donor). The diagnosis of FA was confirmed by a chromosomal instability test. All patients received a conditioning regimen according to the protocols in place at their respective transplant centers at the time of UCBT. HLA disparity was assessed based on the number of mismatches between the patient and the selected UCB unit for sUCB grafts or between the patient and the UCB or adult donor graft with the poorest match for dUCB or UCB/coinfused grafts. This assessment considered HLA antigen levels for HLA-A and HLA-B and allele levels for HLA-DRB1.

A total of 205 patients were identified. Transplantations were performed in 77 EBMT transplant centers across 28 countries. Participating centers were requested to complete a data collection form describing late effects and long-term complications for all patients who survived for longer than 2 years.

To report data to the EBMT, transplant centers are required to obtain informed consent from their patients or patients' legal guardians, following the local regulations applicable at the time of transplantation and in accordance with the Declaration of Helsinki. The Review Board of Eurocord and of the Severe Aplastic Anemia Working Party (SAAWP) of the EBMT and Eurocord approved this study.

Endpoints and Definitions

The primary endpoint was OS, calculated from the date of transplant until death from any cause or last follow-up for survivors. Secondary endpoints included engraftment, grade II-IV acute GVHD (aGVHD), chronic GVHD (cGVHD), and transplantation-related mortality (TRM).

For patients who survived for >2 years after transplantation, late complications, including late organ impairment and the incidence and types of SNs, were described. The diagnosis and grading of aGVHD [28] and cGVHD [29] were done by the transplant centers using standard published criteria. Primary GF was defined as the absence of neutrophil engraftment or evidence of autologous recovery by day-60 post-transplantation. Secondary GF was defined as loss of the graft after initial engraftment, donor chimerism <5%, or persistence of a neutrophil count $<.5 \times 10^9$/L not related to infection or drug toxicity.

Statistical Analyses

Here continuous variables are described as median and range or interquartile range (IQR), and categorical variables are expressed as absolute value and percentage. The median follow-up was calculated using the reverse Kaplan-Meier method. OS rates, expressed as 5-year probability, were calculated using the Kaplan-Meier method, and the log-rank test was used for univariate comparisons.

TRM, engraftment, grade II-IV aGVHD, and cGVHD were expressed as cumulative incidence (CuI) to adjust the estimations for the pertinent competing risks [30]. For engraftment, death from any cause and second transplantation were considered competing events. For TRM, aGVHD, and cGVHD, death from any cause, second transplantation, and GF were considered competing events. Univariate comparisons were performed using Gray's test.

Multivariate analyses were performed using a Cox proportional hazards regression model [31] that included the following clinically pertinent variables: recipient cytomegalovirus (CMV) serostatus, transplantation period, indication for UCBT, conditioning regimen (Flu-based vs not), administration of low-dose radiotherapy (total body irradiation [TBI] or total lymphoid irradiation [TLI]), median age at UCBT, and HLA disparity. Independent variables were incorporated simultaneously in the models using the "enter" method in the Cox regression model. Subsequently, the Cox regressions were replicated using the backward stepwise method. The outcomes obtained from both methodologies were consistently similar. The multivariate analysis results presented in this article reflect the findings obtained using the "enter" method, which facilitated the visual representation of the effects of all variables considered in the models. All *P* values were 2-sided. Statistical analyses were performed with SPSS and R software packages.

RESULTS

Patient, Disease, and Transplantation Characteristics

Patient and transplantation characteristics are summarized in Table 1. From October 1988, the date of the first UCBT [32], to December 2021, a total of 205 patients with FA underwent UCBT (55 related and 150 unrelated) in EBMT centers. Indications for UCBT were BMF in 190 patients (93%) and acute leukemia (AL)/myelodysplasia (MDS) in 15 patients (7%). The median age at transplantation was 9 years (range, 1.2 to 43 years), and 90% (n = 185) of the patients were age <18 years at UCBT. Graft sources included sUCB (n = 162), dUCB (n = 23), intrabone sUCB (n = 2), and UCB coinfused with other cell sources, including BM from the same donor (n = 16) and related haploidentical peripheral blood stem cells (PBSCs) (n = 2). More than one-half (56%; n = 116) of the recipient-UCB pairs had a 0 to 1/6 HLA mismatch. Most patients (96%; n = 196) received a reduced-intensity conditioning regimen. Flu-based regimens were administered to 78% of patients (n = 160) and frequently included cyclophosphamide (Cy) (n = 155). TBI/TLI was administered to 28% of the patients (n = 58), at doses <8 Gy in 55 patients and 8 to 12 Gy in 3 patients (2 with BMF and 1 with AML) who underwent UCBT before 1997. Serotherapy consisted of antithymocyte globulin (ATG; n = 159; 78%) or alemtuzumab (n = 12; 6%). GVHD prophylaxis consisted of cyclosporine with or without steroids (62%) or mycophenolate mofetil with or without steroids (31%). The median infused cell dose was 5.1×10^7 /kg (IQR, 3.3 to 6.8×10^7 /kg) for total nucleated cells (TNCs) and 2.0×10^5/kg (IQR, 1.0 to 4.1×10^5/kg) for $CD34^+$ cells.

Among the patients with available pretransplantation data, 42 out of 108 had received prior androgen treatment and 102 out of 124 were transfusion-dependent. Details of FA pretransplantation treatments are reported in Table 2.

Related UCBT

Fifty-five patients (54 children and 1 adult) with FA underwent related UCBT between 1988 and 2021. (Table 1) In all patients, the indication for transplantation was progressive cytopenia, and Flu-based conditioning was the most frequently used regimen (n = 40; 73%). TBI/TLI was administered to 15% (n = 8) of the patients; serotherapy, to 64% (n = 35). In 73% (n = 40) of the recipients, there was a 0/6 HLA mismatch (MM). One patient had a 3/6 MM (graft was from a haploidentical donor). HLA data were unavailable for 14 patients. The median infused TNC dose was 4.9×10^7/kg (IQR, 3.1 to 7.5×10^7/kg), and the median infused $CD34^+$ cell dose was 2.0×10^5/kg (IQR, 1.0 to 4.1×10^5/kg).

Outcomes after related UCBT are summarized in Table 3. The median follow-up for surviving patients was 10 years (range, .3 to 29 years). The 60-day CuI of neutrophil recovery was 98.1% (95% CI, 93.9% to 100%), with a median time to engraftment of 17 days (range, 7 to 39 days). The 100-day CuI of grade II-IV aGVHD was 17.3% (95% CI, 9.5% to 31.6%). Twelve patients developed cGVHD,

Table 1
Patient and Transplantation Characteristics

Characteristic	Related UCBT		Unrelated UCBT		All Patients	
Patients, n (%)	55	(27)	150	(73)	205	(100)
Male sex, n (%)	26	(47)	80	(53)	106	(52)
Age at diagnosis, yr, median (range)	3	(.1-12)	6	(.1-42)	5	(.1-42)
Age at UCBT, yr, median (range)	8	(1-22)	9	(2-43)	9	(1.2-43)
Children (age <18 yr), n (%)	54	(98)	131	(87)	185	(90)
Adults (age ≥18 yr), n (%)	1	(2)	19	(13)	20	(10)
Indication for UCBT, n (%)						
Cytopenia/BMF	55	(100)	135	(90)	190	(93)
Acute leukemia	0	(0)	10	(7)	10	(4)
MDS	0	(0)	5	(3)	5	(3)
Transplantation period, n (%)						
1988-2000	14	(25)	19	(13)	33	(16)
2001-2010	19	(35)	84	(56)	103	(50)
2011-2021	22	(40)	47	(31)	69	(34)
Recipient CMV serostatus, n (%)						
Negative	22	(40)	61	(41)	83	(41)
Positive	30	(55)	79	(53)	109	(53)
Missing	3	(6)	10	(6)	13	(6)
Graft type, n (%)						
UCB	39	(71)	123	(82)	162	(79)
dUCB	0		23	(16)	23	(11)
sUCB + BM (same donor)	16	(29)	0		16	(8)
sUCB + related haplo	0		2	(1)	2	(1)
Intrabone sUCB	0		2	(1)	2	(1)
HLA disparity, n (%)						
0-1/6 MM	40	(73)	76	(51)	116	(56)
≥2/6 MM	1	(2)	47	(31)	48	(24)
Missing	14	(25)	27	(18)	41	(20)
Serotherapy						
None	16	(29)	8	(5)	24	(12)
ATG	29	(53)	130	(87)	159	(78)
Alemtuzumab	6	(11)	6	(4)	12	(6)
Missing	4	(7)	6	(4)	10	(5)
Conditioning regimen, n (%)						
No Flu	14	(25)	24	(16)	38	(19)
Cy	9	(16)	17	(11)	26	(13)
CU + Bu	4	(7)	5	(3)	9	(4)
Cy + others	0		2	(1)	2	(1)
Bu	1	(2)	0		1	(<1)
Flu-based	40	(73)	120	(80)	160	(78)
Flu ± others	0		3	(2)	3	(1)
Flu + Cy	34	(62)	77	(51)	111	(54)
Flu + Cy + Bu	4	(7)	35	(23)	39	(19)
Flu + Cy + others	1	(2)	4	(35)	5	(2)
Flu + Bu	1	(2)	1	(<1)	2	(1)
Missing	1	(2)	6	(4)	7	(3)
TBI/TLI, n (%)*						
No	47	(85)	100	(64)	147	(72)
Yes	8	(15)	50	(33)	58	(28)
GVHD prophylaxis, n (%)						
CsA-based	40	(73)	88	(59)	128	(62)
MMF-based	12	(22)	52	(35)	64	(31)
Others	0	(0)	5	(3)	5	(2)
Infused TNC dose, $\times 10^7$/kg, median (IQR)	4.9	(3.1-7.5)	5.1	(3.3-6.8)	5.1	(3.3-6.8)
Infused $CD34^+$ cell dose, $\times 10^5$/kg, median (IQR)	2	(1.0-4.1)	2	(1.0-4.0)	2.0	(1.0-4.1)

CsA indicates cyclosporine A; MMF, mycophenolate mofetil.

* TBI/TLI dose 1-6 Gy; only 3 patients received a dose ≥8 Gy.

Table 2
Pretransplantation Therapy in the Patients with FA

Therapy	No.	%
Steroids (N = 101)		
No	81	80
Yes	20	20
Growth factors (N = 101)		
No	84	83
Yes	17	17
Androgens (N = 108)		
No	66	61
Yes	42	39
Other treatments (N = 54)		
No	47	87
Yes	7	13
Chemotherapy	3	
Immunotherapy	2	
Gene therapy	1	
Other	1	
Transfusions (N = 124)		
No	22	18
Yes	102 (35 patients with ≥20 transfusions)	82

Pretransplantation therapy was available for a limited number of patients (54 to 124, depending on type of therapy).

at a median of 179 days (range, 91 to 968 days). The 5-year CuI of cGVHD was 22.7% (95% CI, 13.3% to 38.7%), with 7 patients presenting with extensive cGVHD. The 5-year CuI of TRM was 9.9% (95% CI, 4.3% to 23.1%). GF was observed in 1 patient who received an HLA-identical sibling donor sUCBT in 1990, after conditioning including Cy and 5 Gy of thoracoabdominal irradiation without ATG. The patient died shortly after undergoing a subsequent allogeneic UCBT.

The 5-year OS was 88 ± 4% (Figure 1). Six patients died, including 3 who underwent UCBT before 1998 and died of TRM within the initial 30 days and 3 who died of TRM within the first year after related UCBT. Five-year OS rates after related UCBT according to transplantation period are shown in Figure 2A.

In univariate analyses, Flu-based conditioning was the only factor predictive of improved OS, while none of the factors analyzed had a significant impact on the incidence of GVHD or TRM (Supplementary Table S1). Positive recipient CMV serology was predictive of poor engraftment (results not shown). In multivariate models, none of the tested factors had a statistically significant impact on outcomes after related UCBT (results not shown).

Unrelated UCBT

One hundred and fifty patients with FA underwent unrelated UCBT between 1990 and 2021 (Table 1). Eighty-seven percent (n = 131) were aged <18 years at the time of UCBT. The indication for transplantation was BMF in 90% (n = 135), MDS in 5 patients, and AML in 10 patients. Flu-based conditioning was administered to 80% (n = 120) of the patients; TBI/TLI, to 33% (n = 50); and serotherapy, to 91% (n = 136) . One-half of the recipient-UCB pairs (51%; n = 76) had a 0 to 1/6 HLA mismatch. The median infused cell dose was 5.1×10^7 /kg for TNCs (IQR, 3.3 to 6.8×10^7 /kg) and 2.0×10^5/kg for $CD34^+$ cells (IQR, 1.0 to 4.0×10^5/kg).

UCBT outcomes are summarized in Table 3. The median duration of follow-up for surviving

Table 3
Outcomes of UCBT in FA

Outcome	Related UCBT	Unrelated UCBT	All Patients
Overall survival at 5 yr, % (SE)	88 (±4)	44 (±4)	55 (±3)
CuI of neutrophil engraftment at 60 d, % (95% CI)	98.1 (93.9-100)	78.7 (71.9-86.3)	84.4 (79.3-90.0)
Time to neutrophil recovery, d, median (range)	17 (7-39)	21 (10-62)	20 (7-62)
CuI of grade II-IV aGVHD at 100 d, % (95% CI)	17.3 (9.5-31.6)	31.4 (24.6-40.2)	29.8 (24.1-36.7)
Time to aGVHD, d, median (range)	38 (13-57)	21 (8-78)	22 (8-78)
CuI of cGVHD at 5 yr, % (95% CI)	22.7 (13.3-38.7)	24.3 (17.8-32.2)	23.7 (18.4-30.7)
Time to cGVHD, d, median (range)	179 (91-968)	131 (98-5101)	131 (91-5101)
Extensive form, n (%)	7 (13)	18 (12)	25 (12)
CuI of TRM at 5 yr, % (95% CI)	9.9 (4.3-23.1)	38.8 (31.6-47.6)	31.5 (25.6-38.8)
CuI of SNs at 15 yr, % (95% CI)	3.5 (.5-25.1)	10.3 (4.7-22.8)	8 (3.9-16.6)
Follow-up, yr, median (range)*	10 (.3-29)	7 (.3-22)	7 (.3-29)

* Median follow-up for surviving patients.

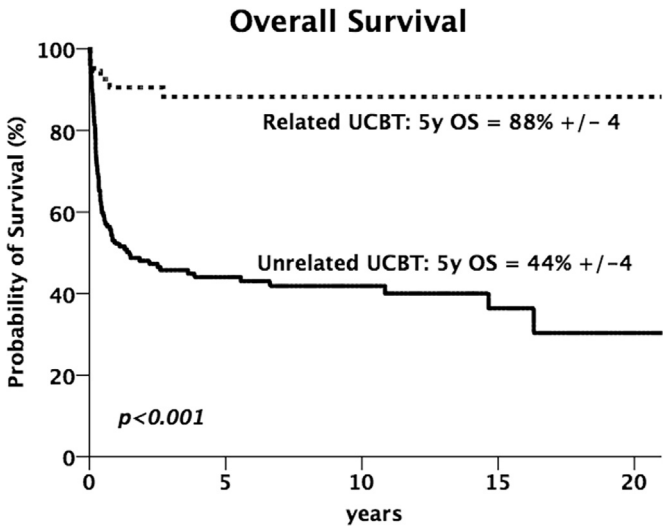

Figure 1. Five-year OS after UCBT for FA by graft origin.

patients was 7 years (range, .3 to 22 years). The 60-day CuI of neutrophil engraftment was 78.7% (95% CI, 71.9% to 86.3%), with a median time to engraftment of 21 days (range, 10 to 62 days). The 100-day CuI of grade II-IV aGVHD was 31.4% (95% CI, 24.6% to 40.2%). Thirty-five patients developed cGVHD (18 with extensive form), within a median of 131 days. The 5-year CuI of cGVHD was 24.3% (95% CI, 17.8% to 32.2%). The 5-year CuI of TRM was 38.8% (95% CI, 31.6% to 47.6%). Primary GF was observed in 36 patients (24%); secondary GF, in 1 patient. Twenty-five patients (17%) underwent a second allogeneic HCT, at a median of 1.8 months (range, .8 to 6.8 months) after their initial UCBT. Of these, 7 were alive at last follow-up, including 1 recipient of related BM, 1 recipient of related PBSCs, 1 recipient of unrelated BM, and 4 recipients of unrelated UCB.

The 5-year OS was 44 ± 4% (Figure 1). Eighty-seven unrelated UCBT recipients died. Causes of death were TRM in 78 patients (GVHD, n = 21; infection, n = 22; GF, n = 12; other, n = 23) and SNs in 6 patients. The specific cause of death was not available for 3 patients. Five-year OS varied according to transplantation period (Figure 2B).

Among the 150 unrelated UCBT recipients were 15 patients (6 children and 9 adults) with AL/MDS (AML, n = 9; acute lymphoblastic leukemia, n = 1; MDS, n = 5) at the time of UCBT, including 3 patients with active disease (1 primary refractory AML and 2 relapse after initial complete remission). Chromosomal abnormalities were observed in 13 patients. Neither molecular data nor information related to the chemotherapy administered prior to UCBT was available for most of the patients. Thirteen patients received Flu-based conditioning, and 11 received TBI (low-dose [<6 Gy] in 10); 12 Gy in 1). Serotherapy was administered to 13 patients. The graft type was sUCB in 6 patients, dUCB in 8 patients,

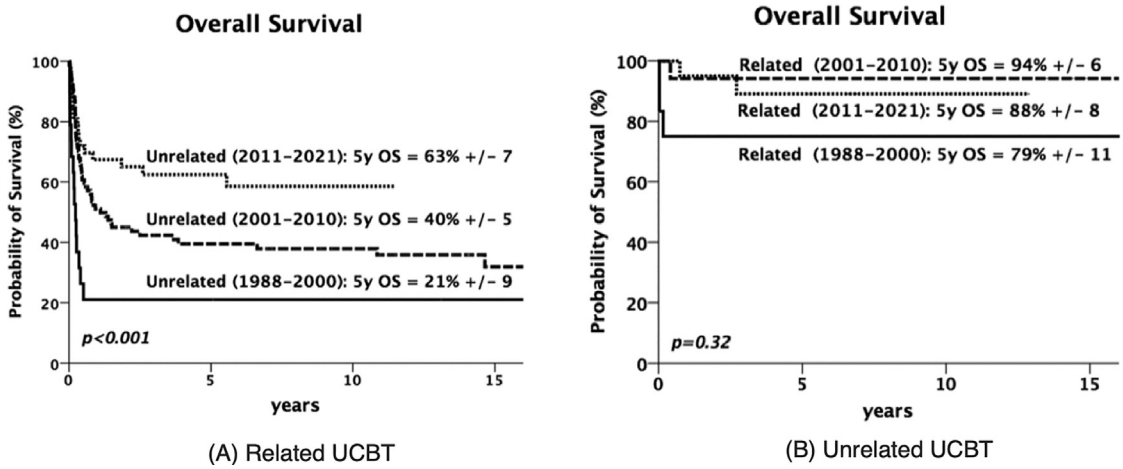

Figure 2. Five-year OS by transplantation period after related UCBT (A) and unrelated UCBT (B) for FA.

and intrabone sUCB in 1 patient. Three patients experienced primary GF and died at 64 days, 121 days, and 146 days after UCBT, despite subsequent allogeneic HCT in 2 of these patients.

The 5-year OS for FA patients who underwent UCBT for AL/MDS was 33 ± 13%. At a median follow-up of 9 years (range, 5 to 16 years), 5 patients (4 adults and 1 child) were alive and in complete remission. Two of these surviving patients developed cGVHD (1 limited and 1 extensive). Ten patients experienced TRM (GVHD, n = 1; GF, n = 3; infections n = 5; idiopathic pneumonia, n = 1). None of the surviving patients who underwent transplantation for AL/MDS developed leukemic relapse or other neoplasms.

In univariate analyses, positive recipient CMV serology, HLA disparity ≥2/6 MM, absence of Flu-based conditioning, and earlier period of transplantation were predictive of poor engraftment. None of the tested factors had a statistically significant impact on the development of aGVHD or cGVHD. Increased TRM was observed with older age, previous use of androgens, TBI/TLI administration, and absence of Flu in the conditioning regimen. Factors predictive of better OS were younger age (<9 years), recent transplantation period, negative recipient CMV serology, absence of pretransplantation androgens, HLA disparity of 0 to 1/6 MM, use of Flu-based conditioning, and absence of TBI/TLI (Supplementary Table S2).

In multivariate analyses, negative recipient CMV serostatus and more recent transplant period were predictive of better engraftment (Table 4). Younger age at UCBT (<9 years) was associated with a lower incidence of aGVHD. Negative recipient CMV serology, Flu-based conditioning, and younger age were predictive of lower TRM. Negative recipient CMV serology, younger age, Flu-based conditioning, and HLA mismatch of 0 to 1/6 were associated with better OS. None of the factors considered in the multivariate model had a statistically significant effect on cGVHD.

Late Complications after UCBT

One hundred and six patients survived for >2 years after their first UCBT (median follow-up of 7 years) and were evaluated for late complications. Data documenting organ-specific late nonmalignant complications were available for 49 patients (Table 5). All patients had a Lansky Performance Scale score ≥70, and 29 of them experienced at least 1 nonmalignant late organ impairment that adversely affected their quality of life. The late complications observed involved different organs and physiologic systems, most frequently the endocrine and reproductive systems. Only 1 death (due to pulmonary complications at 16 years post-UCBT) was attributed to a nonmalignant late complication. cGVHD was evaluated in all the patients who survived at least 100 days post-UCBT. Among the 47 patients who developed cGVHD, 31 survived for >2 years post-UCBT, and only 1 death was attributed to cGVHD.

Malignant complications are described in detail in Table 6. Of the 9 patients diagnosed with SNs after UCBT, 8 underwent unrelated UCBT and 1 underwent related UCBT. The related UCBT recipient was diagnosed with oral SCC at 10 years post-transplantation. The patient had no prior exposure to TBI or TLI but had a long history of extensive cGVHD. The patient was treated with surgery and chemotherapy and was still alive at last follow-up, 19 months after the diagnosis of SCC. The other 8 cases of SNs occurred in unrelated UCBT recipients, including 1 with donor-derived AML and 7 with solid tumors (1 soft tissue sarcoma of the oropharynx, 3 upper gastrointestinal SCCs, and 3 oral cavity SCCs). The solid tumors were diagnosed within a median of 9.7 years (range, 3.6 to 21.8 years) after UCBT.

The patient who subsequently developed donor-derived AML was 8 years old at the time of his first unrelated UCBT. The conditioning regimen consisted of Cy/Flu/TBI 2 Gy. The patient failed to engraft, and a BM smear revealed 33% leukemic blasts. Consequently, he underwent a second unrelated UCBT approximately 2 months after the first UCBT with Cy/Flu conditioning. This time he achieved successful engraftment. However, at 2 years post-UCBT, he was again diagnosed with AML. Fluorescence in situ hybridization analysis showed that the leukemia was of donor origin, diagnosed by sex difference between donor and recipient (female donor and male recipient). No cytogenetic abnormalities or common AML rearrangements were detected. The leukemia showed resistance to chemotherapy, and 1 year after the diagnosis of the AML, the patient received a related haploidentical donor transplant after conditioning with Flu/treosulfan/Cy. He went on to develop severe aGVHD and died of relapsed leukemia at 3 months after his third transplant.

Among the 9 patients who developed SNs post-UCBT, 6 had previously undergone a second allogeneic transplantation due to primary GF (graft source: BM, n = 3; UCB, n = 2; PBSCs, n = 1). At the last follow-up, only 3 patients were still alive; 2 were in persistent remission at 1.6 and 4 years

Table 4
Multivariate Analysis of Outcomes in FA Patients after Unrelated UCBT

Variable		HR	95% CI		*P* Value
OS	Recipient CMV serology (negative vs positive)	.36	.204	.636	<**.001**
	Indication for UCBT (AL/MDS vs BMF)	.524	.226	1.212	.131
	Flu-based conditioning (yes vs no)	.161	.052	.493	<**.001**
	TBI/TLI (no vs yes)	1.13	.583	2.189	.717
	Age at UCBT (<9 yr vs ≥9 yr)	.278	.156	.494	<**.001**
	HLA disparity (0-1/6 MM vs >1/6MM)	.58	.343	.982	**.043**
	Transplantation period*	.932	.533	1.63	.805
Engraftment	Recipient CMV serology (negative vs positive)	1.939	1.227	3.065	**.005**
	Indication for UCBT (AL/MDS vs BMF)	1.128	.544	2.339	.746
	Flu-based conditioning (yes vs no)	.775	.281	2.133	.621
	TBI/TLI (no vs yes)	1.003	.592	1.697	.992
	Age at UCBT (<9 yr vs ≥9 yr)	.807	.503	1.293	.372
	HLA disparity (0-1/6 MM vs >1/6 MM)	1.314	.783	2.206	.301
	Transplantation period*	1.797	1.137	2.84	**.012**
aGVHD	Recipient CMV serology (negative vs positive)	.807	.411	1.585	.533
	Indication for UCBT (AL/MDS vs BMF)	.88	.313	2.475	.808
	Flu-based conditioning (yes vs no)	2.726	.509	14.587	.241
	TBI/TLI (no vs yes)	.781	.367	1.661	.521
	Age at UCBT (<9y vs ≥9y)	.388	.181	.831	**.015**
	HLA disparity (0-1/6 MM vs >1/6MM)	1.192	.576	2.467	.636
	Transplant period*	1.023	.534	1.961	.944
cGVHD	Recipient CMV serology (negative vs positive)	.448	.188	1.067	.07
	Indication for UCBT (AL/MDS vs BMF)	2.072	.654	6.567	.216
	Flu-based conditioning (yes vs no)	.578	.052	6.4	.655
	TBI /TLI (no vs yes)	1.98	.715	5.479	.188
	Age at UCBT (<9 yr vs ≥9 yr)	.602	.251	1.442	.255
	HLA disparity (0-1/6 MM vs >1/6MM)	1.34	.494	3.64	.565
	Transplantation period*	.581	.277	1.22	.151
TRM	Recipient CMV serology (negative vs positive)	.453	.233	.881	**.02**
	Indication for UCBT (AL/MDS vs BMF)	.465	.172	1.255	.131
	Flu-based conditioning (yes vs no)	.22	.062	.786	**.02**
	TBI /TLI (no vs yes)	.988	.462	2.112	.975
	Age at UCBT (<9 yr vs ≥9 yr)	.262	.126	.545	<**.001**
	HLA disparity (0-1/6 MM vs >1/6 MM)	.636	.324	1.247	.188
	Transplantation period*	.878	.464	1.662	.69

Bold type indicates statistical significance.
HR indicates hazard ratio.
* Continuous variable.

after the diagnosis of SNs, and 1 was undergoing treatment after surgical excision.

DISCUSSION

Allogeneic HCT is, currently, the sole available curative therapy for patients with FA. UCB has been used as a source of stem cells for transplantation since the world's first UCBT was performed 30 years ago in a patient with FA [32]. Compared to the general population, FA patients have a 700-fold greater risk of developing malignancies. This high susceptibility to cancer is the result of chromosomal fragility and defective DNA repair pathways that adversely affect genome stability [33–36]. This is particularly problematic in the context of HCT, where DNA repair defects may be exacerbated by the preparative regimen, toxicity, radiation exposure, prolonged immunosuppression, and GVHD,

Table 5
Late Nonmalignant Complications after UCBT in FA Patients

Organ-Specific/Systems	No.*	Reported Complications
No organ-specific complications	20	No organ-specific complications adversely affecting quality of life
Immune system	9	Recurrent infections: viral, bacterial, and, less frequently, fungal
Oral	6	Oral lichen planus, leucoplakia
Ophthalmologic	9	Dry eye syndrome, keratitis, proptosis, retinopathy, cataracts
Cardiovascular	1	Pericarditis
Pulmonary	11	Bronchiolitis obliterans, recurrent bronchitis, bronchiectasis, respiratory failure
Gastrointestinal	2	Chronic diarrhea
Liver	9	Chronic abnormal liver function tests, GVHD, liver fibrosis, iron overload
Renal	7	Nephrotic syndrome, mild to moderate chronic renal failure
Urinary tract	2	Chronic hematuria, bladder-ureteral reflux
Endocrine, genital, or gonadic	25	Thyroid dysfunction, diabetes, Cushing syndrome, endometriosis, dry mucosa, dyspareunia
Neurologic	1	Polyradiculoneuritis, cranial nerve palsy, hearing loss
Bone	7	Osteoporosis, femoral head necrosis, scoliosis
Patients surviving ≥100 d evaluated for cGVHD	**155**	
cGVHD (severity missing for 2) Limited Extensive	47 20 25	Limited or cGVHD

* Long-term data on specific organ complications were available for a subset (n = 49) of the 106 patients who survived for at least 2 years post-UCBT. Twenty-nine of these patients presented with 1 to 7 organ-specific complications.

further increasing the risk of malignancies in this unique population [12,23,37]. Early UCBTs were associated with excessive morbidity, mainly GVHD-related, highlighting the marked hypersensitivity of FA cells to alkylating agents in conditioning regimens [38]. Changes in conditioning regimen intensity to include lower doses of Cy alone or with limited-field radiotherapy, as well as the use of GVHD prophylaxis with ATG or alemtuzumab, have contributed to further improve related HCT outcomes, with 5-year OS exceeding 90% after related HCT for FA in some reports [8-10,15,16,22,24,39].

Early studies of HCT with alternative donor sources showed poor survival and high incidences of GF and GVHD [17,18]. However, advances in transplant protocols such as the addition of Flu, the use of radiation-free conditioning, in-vivo or ex-vivo T-cell depletion (TCD) and the use of new anti-viral prophylaxis drugs improved outcomes after unrelated HCT for FA, with 89% engraftment rates and 52% OS [19,40].

Our retrospective, multicenter study evaluated the outcomes of 205 patients with FA who underwent a first related or unrelated UCBT over the past 3 decades showing better results after related UCBT. Our related UCBT results were comparable to those reported after related HCT with other graft sources in the setting of FA [12,21,41]. In unrelated UCBT, the 5-year OS was 44%, with improving results over time likely due to the use of more effective and less toxic conditioning regimens, new antiviral prophylaxis strategies (such as the use of letermovir), and better HLA parity. Our results are comparable to those reported after unrelated and alternative donor transplantation with in vivo T cell depletion [17,18,20,21]. European registry data show improved survival rates over the years in pediatric patients and young adults undergoing transplantation for FA.

In our unrelated UCBT cohort, Flu-based conditioning was associated with better survival. Conditioning regimens containing Flu induce T cell immunosuppression and facilitate engraftment with minimal toxicity, which likely have a positive effect on survival. Additional prognostic factors also were identified, including younger age, better HLA parity, and negative recipient CMV serology at the time of UCBT.

The use of androgens is a key component of the therapeutic approach for patients with FA who do not meet the criteria for HCT. They are also frequently used in the interim phase before transplantation. In this latter context, it is of interest that in the subgroup of our patients with available data (n = 108), pretransplantation androgens had an adverse effect on transplantation outcomes,

Table 6
SNs after UCBT*

Parameter	Related UCBT; Case 1	Unrelated UCBT							
		Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Indication for UCBT	BMF	BMF	BMF	BMF	BMF	BMF	BMF	BMF	BMF
SN pathology	SCC	AML† (donor- derived)	SCC	SCC	SCC	SCC	Soft tissue Sarcoma	SCC	SCC
SN site	Oral cavity (mandible)	Blood	Upper GI (esophagus; liver mets)	Upper GI (esophagus; lung mets)	Upper GI (esophagus)	Oral cavity (tongue; lung mets)	Oropharynx	Oral cavity (tongue)	Oral cavity
Age at SN, yr	22	10.7	9.7	35	26.2	13	21.7	21.1	13
Time since UCBT, yr	10	2.3	9.7	13.5	21.8	5.6	3.6	12.1	4.6
Age at UCBT, yr	12	8	8	22	4	7	18	9	8
Recipient sex	Female	Male	Male	Female	Female	Male	Male	Female	Female
Recipient CMV serology	Negative	Positive	Positive	Negative	Negative	Positive	Negative	Positive	Positive
HLA MM	0/6	3/6	NA	2/6	1/6	2/6	2/6	2/6	2/6
Serotherapy	No	ATG	ATG	ATG	No	ATG	ATG	ATG	ATG
TBI/TLI	No	Yes	Yes	No	Yes	No	No	No	Yes
Conditioning for first UCBT	Flu/Cy/ epirubicin	Flu/Cy	Cy	Flu/Cy	Flu	Flu/Cy	Flu/Cy	Bu/Cy/Flu	Flu/Cy
Chimerism at day 100	Full donor	Autologous	Full donor	missing	Autologous	Aplasia	Autologous	Autologous	Autologous
Primary GF	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes
New HCT	No	Yes (1 UCBT and 1 haplo)	No	No	Yes	Yes	Yes	Yes	Yes
aGVHD‡	No	No	No	No	No	No	No	No	No
cGVHD (grade) ‡	Yes (extensive)	No	No	Yes (extensive)	No	No	No	No	No
Duration of follow-up, yr	12	3.6	11	15	23	7	4	16	6
Survival status and time (yr) from UCBT to death or last follow-up	Alive (11.7)	Dead (3.6)	Dead (10.8)	Dead (14.6)	Alive (22.2)	Dead (6,6)	Dead (3.8)	Alive (16.2)	Dead (5.6)
Survival post-SN, mo	19	16	13	12	2.5	11.6	2.9	47	11

* Considering the 106 patients who survived for at least 2 years post-UCBT.
† The AML was diagnosed after the second UCBT.
‡ Considering GVHD attributed to first UCBT only; some patients developed GVHD after subsequent UCBT.

with a higher incidence of TRM observed in univariate analysis in the unrelated UCBT cohort. The adverse impact of pretransplantation androgens has been reported previously by other groups [15,17,42].

At a median follow-up of 10 years, only 1 related UCBT recipient and 8 unrelated UCBT recipients developed an SN. The incidence rates that we observed are similar to those reported in the literature after related and unrelated HCT for FA [5,23,24,26,43,44]. The use of UCB may confer a proliferative advantage and specific immunologic properties usually associated with a lower risk of GVHD and better immune reconstitution compared to grafts from other donor types, resulting in a decreased risk of secondary malignancy [45].

Organ-specific complications that impair quality of life are frequent after HCT for FA [4]. In our study, the most frequently occurring complications involved endocrine and gonadal function or were the consequence of cGVHD involving skin, oral, gut mucosa, or pulmonary fibrosis. Endocrine and gonadal complications are common in patients with FA, in which short stature is often treated with growth hormones and female patients require hormone replacement therapy. These complications can be exacerbated by transplantation toxicity [46]. For example, infertility is frequent following transplantation, and successful pregnancy is rarely reported in patients after HCT [47,48]. However, it is important to note that reduced fertility is also frequently observed in FA patients who have not undergone HCT. Unfortunately, owing to the retrospective nature of our registry-based study, we were unable to obtain exhaustive data on specific organ complications and fertility for all the patients who survived for >2 years post-UCBT.

The 5-year survival rate for FA patients who underwent transplantation for AL/MDS was 33%. Remarkably, at the last follow-up, one-third of these patients were still alive without leukemic relapse or solid tumor. We observed no instances of relapsed AML/MDS following UCBT in patients who underwent transplantation for FA or AML/MDS. These findings are particularly intriguing compared to previously published results that show a higher incidence of leukemic relapse in FA patients [49–51]. Satty et al. [51] assessed the outcomes of 30 patients who underwent T cell-depleted allogeneic HCT for the treatment of FA and MDS/AML. Their findings indicated a 5-year OS rate of 66.8% and a disease-free survival of 53.8%, with a CuI of relapse and nonrelapse mortality of 24.3% and 21.9%, respectively. These discrepant findings compared to our data may be related to the small number of patients who underwent transplantation for AML/MDS in our study.

The reported incidence of donor cell leukemia after UCBT is very low (.03%) [52]. In a recent study, Williams et al. [53] estimated the rate of donor-origin malignancies post-allogeneic HCT ranges from .1% to .5%. Approximately 30% of patients relapse after unrelated HCT, and 2% to 5% of these relapses are donor-derived malignancies. The mechanism responsible for these relapses remains unclear, but they potentially could stem from germ line predisposition alleles or clonal hematopoiesis in the donor [35,36].

Most of the SNs observed in our study were oral or esophageal SCCs. These types of malignancies have been described extensively after HCT for FA and may be related to mouth chronic lichen planus-like inflammation due to cGVHD, human papillomavirus infection, or additional mutations resulting from DNA damage in these patients [5,23-26,43].

Although other solid tumors, such as skin, breast, and central nervous system tumors, also are observed more frequently in patients with FA than in healthy individuals of the same age group, we did not find any such cases within our study population. However, the availability of detailed long-term data was restricted to a certain number of patients, and thus we cannot exclude the possibility that the incidence of solid tumors or other late-developing malignancies might be underestimated in our study. A rigorous and lifelong follow-up of patients with FA is of utmost importance given the high risk of secondary tumors in these patients.

The most frequent cause of death was TRM (84 of 93 deaths), attributed mainly to GVHD, infectious complications, and GF observed during the first 2 years post-UCBT. Only 4 cases of TRM occurred after this initial 2-year period. Three of these deaths were directly attributed to GVHD, and 1 was attributed to viral infection in a patient with extensive cGVHD. Better control of GF and the development of new strategies to decrease the risk of aGVHD and cGVHD could potentially improve survival.

It is noteworthy that the deaths observed in patients who survived for >2 years post-UCBT were due exclusively to SNs and included patients whose SN diagnosis was established at >10 years post-transplantation. All of these late deaths attributable to SNs occurred in unrelated UCBT

recipients. This higher frequency of SNs observed in unrelated recipients could be related to increased cell damage related to drug toxicity or cGVHD in these patients, particularly in those who had undergone a second transplantation after experiencing GF.

Our study has some limitations, mainly inherent to its retrospective design. Data related to pretransplantation exposure was sometimes missing, particularly in relation to transfusion history, previous androgen therapy, disease characteristics, molecular and cytogenetic results, and HLA parity. In addition, some patients were lost to follow-up, making the collection of long-term data challenging and leading us to limit our assessment of late effects and secondary malignancies to the patients with updated data by the transplant centers.

CONCLUSION

Overall, the outcomes of FA patients who underwent UCBT were similar to those reported after HCT using other graft sources. Superior results were observed when patients underwent transplantation at a younger age and with a Flu-based conditioning regimen. Improved outcomes have been observed in recent years, particularly after unrelated UCBT. Although long-term, organ-specific complications and SN-related mortality rates were relatively low in our study compared to those reported by other groups, it remains essential to underscore the importance of lifelong screening and early intervention for any mouth lesion in transplant survivors. This approach aims to prevent, detect without delay, and treat late complications and to improve outcomes and long-term survival of patients with FA.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2024.02.024.

APPENDIX 1. PARTICIPATING TRANSPLANTATION CENTERS

Center	Country
Centre Hospitalier Universitaire La Conception	France
Hôpital d'Enfants de la Timone, CHU	France
Hôpital Necker	France
University Hospital Hematology	Switzerland
Leiden University Hospital BMT Centre, Leiden	Netherlands
Bone Marrow Transplant Unit L 4043, National University Hospital	Denmark
Department of Hematology and BMT, Hôpital St. Louis	France
Department of Hematology, University Hospital Gasthuisberg	Belgium
Karolinska University Hospital	Sweden
University of Helsinki	Finland
Oslo University Hospital, Rikshospitalet	Norway
Reina Sofia Hospital, Córdoba	Spain
Utrecht University Medical Centre	Netherlands
Bologna University, S Orsola-Malpighi Hospital	Italy
Servicio de Hematología-Hemoterapi, Hospital U Marqués de Valdecilla, Santander	Spain
Great Ormond Street Hospital Children's Charity, London	United Kingdom
Ospedale Civile, Pescara	Italy
Hadassah University Hospital, Jerusalem	Israel
CHU Bordeaux	France
Institute G Gaslini, Genova	Italy
Clinica di Oncoematologia Pediatrica, Padova	Italy
Ospedale S Camillo-Forlanini, Roma	Italy
Sahlgrenska University Hospital, Goeteborg	Sweden
Inst. Português de Oncologia do Porto	Portugal
University Children's Hospital, Zürich	Switzerland
Azienda Ospedaliera di Rilievo Nazionale Santobono-Pausilipon, Napoli	Italy
Princess Maxima Center, University Hospital for Children (WKZ)	Netherlands
Department of Paediatric Oncology/BMT, Bristol Royal Hospital for Children	United Kingdom
Oncology, Section of Adult Hematology/BMT, King Faisal Specialist Hospital & Research Center	Saudi Arabia
Hacettepe University Children's Hospital, Ankara	Turkey
Hospital Vall d'Hebron, Barcelona	Spain
Centre Hospitalier Universitaire Sainte-Justine, Montréal	Canada
University Hospital Motol	Czech Republic
Acibadem University Atakent Hospital, Istanbul	Turkey
Department of Paediatric Haematology, Manchester	United Kingdom

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Center	Country
Fondazione IRCCS Policlinico San Matteo, Pavia	Italy
Edmond & Lily Safra Children's Hospital, Tel-Hashomer	Israel
King Hussein Cancer Centre Queen Rania Street - Amman	Jordan
Belarussian Research Center for Pediatric Oncology, Hematology and Immunology, Minsk	Belarus
Hospital Ramón y Cajal, Madrid	Spain
Akdeniz University Medical School, Antalya	Turkey
Hôpital Robert Debré, Paris	France
Shariati Hospital, Teheran	Iran
Poznan University of Medical Sciences	Poland
Centre Hospitalier Universitaire de Rennes	France
University Hospital La Fe, Valencia	Spain
Hématology Service, Centre Hospitalier Lyon Sud	France
CRHU de Strasbourg, service d'hématologie – Greffe	France
Hôpital d`Enfants de Vandoeuvre	France
Federal Research Center for Pediatric Hematology, Moscow	Russia
Sydney Children's Hospital	Australia
Department of Hematology and Marrow Transplant, Centre Pierre et Marie Curie, Alger	Algeria
The Children's Hospital at Westmead, Sydney	Australia
Hospital Clínico di Salamanca	Spain
Hematology and Hemotherapy Service, Clinica Puerta de Hierro	Spain
Hematolog Service, Niño Jesus Children's Hospital	Spain
Fundación Favaloro, Buenos Aires	Argentina
Chaim Sheba Medical Center	Israel
Schneider Children's Medical Center of Israel	Israel
Department of Haematological Medicine, GKT School of Medicine, Kings College Hospital London	United Kingdom
Constantiaberg Medi-Clinic, Cape Town	South Africa
Our Lady's Children's Hospital, Dublin	Ireland
Sheffield Teaching Hospitals NHS Trust, South Yorkshire Region (Adult) BMT Programme	United Kingdom
Birmingham Children's Hospital	United Kingdom
University Regensburg	Germany
Hematology Surgery Unit, Azienda Ospedaliero Universitaria Pisana	Italy
Institut d'Hématologie et d'Oncologie Pédiatrique, Lyon	France
Centro Trapianti Unico di CSE Adulti e Pediatrico A O Brotzu, Cagliari	Italy
Cape of Hope, Wroclaw	Poland
Hospital Gregorio Marañón, Madrid	Spain
Division of Paediatric, London	United Kingdom
Hematopoietic Cell Transplant Unit, Medical Park Antalya Hospital	Turkey
CHU Lapeyronie, Département d`Hématologie Clinique, Montpellier	France
CHU Bordeaux Groupe Hospitalier Pellegrin-Enfants, Bordeaux	France
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