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Risk Factor Analysis of Outcomes after Unrelated Cord Blood Transplantation in Patients with Hurler Syndrome

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Allogeneic stem cell transplantation (SCT) is considered effective in preventing disease progression in patients with Hurler syndrome (HS). Unrelated umbilical cord blood (UCB) grafts are suggested as an alternative to bone marrow (BM) or peripheral blood stem cells (PBSC). We studied 93 HS patients receiving an UCB graft to analyze risk factors for outcomes. The median time from diagnosis to transplant was 4.6 months, median follow-up was 29 months, and median number of nucleated CB cells infused was 7.6×10^7/kg. Most of the patients received 1 or 2 HLA disparate grafts, and the most frequently used conditioning regimen was cyclophosphamide + busulfan (Bu/Cy). All patients received anti-T cell antibody. At post transplant day +60, the cumulative incidence of neutrophil engraftment was 85%. A younger age at transplant and a higher $CD34^+$ dose at infusion were favorably associated with engraftment. With the exception of 2 patients, all engrafted patients achieved full and sustained donor chimerism. The 3-year event-free survival (EFS) and 3-year overall survival (OS) rates were 70% and 77%, respectively. In a multivariate analyses, use of Bu/Cy and a shorter interval from diagnosis to transplant were predictors for improved EFS rate (82% for patients transplanted within 4.6 months after diagnosis compared to 57% for the rest). Improved outcomes from early transplantation and immediate availability of CB unit lead us to conclude that CB transplantation is a beneficial option, which should be considered expediently for children with HS.

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KEY WORDS: Hurler syndrome, (Umbilical) cord blood, Stem cell transplantation

INTRODUCTION

Hurler syndrome (HS) is the most severe phenotype in the spectrum of mucopolysaccharidosis type I (MPS I), a type of lysosomal storage disorder. These patients develop progressive and ultimately fatal multisystem deterioration, including psychomotor retardation, severe skeletal manifestations, and life-threatening cardiac and pulmonary complications because of severe deficiency or complete absence of the lysosomal enzyme alpha-L-iduronidase [1]. Because enzyme replacement therapy (ERT), available for MPS I patients since 2003, is not able to prevent central nervous system deterioration, allogeneic stem cell transplantation (SCT) is still considered as the treatment of choice in patients with HS [2,3].

Worldwide, over 500 SCTs have been performed in HS patients, making HS the most frequently transplanted inborn error of metabolism (IEM) [4,5]. Although significant successful clinical results have been reported in HS patients after SCT, provided the transplantation was performed early in life [6], the success of SCT has been limited by donor

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availability, high rates of graft failure, mixed chimerism, and treatment-related morbidity and mortality (TRM) [7]. To reduce these limitations, a risk factor analysis was performed in HS patients registered in the European Blood and Marrow Transplantation (EBMT) database [7]. In this European retrospective study, both T cell depletion and reduced-intensity conditioning (RIC) regimen were found to be risk factors for graft failure, whereas busulphan (Bu) pharmacokinetic targeting protected against graft failure. Recent studies, using cord blood (CB) as a stem cell source for SCT in IEM, showed high rates of full donor chimerism associated with normal enzyme levels postengraftment [8-11]. Because full donor chimerism and normal enzyme levels are suggested to be associated with a superior neurocognitive outcome after SCT, CB has been proposed as an alternative option or even preferential stem cell source in HS patients [6]. Still, little is known about the risk factors influencing various measures of outcome in HS patients after unrelated CB transplantation.

To be able to study a large series of HS patients and to perform a risk factor analysis for myelogenous engraftment and event-free survival (EFS) after unrelated CB transplantation, we conducted a collaborative retrospective analysis of umbilical cord blood transplantation (UCBT) performed in HS patients treated in multiple centers in Europe and at Duke University in the United States.

PATIENTS AND METHODS

Data Collection

This retrospective analysis is based on data reported to the Eurocord Registry from European and non-European centers through a standardized questionnaire that includes information about the patients, CB units, diseases, and transplant outcomes. Data from Duke University was collected for all consecutive transplants performed and registered to the institutional stem cell transplantation database and the Center for International Blood and Marrow Transplant Research (CIBMTR). The collected information was reviewed by 2 physicians and checked for computerized errors to ensure data quality. Overlaps between Eurocord database and Duke University were checked to eliminate overlap or duplicative reporting. All parents and or legal guardians of patients gave informed consent for UCBT according to the Declaration of Helsinki. The present study was approved by the Eurocord and Working Party Inborn Errors of European Blood and Marrow transplant group (EBMT). Patients treated at Duke University Medical Center were enrolled on treatment protocols approved by the hospital's institutional review board. Fourteen of the Duke patients were enrolled on the Cord Blood Transplantation Study (COBLT) supported by the National Heart, Lung Institute of the National Institutes of Health.

Criteria of Patient's Selection

The following criteria were required: (1) diagnosis of HS was confirmed by an increased urinary glycosaminoglycan excretion, a deficiency or absence of alpha-L-iduronidase in peripheral blood leukocytes, and the clinical phenotype; (2) transplantation with a nonexpanded, single, unrelated CB unit; (3) complete clinical data with at least 3 months of posttransplant follow-up; (4) transplants using myeloablative conditioning regimen performed between 1995 and 2007.

Definitions and Endpoints

The main endpoints were (1) EFS, defined as the time from transplantation to autologous reconstitution, graft failure, second transplant, or death; (2) overall survival (OS), defined as the time from transplantation until the date of death. Other endpoints were (1) neutrophil recovery and (2) acute or chronic graft-versus-host disese (aGVHD, cGVHD). Neutrophil recovery was defined as the first day of achieving a neutrophil count of $\geq 0.5 \times 10^9$/L for 3 consecutive days, and graft failure as no sign of neutrophil recovery or transient engraftment of donor cells within 60 days after transplantation or second transplants. HLA matching was scored using low or intermediate resolution typing for HLA Class I A and B and high-resolution typing for DRB1. Chimerism data was available during the first 3 months after UCBT and at last assessment of the patients. Full donor chimerism (on whole blood) was defined as the presence of more than 95% donor-derived hematopoietic cells, mixed chimerism if >10% and <95% were of donor origin and autologous recovery if <10% of cells were donor-derived cells. Data on the methodology of chimerism detection was not available. Enzymes were regarded normal when levels were normal according to the institutional reference range and heterozygous when the value was below the lower limit of normal but not within the patient range. It was called heterozygous when carriers of the disease are having subnormal enzyme levels as well. aGVHD at day 100 was diagnosed and graded according to published criteria [12] and cGVHD at 2 years was graded according to standard criteria [13] and evaluated in patients who survived at least 100 days with sustained engraftment.

Statistical Analysis

The duration of follow-up was the time to the last assessment for survivors. To analyze risk factors for outcomes, we considered variables associated with the recipient (median age at transplant, median weight

at time of transplantation, sex, pretransplant cytomegalovirus [CMV] serology status), the disease (median interval time from diagnosis to transplant, use of "enzyme replacement therapy" prior to transplant (at least 4 doses), the CB unit (HLA-disparity, and median collected and infused total nucleated cell [TNC] and $CD34^+$ cell doses), and the transplant (year of transplant, use of Bu/cyclophosphamide (CY), and the type of GVHD prophylaxis). Because of sample size, the median interval between diagnosis and CBT, median collected and infused nucleated cells, and $CD34^+$ were taken to dichotomize the group. Cumulative incidence curves were used for neutrophil recovery, aGVHD, and cGVHD in a competing risk setting, because death is a competing event [14]. Gray test was used for univariate comparisons [15]. Probabilities of EFS and OS were calculated using the Kaplan-Meier estimate; the 2-sided log-rank test was used for univariate comparisons.

Factors associated with a *P*-value <.10 by univariate analysis (which are described in the Results section) and other relevant factors such as HLA matching and cell dose were included in multivariate analyses, using Cox proportional hazards for EFS and OS, and proportional subdistribution hazard regression model of Fine and Gray for neutrophil recovery [16]. Then, a stepwise regression was performed using a threshold of .05. All tests were 2-sided. The type I error rate was fixed at .05 for determination of factors associated with time to event outcomes. Risk factor analysis for aGVHD and cGVHD was not performed because of the relative small number of events. Statistical analyses were performed with SPSS (SPSS Inc., Chicago, IL) and S-Plus (MathSoft, Inc, Seattle, WA) software packages.

RESULTS

Patients, Donor, and Transplant Characteristics

Ninety-three patients with HS receiving an unrelated CBT between 1995 and 2007 met the eligibility criteria in the EUROCORD and Duke databases. The baseline patient, donor, and transplantation characteristics are shown in Table 1. Overall, the patients were young and small, with a median age of 1.3 years and median weight of 11.5 kg. The majority of patients were serologically negative for CMV pretransplant. The majority of patients were transplanted with HLA mismatched grafts at 1 (54%) or 2 (27%) loci. Two patients had received a previous unsuccessful BM transplant. A total of 40 patients of this report have been previously published [7-10].

The majority of children were conditioned with myeloablative chemotherapy using Bu/Cy with antityymocyte globulin (ATG) (89%) or Campath-1H. All patients received cyclosporine (CsA) containing prophylaxis against GVHD with steroids (75%) as the most common second agent. Given their small size and young age, these patients were transplanted with relatively large doses of cord blood cells, median 10.4×10^7 cells/kg at collection and 7.6×10^7 cells/kg infused. Likewise, the delivered (infused) median CD34 dose was 2.6×10^5/kg.

Table 1. Baseline Patient, Donor, and Transplantation Characteristics

Baseline Characteristics*			
Patient characteristics			
	n	%	Missing
Overall	93		
Sex (male/female)	48/45	52	0
CMV serology (negative)	64	78	11
Previous transplant	2	2	0
	Median	Range	
Age at SCT (years)	1.3	0.2-5	0
Interval diagnosis-transplant (months)	4.6	1-35	1
Follow-up post- SCT (months)	29	3-140	0
Weight (kg)	11.5	5-22	2
Donor characteristics			
	n	%	Missing
Overall	93		
HLA-matching			3
6/6	13	14	
5/6	49	54	
4/6	24	27	
3/6	4	5	
ABO compatibility	36	44	11
	Median	Range	
Cell dose			
Collected NC ($\times 10^7$/kg)	10.4	3-33	2
Collected $CD34^+$ ($\times 10^5$/kg)	3.6	0.5-130	3
Infused NC ($\times 10^7$/kg)	7.6	2-27	2
Infused $CD34^+$ ($\times 10^5$/kg)	2.6	0.4-104	3
Transplantation characteristics			
	Median	Range	Missing
Year of SCT	2004	1995 - 2007	0
	n	%	
Overall	93		
Conditioning regimen			4
Bu/Cy	77	87	
Other	12	13	
GVHD prophylaxis			5
CSA ± Pred	67	75	
CSA/MMF	13	15	
CsA/MTX	8	10	
Serotherapy (ATG: 85 or Campath: 4)	89	100	4

Bu indicates busulphan; CMV, cytomegalovirus; CsA, cyclosporine; Cy, cyclophosphamide; GVHD, graft-versus-host-disease; HLA, human leukocyte antigen; kg, kilogram; MMF, mycophenolate mofetil; MTX, methotrexate; NC, nucleated cells; Pred, prednisolone; SCT, stem cell transplantation.

*CB transplantation was performed in the following centers: Duke (47), Manchester (9), Utrecht (8), Dublin (4), Marseille (3), Barcelona (2), London (2), Madrid (2), Mineapolis (2), Israel (2), Argentina (2), Japan (2), Gent (1), Nancy (1), Paris (1), Padua (1), Prague (1), Helsinki (1), Australia (1), New Zealand (1).

Neutrophil and Platelets Recovery and Chimerism

Cumulative incidence function (CIF) of neutrophil recovery at day 60 was 85%, with 82% engrafting at or before day 42. The median time to neutrophil recovery

was 22 days (10-46). In a univariate analysis probability of neutrophil recovery had a positive impact from (1) younger age at SCT (95% for <1.3 years and 78% for ≥1.3 years; $P = .04$); (2a) higher $CD34^+$ cell dose at infusion (91% for $>2.6 \times 10^5$/kg at infusion and 81% for $<2.6 \times 10^5$/kg at infusion; $P = .004$); (2b) higher $CD34^+$ cell dose at collection (95% for $>3.6 \times 10^5$/kg at infusion and 79% for $<3.6 \times 10^5$/kg at infusion; $P = .001$); (3) year of transplantation (<2004: 79% versus ≥2004: 91%, $P = .05$). Of note, all 13 patients in this series receiving an HLA identical (6 of 6) CB graft recovered neutrophil (median 22, range: 10-46 days: same as for the whole group) recovery compared to 82% for the remainder of patients (P = ns). In multivariate analysis, younger age at transplantation and high infused (postthaw) $CD34^+$ cell dose were independent predictors of early neutrophil recovery ($P = .01$ and $P = .002$, respectively; Table 3).

Eleven patients experienced either autologous reconstitution (n = 6) or secondary graft failure (n = 5) during the 3 months after UCBT. Four of these patients subsequently died because of graft failure (3) or disease progression (1). One patient is alive with disease. Six patients were retransplanted. Chimerism data at 3 months posttransplant was available for 73 of the 79 engrafting patients, and showed that 65 were full chimera, whereas 8 had mixed chimerism. At last assessment, chimerism data was available for all 65 patients who were "alive and engrafted." Sixty-four of them were full chimeras, whereas 2 had mixed but high chimerism (donor chimerism level of 90% and 94% in whole blood cells). Normal alpha-L-iduronidase enzyme level in the blood was found in 97% of "alive and engrafted" patients. The primary and secondary endpoints are further outlined in Table 2.

aGVHD and cGVHD

CIF of aGVHD at day 100 was 31% ± 5%. Twenty-five percent of the patients had a maximum grade II, whereas 3% had grade III and 2% had grade IV. Of the many variables analyzed, only the number of TNC infused (20% for $<7.6 \times 10^7$/kg versus 36% for $\geq 7.6 \times 10^7$/kg; $P = .08$) appeared to be a predictor for the occurrence of aGVHD. CIF of cGVHD at 3 years was 36% (10 extensive; and 12 limited). HLA matching did not have an impact on the incidence of aGVHD or cGVHD.

EFS and OS

The probability of 3-year EFS and 3-year OS rate after unrelated CB transplantation were 70% and 77%, respectively. The probability of 3-year EFS (in univariate analyses) was positively influenced by a shorter interval between diagnosis and transplantation ($P = .007$) and a conditioning regimen containing Bu/Cy ($P = .002$). Additionally, fully matched (6/6) grafts were associated with 100% EFS ($P = .06$) compared to 65% ± 7% and 64% ± 10%, for 5/6 and 4/6 matched grafts, respectively. The results are also illustrated by Kaplan-Meier curves and Log Rank test depicted in Figure 1b-d. Importantly, multivariate analysis also demonstrated that both the interval between diagnosis and transplantation as well as the conditioning regimen were statistically associated with better 3-year EFS ($P = .046$ and $P = .011$, respectively). HLA-matching was not significant in multivariate analyses ($P = .2$). In this group of patients receiving relatively high cell doses from the UCB graft, cell dose was not predictive of survival (Table 3). No uni- and multivariate predictors were found concerning the endpoint probability of 3-year OS.

Enzyme replacement therapy (given in 23 patients prior to CBT) was not found to be a predictor for any of the endpoints, although there appears to be trend for higher EFS (83 ± 8 versus 63 ± 6: $P = .19$) and lower GVHD (19 ± 9 versus 35 ± 6: $P = .16$) in the ERT group. Engraftment was not influenced by ERT.

Causes of Death

Twenty-one patients (23%) died within 3 years post-SCT, 18 from a transplantation related cause (5 viral infection, 3 hemorrhage, 3 multiorgan failure, 3 graft failure, 2 acute respiratory distress syndrome, 1 GVHD, 1 interstitial pneumonitis), and 1 from disease progression after graft failure. In 2 patients, the cause of death was unknown.

Table 2. Primary and Secondary Endpoints

Endpoints			
Primary endpoints			
	n	%	
3-year OS	72	77	
3-year EFS	65	70	
Secondary endpoints	n	%	Missing
Neutrophil recovery*	79	85	0
Chimerism (at latest follow-up) ‡			
Full donor	56	97	7
Mixed	2	3	
Enzyme levels‡			
Normal	61	97	2
Heterozygous	2	3	
CIF of acute GVHD (grade II-IV)♣	29	31	0
(grade III-IV) ♣	5	5	
CIF of chronic GVHD at 3 years¶	22	36	0

EFS indicates event-free survival; GVHD, graft-versus-host-disease; OS, overall survival; CIF, cumulative incidence function.
*Median days 22 (range: 10–46).
‡Of patients alive and engrafted.
♣Absent: 33 (38%), grade I: 26 (30%), grade II: 22 (25%), grade III: 3 (3%), grade IV: 2 (2%).
¶Limited 12 (20%), extensive 10 (16%).

Table 3. Multivariate Predictors of 3-Year EFS and Neutrophil Recovery after First CBT

	3-Year EFS		
	HR	95% CI	*P*-Value
Interval Dx - Tx <4.6 versus ≥4.6 (months)	2.4	1.0-5.7	.046
Conditioning regimen Bu/Cy versus other	0.3	0.1-0.7	.011
HLA-disparity identical versus mismatched	1.8	0.7-4.3	.200
NC dose* <7.6 versus ≥7.6 ($\times 10^7$/kg)	0.9	0.4-1.9	.737
	Neutrophil Recovery		
	HR	95% CI	*P*-Value
Age at Tx <1.3 versus ≥1.3 (years)	0.5	0.3-0.9	.010
$CD34^+$ dose* < 2.6 versus ≥ 2.6 ($\times 10^5$/kg)	2.1	1.3-3.4	.002
Year at Tx <2004 versus ≥2004	1.4	0.9-2.1	.188

CI indicates confidence intervals; Dx, diagnosis; EFS, Event-free survival; HLA, human leucocyte antigen; HR, hazard ratio; NC, nucleated cell; Tx, stem cell transplantation; CBT, cord blood transplantation
*At infusion. Statistically significant *P*-values are underlined.

DISCUSSION

This Eurocord-Duke University collaborative study on the outcomes of cord blood transplants for HS showed that a shorter interval between diagnosis and transplant and a conditioning regimen containing Bu/Cy predicted higher EFS rate. Importantly, almost all "alive and engrafted" patients achieved full donor chimerism and normal enzymes levels in circulating leukocytes. These findings are particularly important because high donor chimerism and enzyme levels improve long-term functional outcomes of children with HS [6,17,18]. Despite small numbers, 6/6 matched (class I on low and class II on high resolution) CV grafts may improve the outcome as well. The relatively high rate of cGVHD in this study, although mainly limited, might be a concern.

Similar to findings from other studies [19-21], a higher and faster neutrophil recovery was associated with CB units providing a higher CD34 cell dose. Although, the CD34 cell dose did not have an impact on the OS or EFS. It is possible that if multiple CB units are available, selecting a unit with a higher cell dose may decrease the time to engraftment and some of the risks associated with prolonged neutropenia. In addition, younger age at transplantation was an individual predictor for higher neutrophil recovery. An explanation for this might be the stage of disease, as GAG storage in the marrow is suggested to be a factor influencing the stem cells homing [22]. Younger children might have less storage in the BM matrix. Also, younger children are physically smaller and tend to receive higher cell doses from the UCB graft.

Until recently, high rates of graft failure and mixed chimerism were reported in studies analyzing the outcome of SCT for HS. A recent European retrospective study showed that these graft failures were mainly associated with RIC regimen and T cell depletion [7]. In this largest study so far, including 146 HS patients, mainly patients receiving BM or PBSC grafts (about 90%) were analyzed. Recently, Prasad et al. [10] demonstrated an 1-year and 5-year OS of 77.3% and 74.5%, respectively, in 45 HS patients receiving a CB transplantation [10]. These results suggest that graft outcomes are at least comparable to the outcomes of non-T-depleted BM/PBSCs transplants (related and unrelated) after myeloablative conditioning reported previously (60%-75%) [7,17,23]. A comparison study in this rare disease, including the all HS patients from the CIMBTR, (EMBT) Promise, and Eurocord databases, receiving an unrelated/related BM and unrelated CBT, would be the best way to study the influence of cell source. Although not statistically significant, probably because of small numbers, but in line with other CB studies [21], using HLA-matched cord blood grafts might influence the outcome: all 13 HS patients receiving on intermediate resolution typed fully matched graft are alive and having full donor chimerism in this study. This suggests that in the future, when CB banks have increased their inventory, the outcomes of these transplants might further improve. For HS, and probably for other IEM as well, the rapid availability of an allogeneic donor appears to be essential, because a longer time interval between diagnosis and transplantation negatively influences the EFS rate. This will probably not only influence the graft outcome data, but also the longer term outcomes, because of progression of disease. Obviously, it is important that these patients need to be tolerating full-intensity conditioning. For those who cannot, ERT might be used to improve patients' tolerance of full-intensity conditioning, for example, where there is a severe associated cardiomyopathy [24]. As found in this study, as in others, ERT does not worsen outcome [24,25], and might therefore be considered in those having a poor clinical condition. In this subgroup of patients it has been shown that ERT can bring them in a better clinical condition [24]. A higher performance scale prior to CBT will probably influence the outcome of this subgroup, as found by others [10]. But for those who can tolerate a full ablative regimen, CBT should not be delayed.

Although the aGVHD and cGVHD rates in this study are similar to children receiving a CBT for acute leukemia [21], this might be a concern because HS patients do not have any advantage from having GVHD. Moreover, it has even been suggested that (extensive) cGVHD might influence the longer term outcomes (eg, neuropsychologic and orthopedic late complications of allogeneic HSCT). In the recently published European series on SCT in HS, reported cGVHD rates were lower, but in that series the

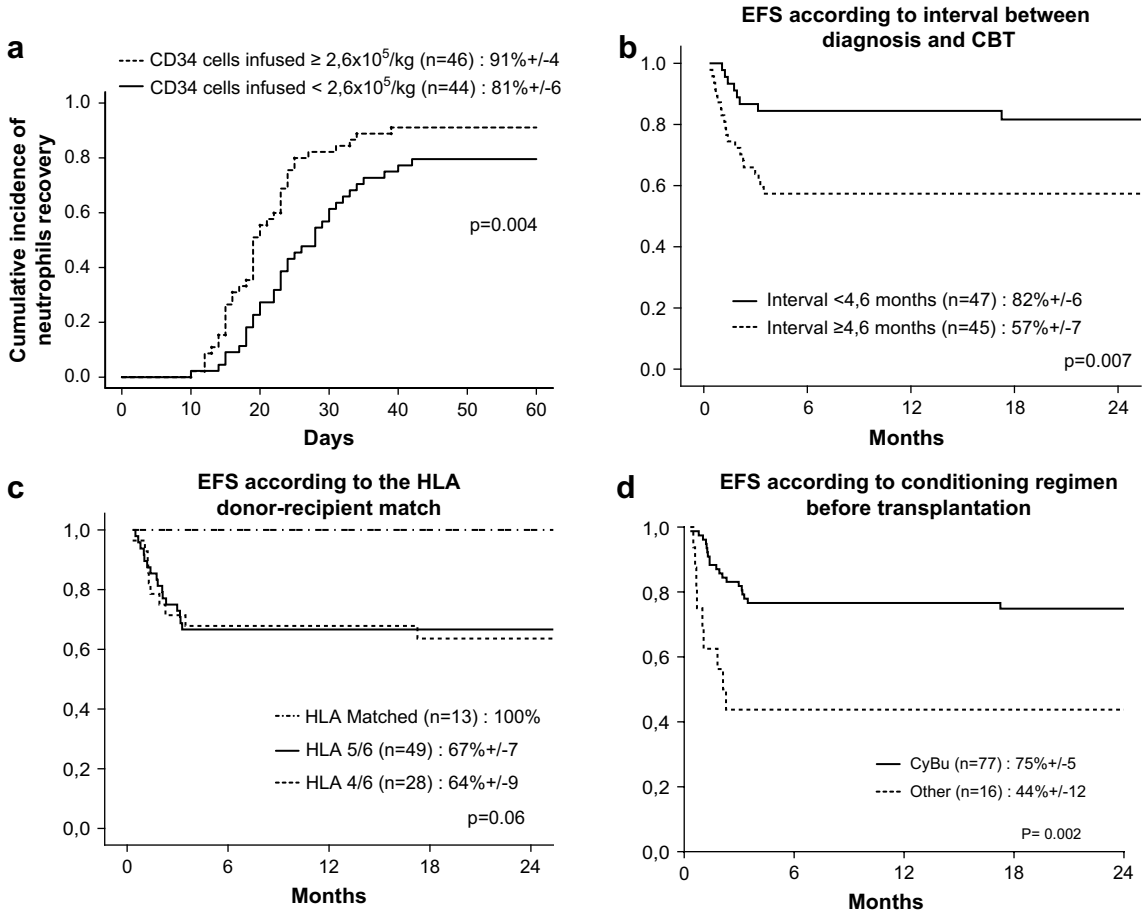

Figure 1. Kaplan-Meier curves for neutrophil recovery according to the number of CD34 cells infused/kg (a), EFS according to the delay between diagnosis and transplantation (b), EFS according to the HLA donor-recipient match (c), and EFS according to conditioning regimen before transplantation (d).

proportion of patients with mixed chimerism was high (30%) [7]. Others reported rates similar as found in this cord blood study [17,26], but these reported data are relatively old in comparison to the European series: worse matching marrow grafts and other transplant practices, like including total body irradiation (TBI) in the conditioning of these young children, might have influenced the GVHD rates as well. On the other hand, in adults, comparing outcomes of matched BM versus CB in a recent meta-analyses showed a favorable effect of using CB on the incidence of cGVHD [27]. Comparison studies of the outcomes (graft outcomes and long-term outcome parameters) of unrelated marrow versus unrelated cord blood versus matched sibling donor, may help resolve the question about the impact of graft source on the incidence of cGVHD. Selection of higher matched donors when the CB banks have extended their inventory or better post-SCT immunosuppressive treatment for this group of patients, might be strategies to influence the occurrence of cGVHD in these children. Limiting the cell dose of the infused CB graft might be a strategy as well, because an infused nucleated cell (NC) dose $>7.6 \times 10^7$/kg showed to be a trend to higher incidence of GVHD.

High rates of full donor chimerism and normal enzyme levels were found in this study, demonstrating that the use of unrelated cord blood is highly associated with higher sustained engraftment in HS patients compared to patients receiving BM as a stem cell source [28]. In studies using BM, the mixed chimerism rate ranged between 30% and 40%. These high rates of full donor chimerism after CBT have been reported in other studies on "CBT in IEM" as well [8-11]. This is an intriguing observation, and might suggest a stronger "graft-versus-marrow" effect of CB cells in comparison to BM/PBSC. The higher degree of HLA-mismatch of the CB grafts (a majority of 1 or 2 mismatches on intermediate resolution typing), might exert this stronger graft-versus-marrow effect without increasing the rate of GVHD. In other words, the "window" between a strong graft-versus-marrow and clinical GVHD might be wider, probably because of the more naïve phenotype of the T cell in the CB graft. This probably stronger "graft-versus-marrow effect" is in line with the lower incidence of relapses after mismatched CBT in children with acute leukemia in comparison to BM [21]. Alternatively, CB-derived natural killer (NK) cells have been demonstrated to be functionally "mature" with comparison of even better

cytolytic activity compared with the BM-derived NK cells [29,30]. This might exert a stronger graft-versus-marrow effect as well. Another explanation might be the more pluripotential capability of the CB stem cell, relative to the adult BM/PB stem cell, with higher proliferative potentials [31-33]. Some animal studies have demonstrated that the addition of mesenchymal stem cells to the SCT product results in less graft rejection, because of the immunomodulating potential of these cells [34,35]. Because mixed chimerism is associated with lower leukocyte enzyme levels, which in turn, leads to worse long-term outcomes, the level of donor chimerism might be an important aspect in the decision on selecting a graft. Further studies to determine the impact of cell source and enzyme levels on the long-term outcomes in neuropsychologic, orthopedic, cardiac, and other organ systems should be carried out.

In conclusion, unrelated cord blood is a good alternative stem cell source for SCT in HS patients, and it might even be the preferred cell source. This is because unrelated cord blood transplantation is (1) associated with full donor chimerism in almost all engrafted patients, which might influence the long-term outcomes; (2) because of its fast availability and the fact that it appears that the interval between diagnoses and transplantation positively influences the outcome. A concern however, might be the relatively higher rate of, mainly limited, cGVHD found in this study. Better matching and selection possibilities in the future might further improve these outcomes by increasing the number of CB units banked.

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