Outcomes after related and unrelated umbilical cord blood transplantation for hereditary bone marrow failure syndromes other than Fanconi anemia

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ABSTRACT

Background
Allogeneic stem cell transplantation is the only curative option for patients with hereditary bone marrow failure syndromes. Umbilical cord blood is an alternative source of stem cells for allogeneic transplantation.

Design and Methods
This multicenter, retrospective study is based on data reported to the Eurocord Registry about patients with hereditary bone marrow failure syndrome who underwent umbilical cord blood transplantation.

Results
Sixty-four patients with hereditary bone marrow failure syndromes were transplanted from related (n=20) or unrelated donors (n=44). Diagnoses were Diamond-Blackfan anemia (21 patients), congenital amegakaryocytic thrombocytopenia (16 patients), dyskeratosis congenita (8 patients), Shwachman-Diamond syndrome (2 patients), severe congenital neutropenia (16 patients) and unclassified (1 patient). In the group of patients who received grafts from related donors, all patients but one received an HLA-matched sibling transplant. The median number of total nucleated cells infused was 5×10^7/kg. The cumulative incidence of neutrophil recovery at 60 days was 95%. Two patients had grade II-IV acute graft-*versus*-host disease, while the 2-year cumulative incidence of chronic graft-*versus*-host disease was 11%. The 3-year overall survival rate was 95%. In the group of patients who received grafts from unrelated donors, 86% had HLA-mismatched grafts and three received two umbilical cord blood units. The median number of total nucleated cells infused was 6.1×10^7/kg. The cumulative incidence of neutrophil recovery at day 60 in this group was 55%. The 100-day cumulative incidence of grade II-IV acute graft-*versus*-host disease was 24%, while the 2-year cumulative incidence of chronic graft-*versus*-host disease was 53%. The 3-year overall survival rate was 61%; better overall survival was associated with age less than 5 years (P=0.01) and 6.1×10^7/kg or more total nucleated cells infused (P=0.05).

Conclusions
In patients with hereditary bone marrow failure syndromes, related umbilical cord blood transplantation is associated with excellent outcomes while increasing cell dose and better HLA matching might provide better results in unrelated umbilical cord blood transplantation.

Key words: cord blood transplantation, hereditary bone marrow failure syndromes, engraftment, HLA compatibility.

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Introduction

Bone marrow failure is a rare disease in children; it can be idiopathic or less often hereditary.[1] Congenital disorders account for approximately one third of cases of bone marrow failure in childhood and include many different genetic diseases, such as Fanconi anemia, dyskeratosis congenita (DC),[2] Diamond-Blackfan anemia (DBA)[3] and others.[4-7] As new genetic tests are now available to make the diagnosis of these disorders possible, their presence should be carefully considered both in children and in adults before any treatment is started. Genomic instability may result in a defect of DNA repair machinery in Fanconi anemia or telomere dysregulation in DC. Mutations affecting ribosome assembly or function are associated with DBA[3] and Shwachman-Diamond syndrome (SDS).[5]

Although little is known about the pathogenesis of bone marrow failure in each of these disorders, allogeneic hematopoietic stem cell transplantation is the only curative treatment for most patients.[8,9] The classical source of hematopoietic stem cells used for transplantation in hereditary bone marrow failure syndromes is bone marrow, since the use of peripheral blood stem cells has been associated with an increased risk of chronic graft-*versus*-host disease (GVHD) and decreased survival rates in non-malignant disorders.[10]

Umbilical cord blood offers an alternative source of hematopoietic stem cells for patients lacking a suitable sibling or HLA-matched unrelated bone marrow donor.[11] This article reports an analysis of the outcome of umbilical cord blood transplantation (UCBT) in patients with hereditary bone marrow failure syndromes, excluding results for patients with Fanconi anemia which have been published previously.[12,13]

Design and Methods

Inclusion criteria

All registered patients who received either a related or an unrelated UCBT for hereditary bone marrow failure syndromes other than Fanconi anemia were included in this study.

This retrospective study is based on data reported to the Eurocord Registry from 32 centers, through a questionnaire concerning the characteristics of the patients, umbilical cord blood units, diseases and grafts and the outcomes of the transplants. The Eurocord Registry has collected data on UCBT performed within and outside Europe since 1989; more than 7,000 transplants have been registered. Using this data-base we identified centers which had performed UCBT for hereditary bone marrow failure syndromes and sent them a questionnaire asking for permission to enter retrospective data in the study; 32 centers gave their consent (the list of participating centers is reported in the acknowledgments section). All data were checked by a Eurocord medical coordinator and entered into the data-base after contacting the transplant centers to collect any missing information.

End-point definitions

The main end-point was overall survival, defined by the time between the date of transplantation and the date of death from any cause or the date of the last follow-up for survivors. The others end-points were neutrophil and platelet recovery, graft failure, and incidences of acute and chronic GVHD. The data of neutrophil recovery was defined as the first of 3 consecutive days with a neutrophil count of 0.5×10^9/L or more; the date of platelet recovery was defined as the first of 7 consecutive days with an unsupported platelet count of 20×10^9/L or more. Graft failure was defined as the absence of hematopoietic recovery at day 60, second transplantation or autologous reconstitution. Acute GVHD was defined and graded according to international criteria. Chronic GVHD was evaluated considering only patients surviving more than 100 days after transplantation with sustained donor engraftment, using previously published criteria.[14]

The conditioning regimens were divided into myeloablative and reduced intensity regimens.[15] Patients were considered to have received myeloablative conditioning when they were given a busulfan dosage of 8 mg/kg or more or total body irradiation at a cumulative dosage greater than 6 Gy; all other conditioning regimens were considered as reduced intensity.

Chimerism was evaluated in the first 3 months after UCBT as reported by the centers or after, in the case of secondary graft failure. Full donor chimerism was defined as the presence of more than 95% of donor cells; mixed chimerism was defined as the presence of more than 5% and less than 95% donor cells, while autologous reconstitution was defined as the presence of less than 5% of donor cells. The method used for chimerism analyses varied according to the centers and included a polymerase chain reaction-based assay, analyzing selected polymorphic short tandem repeat loci, HLA typing, cytogenetics, and fluorescent *in situ* hybridization analysis.

Statistical analysis

The reference date for analyses was March, 2010. This was the date of last follow-up. A cumulative incidence function, with death as a competing event, was used to estimate neutrophil and platelet recovery and the occurrence of acute and chronic GVHD. The Kaplan-Meier method was used to estimate overall survival. For continuous variables, the median was used as the cut-off point.

Univariate proportional hazard regression models were used to identify prognostic factors influencing neutrophil recovery and overall survival after unrelated donor UCBT. The following variables were analyzed: age (<5 years *versus* ≥5 years), HLA compatibility (6/6 and 5/6 *versus* 4/6 and 3/6), ABO match (matched *versus* major and minor incompatibility), number of previous transfusions (<20 *versus* ≥20 red blood cell and/or platelet transfusions), time between diagnosis and UCBT (<29.5 *versus* ≥29.5 months), number of total infused cells (<6.1×10^7/kg *versus* ≥6.1×10^7/kg) and number of infused CD34 cells (<3×10^5/kg *versus* ≥3×10^5/kg). A stepwise backward (Wald) procedure was used to construct a set of independent predictors of each end-point. All predictors with a P value less than 0.05 were considered to be statistically significant. Multivariate analysis was not performed because of the limited number of patients.

The statistical analyses were performed with SPSS15.0 (SPSS Inc. Chicago, IL, USA) and R version 2.9.0 (R Development Core Team (2009), Vienna, Austria) software packages.

Results

From 1994 to 2008, 64 patients with hereditary bone marrow failure syndromes were reported to Eurocord Registry from 32 transplant centers. The patients were separated into two groups: 20 patients who received a related sibling UCBT and 44 patients who received an unrelated allograft. The groups were analyzed separately without any attempt to make comparisons between the two groups because of the heterogeneity of the diseases and different outcomes related to the differences of HLA matching.

Results of cord blood transplantation from related donors

Patient, disease and transplant characteristics

Table 1 details the patient, disease and transplant characteristics for recipients of related UCBT.

The conditioning regimen varied according to transplant center and disease: 16 patients received a myeloablative conditioning regimen based on busulfan (n=16, dosage ranging between 14 and 20 mg/kg) associated with cyclophosphamide (n=14) and/or fludarabine (n=4) and/or thiotepa (n=5). Anti-thymocyte globulin was associated with myeloablative conditioning in seven cases. A reduced intensity conditioning regimen was administered to four patients: in two cases, the regimen included cyclophosphamide (total dose lower than 200 mg/kg) associated with anti-thymocyte globulin, in one case it included cyclophosphamide, monoclonal antibody and anti-thymocyte globulin, while the remaining patient received fludarabine, cyclophosphamide and anti-thymocyte globulin. GVHD prophylaxis consisted of cyclosporine either alone or in combination with methotrexate, steroids or mofetil mycophenolate.

Engraftment

Nineteen out of the 20 patients engrafted. One patient died at day +43 without achieving neutrophil recovery. The cumulative incidence of neutrophil recovery was 95%

Table 1. The characteristics of patients receiving related or unrelated UCBT.

Variables	Related n=20	Unrelated n=44
Age (years) – (total=20/44), median (range)	5.7 (2-12)	5 (0.3-26)
Gender – male – (total=20/44), n (%)	12 (60)	28 (64)
Weight (kg) - (total=20/36)*, median (range)	19 (9-30)	14 (5-60)
Cytomegalovirus positive (patients) – (total=20/44), n (%)	10 (52)	28 (64)
Diseases, n (%)		
Diamond-Blackfan syndrome	13 (65)	08 (18)
Congenital amegakaryocytic thrombocytopenia	03 (15)	13 (30)
Dyskeratosis congênita	02 (10)	06 (14)
Severe congenital neutropenia	01 (5)	15 (34)
Schwachman-Diamond syndrome	01 (5)	01 (2)
Unclassified hereditary bone marrow failure syndrome	0	01 (2)
Transfusion (red cells and/or platelets), n (%)		
0-20units	08 (48)	22 (51)
>20 units	09 (52)	21 (49)
Previous treatment, n (%)		
No treatment	04 (22)	3 (7)
Prednisone-based	12 (67)	17 (41)
Others (G-CSF/cyclosporine/ATG/androgens/immunoglobulin)	02 (11)	22 (52)
ABO donor/patient, n (%)		
ABO match	10 (56)	21 (49)
Major incompatibility	04 (22)	12 (28)
Minor incompatibility	04 (22)	10 (23)
HLA[1] compatibility – single UCBT (total=20/40)*, n(%)		
6/6 match	19 (95)	04 (10)
5/6 match	0	23 (58)
4/6 match	0	12 (30)
3/6 match	01 (5)	1 (3)
HLA[1] compatibility – double UCBT (total=3), n		
02 units 6/6 match	0	1
01 unit 5/6 match – 01 unit 4/6 match	0	1
02 units 4/6 match	0	1
Time: diagnosis-transplant (months), median (range)	64 (5-149)	29 (1.75-239)
Conditioning regimen, n (%)		
Reduced intensity	04 (20)	14 (32)
Myeloablative	16 (80)	30 (68)
GVHD prophylaxis, n (%)		
Cyclosporine alone	09 (47)	6 (14)
Cyclosporine-based (methotrexate/steroid/MMF)	10 (53)	34 (77)
Infused cells, median (range)		
Total nucleated cells ($\times 10^7$/kg); (total=19/42)*	5.0 (0.8-10.0)	6.1 (0.32-18)[2]
CD34 ($\times 10^5$/kg); (total=15/28)*	1.7 (0.35-10.0)	3.0 (0.06-9.4)[2]

*G-CSF: granulocyte colony-stimulating factor; ATG: anti-thymoglobulin; UCBT: umbilical cord blood transplantation; GVHD: graft-versus-host disease; MMF: mycophenolate mofetil; [1]HLA: antigen level HLA-A and B and allele level HLA-DRB1; [2]The number of cells included the double grafts. * some missing data for these variables.*

on day 60 and the median time to neutrophil engraftment was 25 days (range, 8 to 43 days). The cumulative incidence of platelet recovery was 85% on day 180 and the median time to this recovery was 38 days (range, 13 to 97 days) (Table 2). Chimerism results were available for 14 patients. Twelve patients reached full chimerism and two patients (one each with DBA and congenital amegakaryocytic thrombocytopenia [CAMT]) reached mixed chimerism. One patient with mixed chimerism (the one with CAMT) at the first analysis had secondary graft failure and received a bone marrow transplant from the same donor 208 days after UCBT; he is alive 25 months after the second allograft. The other patient (the one with DBA) is alive 65 months after UCBT with autologous reconstitution and full hematologic recovery. Of the two patients with mixed chimerism, the patient with DBA received myeloablative conditioning, while the patient with CAMT received reduced intensity conditioning. The patient with primary graft failure received myeloablative conditioning.

Table 2. Outcomes of patients who received related or unrelated UCBT.

Variables	Related (n=20)	Unrelated (n=44)
Neutrophil recovery–n (%)	19 (95)	25 (57)
Time, days–median (range)	25 (8-43)	24 (7-67)
Cumulative incidence at day 60, %	95	55
Platelet recovery–n (%)	18 (90)	23 (52)
Time- days, median (range)	38 (13-97)	51 (11-152)
Cumulative incidence at day 180, %	85	50
Chimerism before day 100, n (%)		
Full donor	12 (86)	20 (65)
Mixed	2 (14)	4 (13)
Autologous reconstitution	-	7 (22)
Acute GVHD - n(%)		
0-I	18 (90)	29 (66)
II	0	8 (18)
III	1 (5)	2 (5)
IV	1 (5)	5 (11)
Cumulative incidence at day 100,[1] %	5	24
Chronic GVHD, (total=19/25), n	**2**	**13**
Limited	-	5
Extensive	2	8
Cumulative incidence at 2 years, %	11	53
Follow up – months, median (range)	62 (12-186)	45 (4-147)
Overall Survival at 2 years, %	95 (95%CI3: 85-100)	61 (95%CI: 47-75)
Diagnosis - alive/dead		
Diamond Blackfan Anemia	13/0	3/5
CAMT	2/1	9/4
Dyskeratosis congenita	1/1	0/6
Severe congenital neutropenia	1/0	11/4
Shwachman Diamond syndrome	1/0	1/0
Unclassified HBMFS	-	1/0
Causes of death by diagnosis		
Rejection	1DC	3DBA, 1SCN, 2CAMT, 1DC
GVHD	-	1DC
Toxicity[2]	-	2DBA
Hemorrhage	-	2DC, 1CAMT
Infections	-	3SCN, 1DC, 1CAMT
Lung fibrosis	1 CAT	-
Unknown	-	1DC

GVHD: graft-versus-host disease; CI: confidence interval; CAMT: congenital amegakaryocytic thrombocytopenia; HBMFS: hereditary bone marrow failure syndrome; [1]acute GVHD grade II –IV; [2]toxicity: veno-occlusive disease; acute respiratory distress syndrome.

Graft-versus-host disease

Acute GVHD was observed in only two patients. One had grade III and the other had grade IV acute GVHD. Both patients were children, transplanted with an HLA identical cord blood unit; the cumulative incidence of chronic GVHD at 2 years was 11%; two patients developed extensive chronic GVHD (Table 2, Figure 1).

Overall survival

The estimated 3-year overall survival was 95% (95%CI: 85-100%) (Figure 2). The median follow-up time was 62 months (range, 12 to 186 months). There were two deaths. One patient with DC died from rejection and infection, the other with CAMT died from lung fibrosis more than 10 years after transplantation. Although myeloablative conditioning was given to both patients who died, the limited number of events precludes the possibility of finding any correlation between the type of conditioning used and survival or survival with remission of the original disease.

Results of cord blood transplantation from unrelated donors

Patient, disease and transplant characteristics

Table 1 details patient, disease and transplantation characteristics for recipients of unrelated UCBT. Two patients with DC and CAMT received unrelated UCBT as rescue for graft failure after having previously received an unrelated bone marrow transplantation. The patient with DC died of a fungal infection, without neutrophil engraftment, 32 days after the unrelated UCBT. The patient with CAMT engrafted and is alive 89 months after UCBT.

Treatments before transplantation are listed in Table 1. All patients with severe congenital neutropenia (SCN) received granulocyte colony-stimulating factor treatment before the transplant. Three patients received two umbilical cord blood units.

The conditioning regimen varied according to transplant center and disease: 30 patients received myeloablative conditioning based on total body irradiation (>6 Gy) (n=2) or busulfan (n=28, dose ranging between 8 and 20 mg/kg) associated with cyclophosphamide (n=23) or fludarabine (n=4) or melphalan (n=1). Anti-thymocyte globulin was associated with myeloablative conditioning in 23 cases. A reduced intensity conditioning regimen was administered to 14 patients: in six cases it included cyclophosphamide (total dose <200 mg/kg) + anti-thymocyte globulin (n=2) or associated with busulfan (total dose <6 mg/kg) (n=2) or fludarabine (n=2); in the remaining eight cases reduced intensity conditioning was based on fludarabine + melphalan and anti-thymocyte globulin (n=5) or fludarabine associated only with anti-thymocyte globulin (n=2) or monoclonal antibody (n=1). Myeloablative conditioning was given to five patients with DBA, five with DC, six with CAMT, 13 with SCN, and one with SDS, while reduced intensity conditioning was given to three patients with DBA, one with DC, seven with CAMT, two with SCN and one with unclassified congenital aplastic anemia.

Other transplant characteristics are listed in Table 1. In particular, GVHD prophylaxis in three quarters of patients consisted of cyclosporine in combination with methotrexate, steroids or mycophenolate mofetil.

Engraftment

The 60-day cumulative incidence of neutrophil recovery

was 55% and the median time to neutrophil engraftment was 24 days (range, 7 to 67 days). The 180-day cumulative incidence of platelet recovery was 50% with a median time to engraftment of 51 days (range, 11 to 152 days).

Chimerism results were available for 31 patients: 20 patients had full donor chimerism, four patients had mixed chimerism and seven patients had autologous reconstitution. In three patients mixed chimerism was transient and followed by full donor chimerism; one patient with mixed chimerism (with SCN) had secondary graft failure 1 month after transplantation; he subsequently received a double UCBT and is alive after 39 months. Three patients (1 with SCN, 1 with CAMT and 1 with DBA) with autologous reconstitution died, two due to infection and marrow failure (one each with CAMT and DBA) and one due to viral infection (the patient with SCN). One patient (with CAMT) with autologous reconstitution received a related peripheral blood haploidentical stem cell transplant and is alive after 44 months. Two patients for whom information on chimerism is not available are alive 4 months (SCN) and 84 months (CAMT) after UCBT, and one (with DBA) had 70% donor chimerism at the 1-year evaluation.

Primary graft failure occurred in 17 (39%) patients; 12 of them died. Among the five surviving patients, four had autologous reconstitution and one was alive 122 months after a second stem cell transplantation. The numbers of patients were too small to make any correlations between engraftment and number of HLA incompatibilities or the number of cells infused.

Graft-versus-host disease

The 100-day cumulative incidence of grade II-IV acute GVHD was 24%. The 2-year cumulative incidence of chronic GVHD was 53%; it was extensive in eight out of 25 cases (Table 2; Figure 1).

Overall survival

The overall survival rate at 3 years was 61% (95% CI: 47-75%) with a median follow up at 45 months (range, 4 to 147 months) (Figure 2). The causes of death are listed in Table 2.

Nineteen patients died, 13 of whom had received myeloablative conditioning and six reduced intensity conditioning. Nineteen patients had graft failure, ten of whom had received myeloablative conditioning and nine reduced intensity conditioning. Four patients had mixed chimerism: three had received myeloablative conditioning and one had had reduced intensity conditioning. Seven patients had autologous reconstitution, three after myeloablative conditioning and four after reduced intensity conditioning. Because of the heterogeneity of the diseases, changes in transplant practices over time and the small numbers of patients it was impossible to find any correlation between outcome and the conditioning regimen employed.

Two patients had acute leukemia before transplantation. One had SCN and was transplanted in complete remission before unrelated UCBT; 83 months after the transplant, this patient is alive in remission with limited chronic GVHD. The other had DBA; he had refractory disease before transplantation and died from graft failure. Two patients had myelodysplastic syndrome before transplantation. One woman had SCN and at the time of unrelated UCBT had refractory anemia with excess of blasts. The transplant was successful but she developed limited chronic GVHD and died of a fungal infection 1 year after UCBT. The other patient also had SCN with juvenile myelomonocytic leukemia; she died of graft failure 2 months after UCBT.

In univariate analysis two variables were associated with improved overall survival: age under 5 years (RR: 0.29, range 0.1-0.8, P=0.018) and a higher number of total nucleated cells infused (≥ 6.1×10^7/kg: RR: 0.31, range 0.11-0.86, P=0.03). The overall survival at 3 years was 37% (95% CI: 17-57%) in patients given an unrelated donor UCBT with a lower dose of total nucleated cells (<6.1×10^7/kg) and 81% (95% CI: 63-99%) for those receiving a higher dose (≥6.1×10^7/kg) (P=0.01) (Figure 3).

Related and unrelated cord blood transplants by type of disease

There were 21 patients with DBA: 13 received a related UCBT and eight an unrelated UCBT. All DBA patients

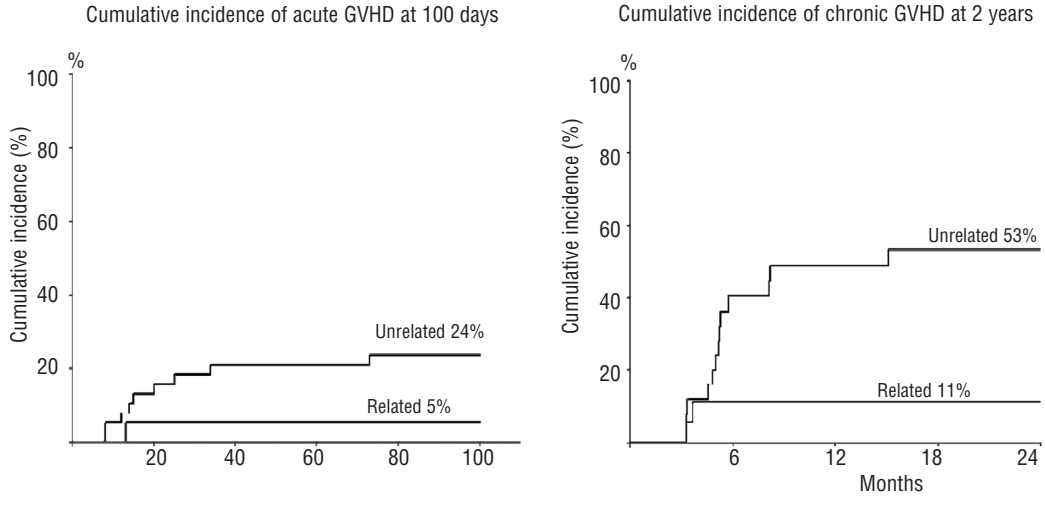

Figure 1. Cumulative incidence of acute GVHD at 100 days and of chronic GVHD at 2 years after UCBT in patients transplanted with grafts from a related or unrelated donor.

who received a related graft are alive with a median follow-up of 65 months (range, 12 to 186 months). Of the patients with DBA who had an unrelated UCBT, three patients are alive with a median follow-up of 31 months (range, 28 to 57 months).

In the DC group, all patients died except one who is alive at 126 months after an HLA-matched sibling UCBT. Two patients had a related UCBT and one died 1 month after transplantation of a fungal infection. In the group given unrelated grafts, three had been conditioned with cyclophosphamide (120 mg/kg), busulphan (16 mg/kg) and anti-thymocyte globulin; death occurred 4, 3 and 39 months post-transplant from GVHD, an unknown cause and hemorrhage from gastrointestinal angiodysplasia, respectively. Two patients received fludarabine (100 and 125 mg/m^2), busulphan (8 mg/kg) and anti-thymocyte globulin. These patients died of rejection and hemorrhage 2 months post-transplant. One patient received fludarabine (150 mg/m^2), cyclophosphamide (50 mg/kg) and anti-thymocyte globulin and died 1 month post-transplant of a fungal infection.

There were 16 patients with SCN, one of whom had a related UCBT, whereas the other 15 were given unrelated grafts. Three patients were transplanted for leukemia or myelodysplastic syndrome. The others (13 patients) were transplanted because of a lack of response to granulocyte colony-stimulating factor and 11 are alive (1 who had had a related transplant and 10 who had had an unrelated UCBT). The median follow-up was 41 months (range, 4-142 months).

There were 16 patients with CAMT (3 of whom had a related transplant and 13 who had an unrelated transplant). Of the three given a related transplant, two are alive at 18 and 25 months after the transplant and one died 124 months after transplantation. Of the 13 patients with CAMT who received an unrelated UCBT, four died within 2 months after transplantation and the others are alive with a median follow-up of 65 months (range, 25-121 months).

Discussion

Hereditary bone marrow failure syndromes other than Fanconi anemia are rare diseases in children and this explains the relatively low number of patients transplanted with allogeneic cord blood cells. This study, although being the largest reported so far, suffers from some limitations related to the relatively small number of patients and the retrospective nature of the study with transplants performed over a very long time interval (1994-2008). During this long period many changes have been observed including more refined selection of patients, new methods of conditioning, GVHD prevention and treatment as well as optimization of supportive care. Despite these limitations, we think that it is important to report our results in the attempt to make some recommendations for the future.

Our data indicate that UCBT is an excellent option for children with hereditary bone marrow failure syndromes when the donor is an HLA-matched sibling donor. Our results are in agreement with those of a previously published analysis which compared outcome of patients undergoing HLA-identical sibling UCBT with that of HLA-identical sibling bone marrow transplant recipients and showed similar overall survival in children with malignant and non-malignant diseases.[16] Banks of related cord blood have been established; they are not, however, sufficiently developed despite the excellent results observed not only in marrow failure but also in other hereditary disorders

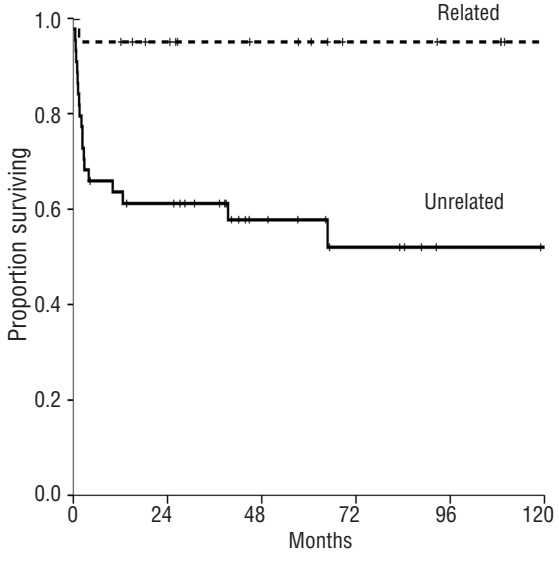

Figure 2. Overall survival of recipients of related or unrelated UCBT. The estimate overall survival at 3 years in patients transplanted with a related graft was 95% [95% confidence interval (CI) 85-100%] whereas that in the group transplanted with an unrelated graft was 61% (95% CI 47-75%).

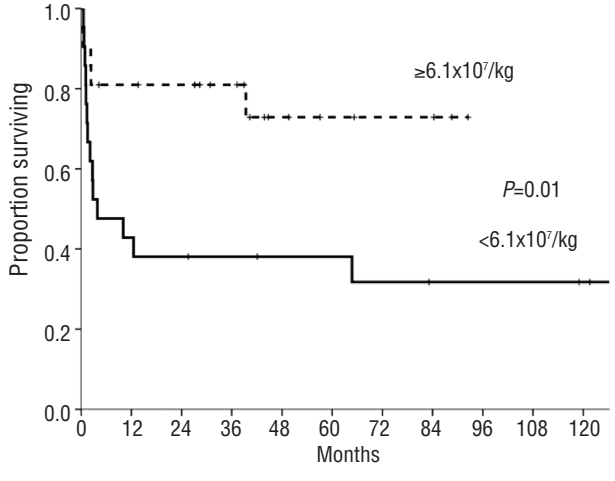

Figure 3. Overall survival in patients given an unrelated donor UCBT according to the number of total nucleated cells infused. The overall survival at 3 years was 37% (CI 17-57%) for patients given a graft with less than 6x10^7/kg total nucleated cells and 81% in patients receiving 6x10^7/kg or more (*P*=0.01).

such as hemoglobinopathies, metabolic disorders and congenital immune deficiencies.[17,18] Another factor in favor of freezing cord blood cells from an HLA-identical sibling is the absence of risk for the donor.

An important observation is that the risk of graft failure after unrelated UCBT was high in this cohort of patients. The risk of rejection can be overcome by better selection of the cord blood units and by modifications of the conditioning regimen. We previously showed, in non-malignant diseases, that it was necessary to increase the number of nucleated cells and $CD34^+$ cells infused and to decrease the number of HLA mismatches.[19] The current recommendation is to infuse more than 4×10^7 nucleated cells/kg and choose a donor with no more than one HLA mismatch defined by antigen typing for HLA class I loci and allele typing for HLA-DRB1. Importantly, we confirm in this small series of patients that a higher cell dose is associated with a better survival; unfortunately the number of patients was too small to study the influence of number of HLA mismatches in the donor/recipient pair or the impact of previous transfusions. If a cord blood unit with enough number of cells cannot be found a double cord blood transplant should be prospectively evaluated. In our series only three patients were transplanted with two units and all died without signs of engraftment. Other approaches aimed at facilitating engraftment can be used in phase I-II protocols,[20] including *ex vivo* expansion with copper chelators and cytokine cocktails,[21] intra-bone injection of the cord blood graft[22] or Notch ligand *ex vivo* expansion.[23] Greater HLA histocompatibility of the units selected for transplantation should also be able to improve the outcome of patients with hereditary bone marrow failure syndromes given an unrelated UCBT.

Modifications of the conditioning regimen might also contribute to improve outcomes. As conditioning with fludarabine, low-dose total body irradiation and low-dose cyclophosphamide has improved outcomes after unrelated UCBT in Fanconi anemia,[17] it is reasonable to speculate that a similar conditioning regimen could be used in hereditary bone marrow failure syndromes other than Fanconi anemia. In our series of patients, this hypothesis was impossible to analyze because of the large variety of conditioning regimens used in a small number of patients. It would be very important in the future to reach a consensus on a common conditioning protocol for each disease category.

Our results in DBA seem to be comparable with outcomes reported after transplantation with other sources of hematopoietic stem cells.[24,25] In our series, all 13 patients with DBA given a related UCBT and, three out of eight given an unrelated UCBT, are alive. The Centre of International Blood and Marrow Transplant Registry (CIBMTR) reported outcomes of 61 patients with DBA; 41 (67%) were transplanted from an HLA identical sibling and 20 (33%) from an unrelated bone marrow donor. The 3-year overall survival of the CIBMTR series was 76% when the donor was an HLA-matched sibling and 39% when the donor was an unrelated volunteer.[24]

Results of bone marrow transplantation in DC are extremely poor because of the underlying disease which is associated with a high incidence of both early and late fatal complications, mainly of pulmonary and vascular origin.[26-28] In our series of eight patients, all patients but one died. This outcome is similar to that previously reported in the literature, with very few patients surviving long-term after bone marrow transplantation. The indication for hematopoietic stem cell transplantation in DC is controversial and there is not currently a well-defined method for preventing late complications due to the underlying genetic disease.

The indications for offering UCBT to our patients with SCN were lack of response to granulocyte colony-stimulating factor therapy and/or evolution towards either myelodysplastic syndrome or leukemia. Our results in this subgroup of patients also seem to be comparable to those obtained with bone marrow transplantation, supporting the concept that UCBT is a suitable option for these patients.[29,30]

The results for patients with a diagnosis of CAMT or SDS also show that umbilical cord blood is a valid alternative to stem cell transplantation, the outcome of UCBT recipients being comparable to that in patients receiving unrelated bone marrow donor.[31-34]

In conclusion, these results show that UCBT is a reasonable option for the treatment of patients with hereditary bone marrow failure syndromes, especially if a sibling donor is used. In patients given an unrelated UCBT, only cord blood units containing a high number of cells and with stringent HLA matching should be considered to improve the results.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

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Appendix

In addition to the authors' institutions, the Eurocord-EBMT transplant centers were as follows: Hôpital d'enfants de la Timone, Dr. Gerard Michel, Marseille, France; Hospital Vall d'Hebron, Dr. José Sanches de Toledo Codina, Barcelona, Spain; Akdeniz University Medical School, Dr. M. Akif Yesilipek, Antalya, Turkey; Pediatric University Teaching Hospital, Dr. Sabina Sufliarska, Bratislava, Slovakia; St. Mary's Hospital, Dr. Josu de la Fuente, London, United Kingdom; Startship Hospital Hematology/Oncology, Dr. Lochie Teague Auckland, New Zealand; Hôpital Saint-Justine, Dr. Michel Duval, Montreal, Canada; Hospital Amaral Carvalho, Dr. Vergilio Colturato, Jaú, Brazil; Hospital for Children & Adolescents, Dr. Ulla Pihkalla, Helsinski, Finland; University Hospital, Dr. Bernhard Kremens, Essen, Germany; Hospital de la Santa Creu i Sant Pau, Dr. Isabel Badell Serra, Barcelona, Spain; University Children`s Hospital, Dr. Johan Arvidson, Uppsala, Sweden; Inst. Portugues de Oncologia do Porto, Dr. Antônio Campos, Porto, Portugal; Inst. Portugues Oncologia, Dr. Manuel Abecasis, Lisboa, Portugal; Ospedale Infantile Regina Margherita, Dr. Franca Fagioli Torino, Italy; King Faisal Specialist Hospital & Research Centre, Dr. Mahmoud Aljurf, Riyadh, Saudi Arábia; University Hospital Motol, Dr. Petr Sedlacek, Prague, Czech Republic; Edmond & Lily Safra Children`s Hospital, Dr. Amos Toren, Tel-Hashomer, Israel; Hôpital Robert Debre, Dr. Jean-Hugues Dalle, Paris, France; Universitaetsklinikum, Dr. Arndt Borkhardt, Düsseldorf, Germany; Niño Jesus Children`s Hospital, Dr. Miguel Angel Diaz, Madrid, Spain; Royal Hallamshire Hospital, Dr. John Snowden, Sheffield, United Kingdom; Hôpital de Hautepierre, Dr. P. Lutz, Strasbourg, France; University of California in San Francisco, Morton Cowan, USA; Miami Children's Hospital Bone Marrow Transplantation, Dr. Charles August, USA.

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