Early and late outcomes after cord blood transplantation for pediatric patients with inherited leukodystrophies

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Key Points

- A 6-year overall survival of 61% was observed in leukodystrophy patients after cord blood transplantation.

- Mismatched cord blood donors, symptomatic disease, and lower PS before cord blood transplantation were predictors of lower survival.

Leukodystrophies (LD) are devastating inherited disorders leading to rapid neurological deterioration and premature death. Hematopoietic stem cell transplantation (HSCT) can halt disease progression for selected LD. Cord blood is a common donor source for transplantation of these patients because it is rapidly available and can be used without full HLA matching. However, precise recommendations allowing care providers to identify patients who benefit from HSCT are lacking. In this study, we define risk factors and describe the early and late outcomes of 169 patients with globoid cell leukodystrophy, X-linked adrenoleukodystrophy, and metachromatic leukodystrophy undergoing cord blood transplantation (CBT) at an European Society for Blood and Marrow Transplantation center or at Duke University Medical Center from 1996 to 2013. Factors associated with higher overall survival (OS) included presymptomatic status (77% vs 49%; P = .006), well-matched (≤1 HLA mismatch) CB units (71% vs 54%; P = .009), and performance status (PS) of >80 vs <60 or 60 to 80 (69% vs 32% and 55%, respectively; P = .003). For patients with PS≤60 (n = 20) or 60 to 80 (n = 24) pre-CBT, only 4 (9%) showed improvement. Of the survivors with PS >80 pre-CBT, 50% remained stable, 20% declined to 60 to 80, and 30% to <60. Overall, an encouraging OS was found for LD patients after CBT, especially for those who are presymptomatic before CBT and received adequately dosed grafts. Early identification and fast referral to a specialized center may lead to earlier treatment and, subsequently, to improved outcomes.

Introduction

Leukodystrophies (LD) are a heterozygous group of rare inherited diseases that affect the development and maintenance of brain myelination. Although the age of onset and clinical course varies among this group of diseases, all inherited leukodystrophies are characterized by progressive neurological deterioration and premature death. They often arise from either a lysosomal storage disease (LSD), such as metachromatic leukodystrophy (MLD) and globoid cell leukodystrophy–Krabbe disease (GLD), or a peroxisomal disorder such as X-linked adrenoleukodystrophy (X-ALD).

The full-text version of this article contains a data supplement.

Hematopoietic stem cell transplantation (HSCT) has been shown to arrest or slow disease progression for MLD, GLD, and X-ALD, particularly when performed in presymptomatic patients or patients with early-stage disease.[1,2] In patients with a LSD, HSCT works through engraftment of donor cells that can cross the blood-brain barrier, providing a source of cellular enzyme replacement through cross-correction of host cells by enzyme-replete donor cells.[3] Conversely, in X-ALD, in which the defected protein is not an enzyme but a transporter protein, the exact mechanism of action of HSCT is not completely understood.

Umbilical cord blood (CB), related or unrelated, provides an alternative source of hematopoietic stem cells for transplantation. After over 2 decades of experience, researchers have well described the benefits of CB. Particularly relevant to patients with LDs, a rapidly progressive disease, CB is readily available, allowing for shorter time to transplant. In patients with LDs, the early outcomes of umbilical cord blood transplantation (CBT) have been described.[4-10] These studies suggest that CBT is most beneficial when performed early, preferably before the onset of symptoms. Although it would be ideal to compare the early and late outcomes on the basis of cell source such as those performed for Hurler's disease,[11] this was not possible because of the very limited numbers of patients receiving other cell sources, leading us to focus on cord blood only. In this report, we describe the results of a collaboration among Eurocord, the European Society for Blood and Marrow Transplantation (EBMT), and Duke University to define risk factors and describe the early and late outcomes in a large cohort of patients with LDs (MLD, GLD, and X-ALD) treated after CBT.

Patients and methods

Data collection and patients

In this retrospective, multicenter study, patients (children and adults) with leukodystrophies (MLD, GLD, or X-ALD) who received related or unrelated donor CBT between September 1996 and August 2013 were included. Data were collected from the Eurocord Registry from EBMT centers through standardized questionnaires that included information about the patients, donors, diseases, and transplant outcomes. Data on patients from Duke University were collected through similar questionnaires as those used by the Eurocord-EBMT. Missing data were completed by institutional data managers. An additional follow-up questionnaire was developed for long-term outcomes and sent out to participating centers. Symptomatic patients were categorized into disease subtype on the basis of age of onset of symptoms; presymptomatic patients were categorized on the basis of age of onset of the index case in the family. MLD patients were classified as late infantile (0-4 years), early juvenile (4-6 years), late juvenile (6-16 years), or adult (>16 years). Patients with GLD were classified as early infantile (<6 months), late infantile (6-11 months), juvenile (1-16 years), or adult (>16 years). Patients with ALD were classified as childhood (0-10 years), adolescent (10-18 years), or adult (>18 years). All patients with ALD showed evident cerebral disease on magnetic resonance imaging (MRI) at time of transplantation. Part of this cohort (n = 70) has been reported in previous studies.[5,12,13] This study was performed in agreement with the Helsinki Declaration of 1975, revised in 2008. All patients or their legal representatives gave informed consent. Eurocord and the Working Party for Inborn Errors of EBMT approved the European part of this study. In the United States, approval was given by the institutional review board of Duke University.

Outcomes of interest

Outcomes of interest were overall survival (OS) and event-free survival (EFS). OS was defined as the time from transplantation to death. EFS was defined as time from transplantation to last assessment without an event. Events were considered to be autologous reconstitution (documentation of <5% donor-derived engraftment), graft failure (lack of neutrophil recovery or transient engraftment of donor cells after transplantation, requirement for a second transplant, or both), or death. All surviving patients were censored at date of last contact.

Other outcomes of interest were neutrophil recovery, defined as the first day of achieving a neutrophil count of $\geq0.5 \times 10^9$/L for 3 consecutive days, incidence of acute and chronic graft- versus-host disease (GVHD), donor chimerism, enzyme level (arylsulfatase A and galactocerebrosidase tested in blood cell lysates for MLD and GLD, respectively), very long chain fatty acid (VLCFA) level tested in blood cell lysates for X-ALD, and long-term outcomes. Acute GVHD grade II-IV at day 100 was diagnosed and graded according to published criteria.[14] Chronic GVHD at 5 years was graded according to standard criteria[15] and evaluated in patients who survived at least 100 days with sustained engraftment. Long-term outcomes included performance score (PS), either Lansky or Karnofsky on the basis of patient age, at 12 months and at latest follow-up time point; overall disease status (symptomatic, defined as clinical disease according to the local clinician, or presymptomatic, defined as no clinical disease according to the local clinician); descriptive neurological status (presence and severity of peripheral neuropathy, presence of seizures, mental development [tested by Bayley Scales of Infant Development, Stanford-Binet Intelligence Scale, Wechsler Preschool and Primary Scale of Intelligence—Revised, Wechsler Intelligence Scale for Children—III]), vision (normal, low: <20/60; blind: <20/400), hearing (normal, <25 dB hearing loss; mild hearing loss, 26-55 dB; severe hearing loss, >56 dB), and cerebral atrophy observed by magnetic resonance imaging [MRI]); incontinence; independence in daily living; school attendance; and school performance. Furthermore, gall bladder disease was registered for patients with MLD[16,17] and adrenal insufficiency for patients with X-ALD (as reported by local clinicians).

Statistical analysis

Probabilities of EFS and OS were calculated using the Kaplan-Meier estimate; the 2-sided log-rank test was used for univariate comparisons. Cumulative incidence curves were created for neutrophil recovery; acute GVHD and chronic GVHD were analyzed in a competing risk setting. In univariate analyses, we considered variables associated with the recipient (median age at transplant, median weight at time of transplantation, sex, pretransplant cytomegalovirus serology status), the disease (type of diagnosis, and median interval time from diagnosis or [in ALD only] first abnormal brain MRI to transplant), the cord blood unit (HLA disparity, and median collected and infused total nucleated cells and CD34$^+$ cell doses), and the transplant (year of transplant, use of myeloablation, antithymocyte globulin [ATG], and the type of GVHD prophylaxis). Factors associated with $P <.10$ in univariate analysis

Table 1. Baseline patient, donor, and transplantation characteristics

Characteristics	Baseline characteristics*	
	n	%
Patient		
Overall	169	
MLD	66	39.1
GLD	47	27.8
X-ALD	56	33.1
Child (<18 y)/adult	161/8	95.3/4.7
Sex (male/female)	118/51	69.8/30.2
Cytomegalovirus serology (negative)	127	77.9
	Median	**Range**
Weight, kg	19.5	2.74-75.0
Age at SCT, y		
Overall	5.1	0.1-43.3
MLD	4.3	0.1-22.7
GLD	0.6	0.1-16.7
X-ALD	8.2	2.4-43.3
Interval diagnosis-transplant, mo		
Overall	2.8	0.6-147.9
MLD	3.0	0.6-70.3
GLD	1.6	0.6-60.0
X-ALD	5.4	0.6-147.9
Performance score pre-SCT		
<60	29	19.6
60-80	29	19.6
>80	90	60.8
Donor	**n**	**%**
sCB	156	92.3
dCB	13	7.7
Unrelated/related	168/1	99.4/0.6
HLA matching		
6/6	27	18.1
5/6	56	37.6
4/6	65	43.6
3/6	1	0.7
CB cell dose	**Median**	**Range**
Collected NC, $\times 10^7$/kg	8.0	2.1-67.2
Collected $CD34^+$, $\times 10^5$/kg	2.7	0.01-28.5
Infused NC, $\times 10^7$/kg	5.7	1.2-50.3
Infused $CD34^+$, $\times 10^5$/kg	2.1	0.01-32.4
Transplantation	**n**	**%**
Conditioning regimen		
MAC	163	97
Bu/Cy/(TT)	135 (1)	
Bu/Fluda/(Cy)(Mel)(TT)	9 (4)(3)(3)	
Fluda/TT/Mel	3	
Bu/Mel/other	1	
TBI/Cy	4	

Table 1. (continued)

Characteristics	Baseline characteristics*	
	n	%
RIC	5	3
Fluda/Mel	1	
Mel/other	1	
Fluda/other	2	
Cy/Fluda/TBI	1	
GVHD prophylaxes		
CsA based	156	96.9
+steroids	34	
+MMF	29	
+Mtx	4	
Tacrolimus-based	5	3.1
+MMF	4	
+Mtx	1	
Serotherapy (ATG before day 0)	162	96.4
	Median	**Range**
Year of HCT	2006	1996-2013
Follow-up post SCT,† mo	76.3	3.3-211

ATG, anti-thymocyte globulin; Bu, busalfan; CsA, cyclosporine; Cy, cyclophosphamide; dCB, double cord blood; Fluda, fludarabine; MAC, myoablative conditioning; Mel, melphalan; MMF, mofetil; Mtx, methotrexate; NC, neutrophil count; RIC, reduced intensity conditioning; sCD, single cord blood; SCT, stem cell transplantation; TBI, total body irradiation; TT, thiotepa.

*CB transplantation was performed in the following centers: Duke (102), Utrecht (11), Marseille (6), Australia (6), Saudi Arabia (5), Madrid (4), Gent (4), Brussels (4), Paris (4), Milano (2), Murcia (2), Barcelona (2), Montréal (2), Budapest (2), Leiden (1), Leuven (1), Jerusalem (1), Porto (1), Hannover (1), Lisboa (1), Berlin (1), Manchester (1), Antalya (1), Poland (1), Nancy (1), Israel (1), and Bratislava (1).

†Median follow-up of survivors.

and factors considered relevant risk factors were included in multivariate analyses, using Cox proportional hazards for EFS, OS, neutrophil recovery, and GVHD. Subsequently, a stepwise regression analysis was performed using a threshold of 0.05. All statistical analyses were performed using SPSS (version 19; SPSS Inc., Chicago, IL) and R (version 3.32.0; R Foundation for Statistical Computing, Vienna, Austria) software packages. Figures were created with GraphPad Prism (version 7.02; GraphPad Software, La Jolla, CA).

Results

Patient, donor, and transplant characteristics

One hundred and sixty-nine patients were included: 66 MLD, 47 GLD, and 56 X-ALD. Overall, the median age at time of CBT was 5.1 years (range: 0.1-43.3); patients with X-ALD were the oldest, with a median age of 8.2 years, followed by MLD (4.3 years) and GLD (0.6 years). The majority of the patients received myeloablative conditioning (97%) with busulfan (Bu)/cyclophosphamide (Cy) as the most frequent regimen (83.4%). Ninety-two percent received a single CB graft, with a median total nucleated cell dose (TNC) of 5.7×10^7 cells/kg and a median $CD34^+$ dose of 2.1×10^5/kg. A cyclosporine-based regimen was used as GVHD prophylaxis in 97% of the patients, and 96% received ATG as serotherapy. Median follow-up for survivors was 76 months (range: 3-211). Patient, donor, and transplant characteristics are shown in Table 1.

Table 2. Primary and secondary endpoints

Endpoints	%	Events, n
Primary		
6-y OS overall	61	
MLD	67	
X-ALD	59	
GLD	55	
6-y EFS overall	59	
MLD	66	
X-ALD	56	
GLD	53	
Secondary		
Neutrophil engraftment (day 60)*	86.3	
Platelet engraftment (day 180)†	68	
Graft failure (primary/secondary)	3.6/8.3	6/14
Chimerism (within 100 d)		
Full donor	83.2	104
Mixed	16.8	21
CIF of acute GVHD		
Stage II-IV	35.3	59
Stage III-IV	20.2	21
CIF of chronic GVHD at 5 y	30.2	44
Limited/extended		28/15

CIF, cumulative incidence function.
*Median, 21; range, 11-83.
†Median, 52; range, 13-200.

Neutrophil and platelets recovery and chimerism

The cumulative incidence of neutrophil engraftment at day 60 was 86.3% (range: 81.2% to 91.7%; Table 2), with a median time to engraftment of 21 days (range: 11-83). In univariate analysis, factors associated with a higher probability of neutrophil recovery included shorter interval between diagnosis and CBT (≤2.84 months: 91.5%, vs >2.84 months: 80.4%; P = .01), higher infused $CD34^+$ cell dose (≤2.05 × 10^5/kg: 82.7%, vs >2.05 × 10^5/kg: 88.6%; P = .05), and higher infused TNC (≤5.73 × 10^7/kg: 82.7%, vs >5.73 × 10^7/kg: 88.9%; P = .008). The cumulative incidence of platelet recovery was 68 ± 6% at day 180, and the median time to platelet recovery (>20 000/μL) was 52 days (range: 13-200 days). Twenty patients (12%) experienced either autologous reconstitution (n = 6; 3.5%) or secondary graft failure (n = 14; 8%) during the first 3 months after CBT. Thirteen of these patients subsequently died because of disease progression (n = 3) or graft failure (n = 10). Eight patients received a second transplant using CB (n = 5), peripheral blood stem cells (n = 1), or not specified (n = 2) as the donor source. Of these, 6 patients survived long term, and 2 died (1 because of disease progression, and 1 transplant-related mortality). One patient with autologous recovery survived long term without a second transplant. Chimerism at day 100 was available for 125 out of 148 engrafted patients. Full chimerism was achieved in 104 (83.2%) of the patients, and mixed chimerism in 21 (16.8%). Chimerism at last assessment was available for all 100 survivors (full chimerism, n = 87; mixed chimerism, n = 13). Of patients who were "alive and engrafted," normal enzyme levels were found in 94.8% and 96.6%, for MLD and GLD, respectively.

Acute and chronic GVHD

The cumulative incidence of acute GVHD grades II-IV and III-IV at day 100 was 35.3% ± 7%, and 20.2% ± 8% (Table 2), respectively. Univariate analysis showed that a longer interval between diagnosis and CBT was associated with a higher probability of acute GVHD grade II-IV (47.6% for ≤2.84 and 25% for >2.84; P = .002). The cumulative incidence of chronic GVHD at 5 years was 30.2% ± 5% (15 extensive and 28 limited). In univariate analysis, higher PS at the time of CBT was associated with a higher incidence of chronic GVHD (12.1% for PS ≤ 60, 20.8% for PS 60-80, and 41.6% for PS > 80; P = .009; 65% was limited chronic GVHD). Only 6 of the patients with chronic GVHD and a lower PS before CBT (n = 2 for <60, and n = 4 for 60-80) were still alive at latest follow-up.
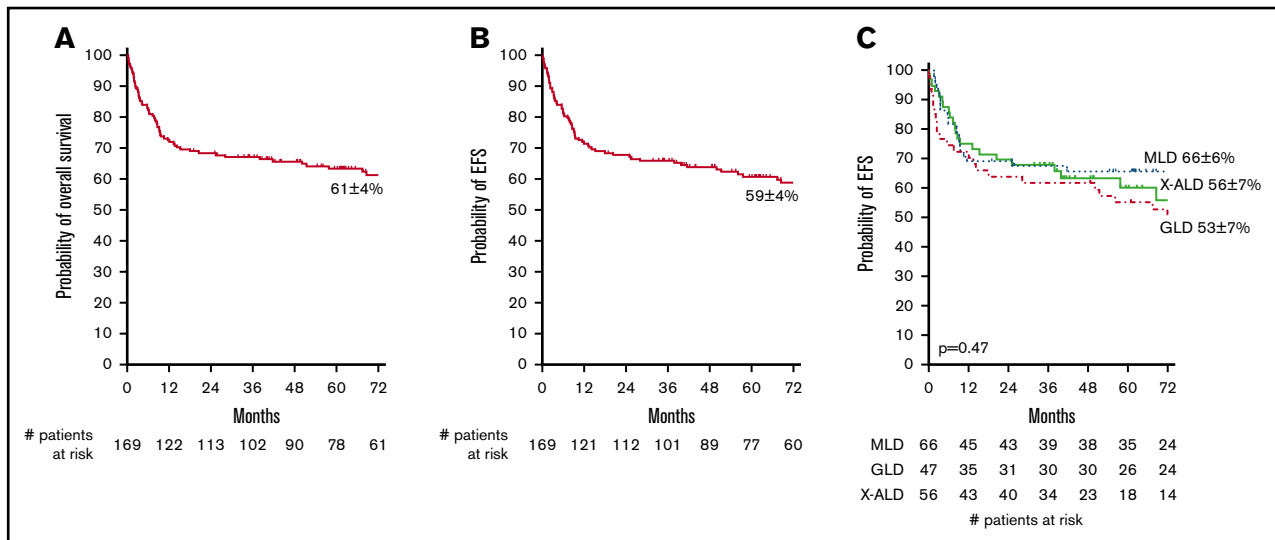
Figure 1. Six-year overall and event-free survival. (A) OS. (B) EFS. (C) EFS per LD type. Events for EFS were considered to be autologous reconstitution, graft failure, or death.

Table 3. Multivariate predictors of 6-year OS and EFS

6-year survival	HR	95% CI	P
OS			
HLA 0-1 vs ≥2 HLA mismatches	1.8	1.0-3.3	.04
Presymptomatic vs symptomatic	2.0	1.0-3.7	.04
Collected TNC ≥ 5.0 × 10⁵ vs collected TNC < 5.0 × 10⁵	1.5	0.7-3.2	.34
EFS			
HLA 0-1 vs ≥2 HLA mismatches	1.7	1.0-2.9	.059
Presymptomatic vs symptomatic	1.8	1.0-3.2	.057
Collected TNC ≥ 5.0 × 10⁵ vs collected TNC < 5.0 × 10⁵	1.6	0.7-3.4	.227

OS, EFS, and causes of death

The 1-year and 6-year OS among all patients was $73 \pm 3\%$ and $61 \pm 4\%$ (Figure 1A), respectively, with a median follow-up of 76 months (range: 12-211). Similar OS was observed for the 3 LD types. Improved OS was observed in patients with late-onset disease in MLD and early-onset disease in patients with GLD or X-ALD (supplemental Figure 1), although this should be interpreted with caution because classification of patients might have been based on an index case. In univariate analysis, several clinical factors were associated with improved OS including recipients of 5/6 or 6/6 HLA-matched grafts (71% vs 54% for 3-4/6 HLA-matched grafts; $P = .009$), absence of cerebral atrophy on MRI prior to CBT (68% vs 35% for patients with cerebral atrophy; $P < .001$), PS before CBT > 80 (69% in comparison with 55% and 32% for patients with PS 60-80 or <60, respectively; $P = .003$). Presymptomatic or mildly affected patients also experienced higher OS than did symptomatic patients (77% vs 49%; $P = .006$). OS was not influenced by year of transplantation (median 2006; $59 \pm 5\%$ vs $63 \pm 7\%$; $P = .44$). Further analysis revealed that differences in OS between presymptomatic and symptomatic patients were most notable in GLD and X-ALD patients (GLD: 78% vs 36%, $P = .02$; X-ALD: 88% vs 47%, $P = .02$; and MLD 70% vs 62%, $P = .64$). In multivariate analysis, recipients of 5/6 or 6/6 HLA-matched grafts (hazard ratio [HR], 1.8; 95% confidence interval [CI], 1.0-3.3; $P = .04$) as well as pre-symptomatic disease status (HR, 2.0; 95% CI, 1.0-3.7; $P = .04$) were significantly associated with higher OS at 6 years.

In the overall cohort, the 1-year EFS was $72 \pm 4\%$ and the 6-year EFS $59 \pm 4\%$ (Figure 1B). Although there was a trend toward improved EFS for patients with presymptomatic disease and those who received 5 or 6/6 HLA-matched grafts, no clinical factors were significantly associated with EFS in multivariate analysis (Table 3). Notably, presymptomatic GLD patients had significantly increased EFS in comparison with that of symptomatic GLD patients (78% vs 32%; $P = .009$; Figure 2).

Sixty-nine patients died within 6 years after CBT (MLD n = 23; GLD n = 25; X-ALD n = 21). Forty-three patients died of transplant-related causes (infection: n = 18; GVHD: n = 9; pulmonary disease: n = 7; multisystem organ failure: n = 4; or other: n = 5) and 21 from disease progression. Additional causes of death are provided in supplemental Table 1.
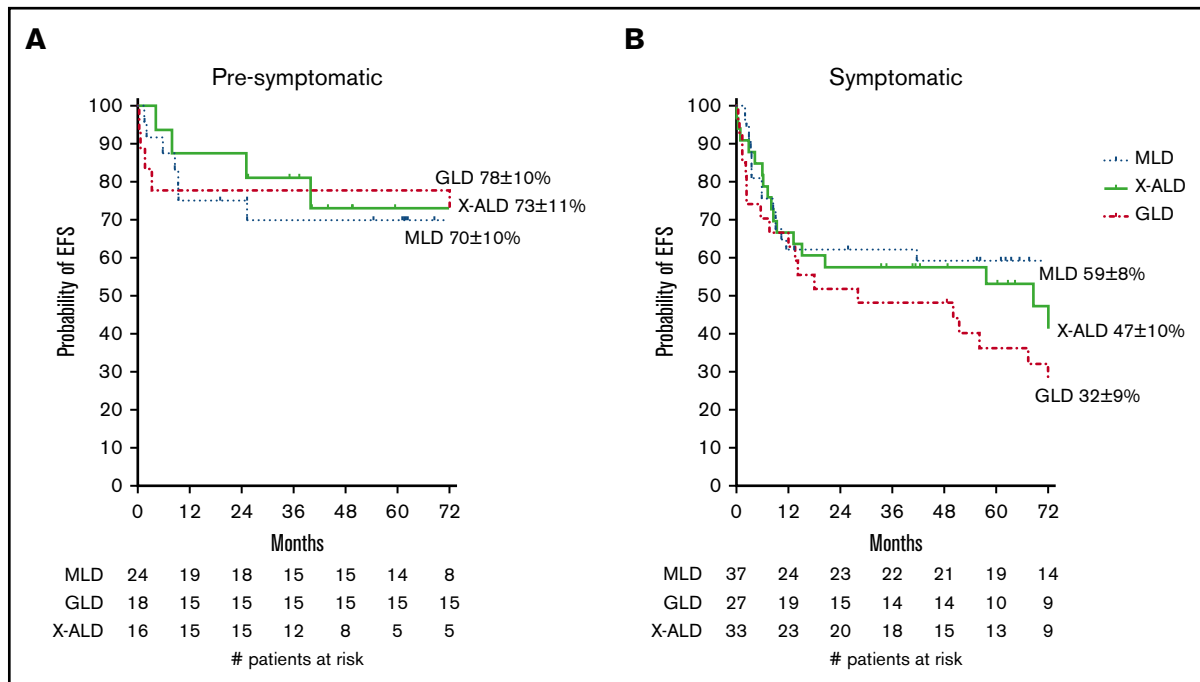
Figure 2. EFS for patients at time of CBT. EFS is given for presymptomatic (A) and symptomatic (B) patients. Events were considered to be autologous reconstitution, graft failure, or death.
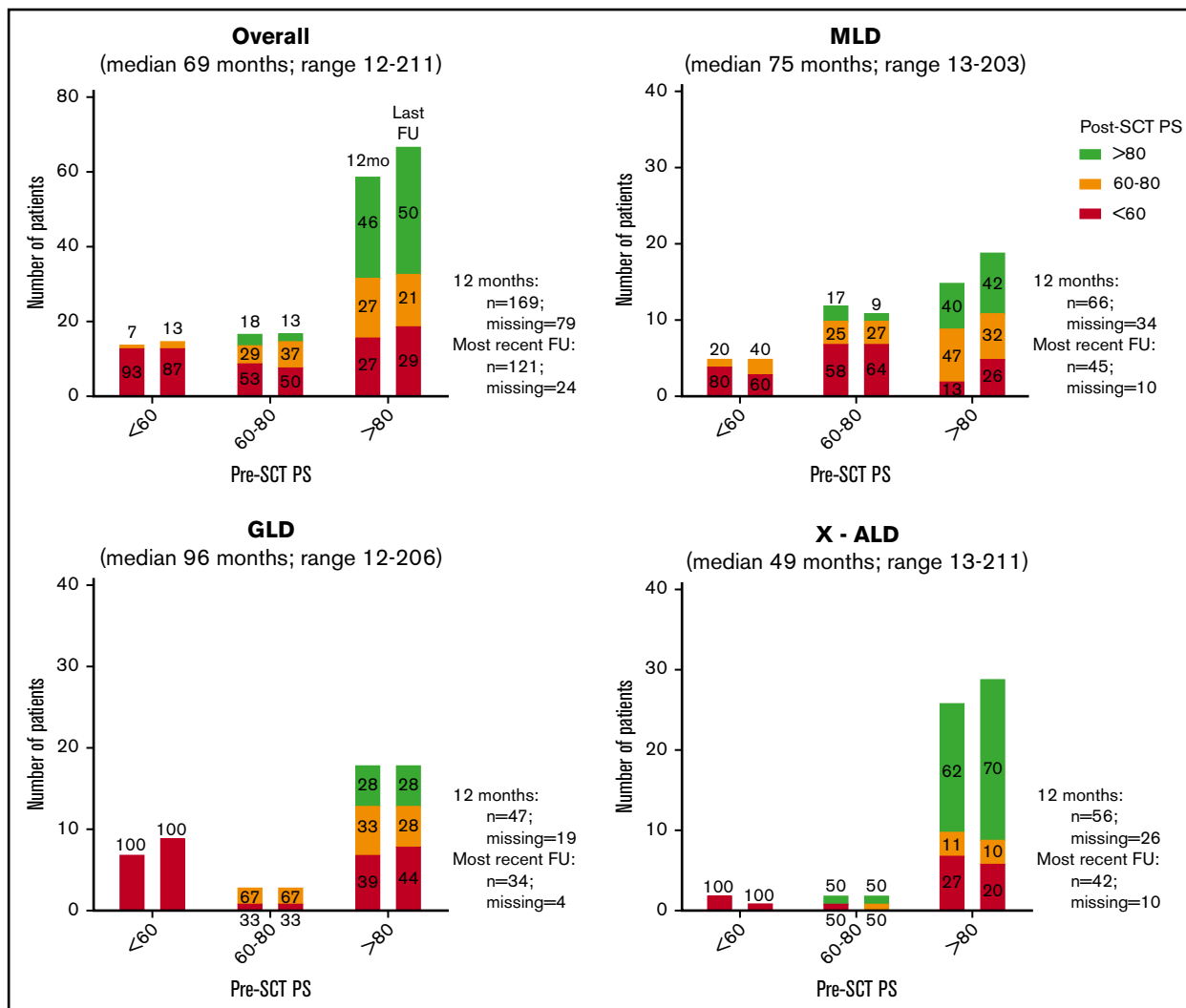
Figure 3. Performance scores before and after CBT at 12 months and at most recent follow-up. Most recent follow-up consists only of patients who survived ≥12 months. Percentages show proportions of patients of corresponding pre-HCT PS. All paired bars follow the sequence of 1 year and most recent follow-up.

Functional and disease-related outcomes

To compare functional outcomes after CBT, we used the pre- and posttransplant PS and retrospectively assigned disease status on the basis of symptoms present at the time point of interest. Pre- and posttransplant PS were available for 119 patients. Among survivors with normal pretransplant functional status (PS > 80), 50% had a PS > 80 at last follow-up (median 69 months; range: 12-211; Figure 3), and the remaining showed a decline in PS to 60-80 (20%) or <60 (30%). For patients with lower pretransplant PS (≤60, n = 20; 60-80, n = 24), only 4 patients demonstrated improved PS after CBT and at last follow-up. When decline in PS occurred after CBT, it most commonly occurred during the first year and was stable afterwards (Figures 3 and 4). Changes in performance scores according to LD type are shown in Figure 4. In addition, changes in performance score according to the different clinical phenotypes per LD can be found in supplemental Figure 2.

Data on disease-related outcomes was available for all patients pre-CBT (n = 169) and for 98 patients who survived more than 1

year post-CBT (Tables 4 and 5). In patients with enzyme testing results post-CBT, 93% and 95% of patients for MLD and GLD, respectively, achieved normal enzyme levels (arylsulfastase A or galactocerebrosidase), according to local references. In patients with LSDs (MLD and GLD), 40% and 18% of patients were presymptomatic pre- and post-CBT, respectively (Table 4). Of the presymptomatic patients, 62% remained without symptoms at last follow-up. Vision and hearing stabilized or improved in the majority of patients after CBT (94% and 96%, respectively). Seizures were reported in 24% of patients post-CBT. Neuropathy, as detected by clinical exam or symptoms, was absent or mild in 61.5% of patients pre-CBT and remained stable or improved in 72% post-CBT. Data on school performance were available for most patients alive at latest follow-up post-CBT (81%). In this primarily pediatric cohort, 28% were identified as having age-appropriate school performance. Additional educational support was provided to 71% of patients with available data. Gallbladder disease was observed in 12% (n = 3) of patients with MLD after CBT. All 3 patients required cholecystectomy. Comparatively, patients with

X-ALD appear to have better late outcomes (Table 5). Of presymptomatic patients, 100% remained without symptoms at last follow-up. Neuropathy was uncommon (absent or mild in 96%) pre-CBT and remained stable in 89%. Although hearing was rarely affected (96% with normal or mild hearing loss) and remained stable or improved in 93%, vision was affected more often. Normal vision was seen in 71% pre-CBT and worsened in 20% post-CBT. Seizures were reported in 18% post-CBT. Almost all patients (92.6%) experienced stable adrenal function. Data available on school performance showed that 74% had age-appropriate school performance; educational support was provided to 32%.

The most frequent interventions and complications after CBT were G-tube placement (13 with MLD, 20 patients with GLD, and 9 with X-ALD), followed by issues with dentition (9 with MLD, 14 with GLD, and 2 with X-ALD) and surgery (9 MLD, 9 GLD, and 2 X-ALD). Late pulmonary toxicity was seen in 16 patients (3 MLD, 4 GLD, and 9 X-ALD) and cardiac toxicity in 14 patients (5 MLD, 7 GLD, 2 X-ALD; supplemental Table 2).

Discussion

To the best of our knowledge, this retrospective study, spanning over 20 years of clinical experience, is the largest to describe both early and late outcomes after CBT in patients with leukodystrophies undergoing CBT. In this joint study of Eurocord, Inborn Errors Working Party EBMT, and Duke University, we demonstrate a promising 1-year and 6-year OS (73% and 61%, respectively) and EFS (72% and 59%, respectively). Importantly, we observed an OS at 6 years of nearly 80% in patients who were presymptomatic at time of CBT. Furthermore, the majority of these patients (53%) maintained a performance score >80 after CBT at latest follow-up. This confirms previous smaller analyses[6,18,19] showing that leukodystrophy patients transplanted prior to clinical symptoms experience long-term survival while maintaining cognitive and motor function, in comparison with symptomatic or nontransplanted patients who all will deteriorate or die prematurely. Our results emphasize the importance of early diagnosis and treatment.

We observed rapid and robust neutrophil and platelet engraftment, which supports other studies of CBT in LDs.[4,20] Time to neutrophil recovery was predicted by higher infused CD34$^+$ cell dose and higher infused TNC, as has been previously reported.[4,11,20] In multivariate analysis of OS, patients who received grafts matched at 5-6/6 HLA loci or who were presymptomatic at time of CBT experienced improved OS. Conversely, those with poor performance status were at higher risk for morbidity (supplemental Figure 3). Although a recent report described >95% of patients as alive and engrafted at 8 years after CBT for LSD in specialized centers,[21] these patients all met strict eligibility criteria and received harmonized conditioning regimens and GVHD prophylaxis. It is important to acknowledge that our report reflects transplants that occurred in nearly 30 centers over a timeframe of almost 20 years. An incompletely understood observation was the higher incidence of (mainly limited) chronic GVHD in the higher performance status group of patients. This may be due to the very low number of survivors in the lowest performance group (only 9 of 29 survived). It is likely that refinements in patient eligibility and donor selection and improvements in supportive care that have occurred over the years will translate into improved outcomes in contemporary patient cohorts.[22]
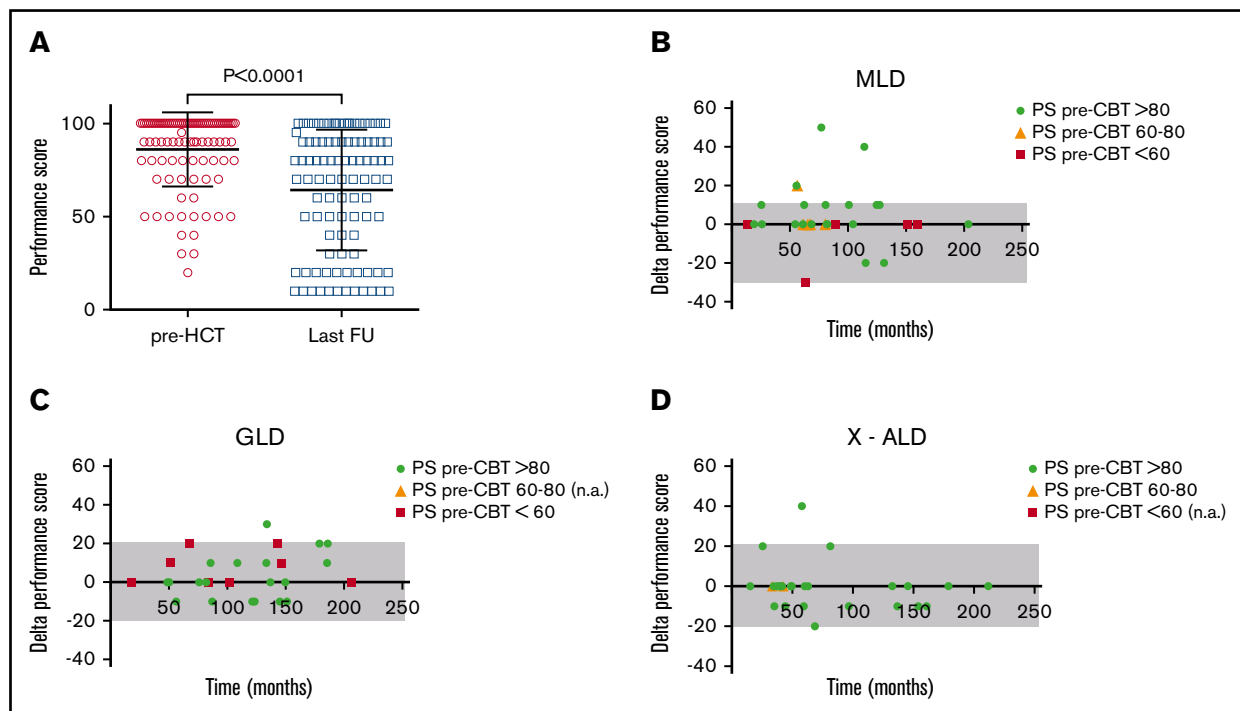
Figure 4. Evolution of performance scores before and after CBT. (A) Individual PS of patients with ≥12-month survival before and at last follow-up after CBT. (B-D) The δ of PS at 12 months and at last follow-up for MLD (B), GLD (C), and X-ALD (D). A positive δ is associated with decline in PS. Color coding for pre-CBT performance score is provided within each panel. FU, follow-up, n.a., not applicable.

Table 4. Functional outcome descriptives pre-HCT and at most recent follow-up in MLD and GLD patients

Pre-HCT (n = 113)			Most recent follow-up (median = 87 mo, range: 13-206; n = 63)		
Patient characteristics	**n (%)**	**Missing**	**Patient characteristics**	**n (%)**	**Missing**
Enzyme levels			**Enzyme levels**		
MLD (arylsulfatase A)		12	MLD (arylsulfatase A)		11
Low	54 (100)		Normal	28 (93.3)	
Normal	0 (0)				
GLD (galactocerebrosidase)		4	GLD (galactocerebrosidase)		3
Low	43 (100)		Normal	18 (94.7)	
Normal	0 (0)				
Presymptomatic	42 (39.6)	7	Presymptomatic	10 (18.2)	8
Mental development			**Mental development**		
Cognitive		40	Cognitive		25
Very low	16 (21.9)		Very low	15 (39.5)	
Low	18 (24.7)		Low	8 (21.0)	
Average	34 (46.6)		Average	15 (39.5)	
Above average	5 (6.8)				
Motor		39	Motor		52
Very low	16 (21.6)		Very low	10 (90.9)	
Low	19 (25.7)		Low	0 (0)	
Average	34 (45.9)		Average	1 (9.1)	
Above average	5 (6.8)		Above average	0 (0)	
Seizures (present)	8 (7.1)	7	Seizures (present)	13 (23.6)	8
Neuropathy		9	**Neuropathy**		9
Absent	36 (34.6)		Stable	37 (68.5)	
Mild	28 (26.9)		Improved	2 (3.7)	
Severe	40 (38.5)		Worsened	15 (27.8)	
Vision		15	**Vision**		11
Low	10 (10.2)		Stable	47 (90.4)	
Blind	2 (2.0)		Improved	2 (3.8)	
Normal	86 (87.8)		Worsened	3 (5.8)	
Hearing		14	**Hearing**		11
Mildly affected	6 (6.1)		Stable	48 (92.3)	
Severely affected	2 (2.0)		Improved	1 (1.9)	
Normal	91 (91.9)		Worsened	3 (5.9)	
School attendance*		9	**School attendance***		6
Regular	18 (47.4)		Regular	11 (21.6)	
Additional support	14 (36.8)		Additional support	36 (70.6)	
No attendance	6 (15.8)		No attendance	4 (7.8)	
School performance*		15	**School performance***		10
Appropriate for age	25 (75.8)		Appropriate for age	15 (35.8)	
Lower	8 (24.2)		Lower	27 (64.2)	
Independence		16	**Independence**		9
Appropriate for age	52 (53.6)		Appropriate for age	15 (27.8)	
Needs assistance	45 (46.4)		Needs assistance	39 (72.2)	
Continence (incontinent)	59 (65.6)	23	Continence (incontinent)	21 (38.9)	9
Gallbladder disease† (present)	9 (27.3)	33	Gallbladder disease† (present)	3 (11.5)	17

*Only for pediatric patients.
†Only for MLD.

Table 5. Functional outcome descriptives pre-HCT and at most recent follow-up in X-ALD patients

Pre-HCT (n = 56)			Most recent follow-up (median = 49 mo, range: 25-211; n = 35)		
Patient characteristics	n (%)	Missing	Patient characteristics	n (%)	Missing
Enzyme levels			**Enzyme levels**		
X-ALD (free fatty)		17	X-ALD (free fatty)		18
Normal	0 (0)		Normal	1 (5.9)	
High/elevated	39 (100)		High/elevated	16 (94.1)	
Presymptomatic	16 (32.7)	7	Presymptomatic	15 (51.7)	6
Mental development			**Mental development**		
Cognitive		18	Cognitive		22
Very low	0 (0)		Very low	1 (7.7)	
Low	10 (26.3)		Low	2 (15.4)	
Average	22 (57.9)		Average	7 (53.8)	
Above average	6 (15.8)		Above average	3 (23.1)	
Motor		19	Motor		27
Very low	0 (0)		Very low	5 (62.5)	
Low	10 (27.0)		Low	1 (12.5)	
Average	21 (56.8)		Average	1 (12.5)	
Above average	6 (16.2)		Above average	1 (12.5)	
Seizures (present)	5 (10.2)	7	Seizures (present)	5 (17.9)	7
Neuropathy		9	**Neuropathy**		8
Absent	31 (66.0)		Stable	23 (85.2)	
Mild	14 (29.8)		Improved	1 (3.7)	
Severe	2 (4.2)		Worsened	3 (11.1)	
Vision		7	**Vision**		5
Low	12 (24.5)		Stable	23 (76.7)	
Blind	2 (4.1)		Improved	1 (3.3)	
Normal	35 (71.4)		Worsened	6 (20.0)	
Hearing		8	**Hearing**		5
Mildly affected	5 (10.4)		Stable	27 (90.0)	
Severely affected	2 (4.2)		Improved	1 (3.3)	
Normal	41 (85.4)		Worsened	2 (6.7)	
School attendance*		5	**School attendance***		6
Regular	35 (79.5)		Regular	15 (53.6)	
Additional support	7 (15.9)		Additional support	9 (32.1)	
No attendance	2 (4.6)		No attendance	4 (14.3)	
School performance*		6	**School performance***		6
Appropriate for age	33 (82.5)		Appropriate for age	17 (73.9)	
Lower	7 (17.5)		Lower	6 (26.1)	
Independence		14	**Independence**		10
Appropriate for age	31 (73.8)		Appropriate for age	16 (64.0)	
Needs assistance	11 (26.2)		Needs assistance	9 (36.0)	
Continence (incontinent)	4 (10.0)	16	Continence (incontinent)	3 (12.5)	11
Adrenal insufficiency		32	**Adrenal insufficiency**		8
Absent	4 (16.6)		Stable	25 (92.6)	
Glucocorticoids	18 (75)		Worsened	2 (7.4)	
Mineralcorticoids	1 (4.2)				
Combined	1 (4.2)				

*Only for pediatric patients.

It has been well described that PS is an important predictor for survival and late outcomes after HSCT, including CBT.[5-8,18,19,23,24] Although PS is not the ideal tool for assessing neurocognitive development, this was the best available surrogate of cognitive function for long-term follow-up. It is important to note that at most recent follow-up, there were some patients with discrepant PS and neurocognitive scores (ie, PS > 80, but a low or very low score on mental development, or vice versa). Nevertheless, PS generally correlated with disease status and was able to quantify overall well-being that, even if less specific, can include general characteristics of the disease. Our results also demonstrated that there was minimal or no decline in PS beyond 1 year after CBT. Notably, presymptomatic disease was correlated with a higher probability of overall and event-free survival. Combining the PS before CBT and presymptomatic status could be used as a tool to predict outcomes. However, prospective studies that include longitudinal assessment of cognitive and motor function along with quality-of-life measures are warranted.

Moreover, this study emphasizes the importance of presymptomatic status and short duration from diagnosis to transplant on both early and late outcomes. These results provide further support that donor cord blood should be strongly considered when a noncarrier sibling donor is lacking. Because of the rapid course of these diseases, CB has some practical advantages above unrelated donors. Although haploidentical related donors are also readily available, most of these donors will be disease carriers. Previous studies of HCT in other LSDs have demonstrated an association between lower enzyme levels and worse late outcomes.[25] Therefore, haploidentical donors are not routinely recommended for patients with leukodystrophies. Previous studies have also demonstrated that patients who achieved full-donor chimerism experienced improved late outcomes.[25,26] Although these studies were conducted in other LSDs, all studies with CB as a donor source in LD showed high rates of full-donor chimerism.[4-6] These results also support the use of newborn screening (NBS), which allows identification of neonates eligible for CBT at a time when they still experience maximal benefit. In select US and EU member states, NBS for GLD or X-ALD has been or will be implemented in upcoming years.[6,27,28] To date, NBS for MLD is not available, but our results, along with those from other studies, provide evidence that early diagnosis and transplant prior to onset of symptoms improve early and late outcomes after CBT.[8,9,12,24]

This study recognizes that the long-term outcomes of many children are affected to various extents by their underlying disease, the transplant procedure, or a combination of both. Although nearly half of the children in this study were able to perform at an age-appropriate level at school, many needed additional support services to achieve that level of performance, especially MLD and GLD patients. Although these results are better than those of the natural course in nontransplanted patients,[29,30] more research concerning the effects of transplantation on functional outcomes and quality of life is warranted to optimize late outcomes, including the quality of life of these patients.

Further research is also needed to better understand the duration for which CBT can provide a therapeutic effect. It remains unclear whether the cross-correction of the deficient enzyme after CBT completely halts disease in MLD and GLD, because significant posttransplantation peripheral nerve disease has been reported by others.[6,8] Lentiviral haemopoietic stem cell gene therapy that aims for supranormal enzyme levels may provide a solution for this in the future, as a recent report suggests for MLD patients. Although

promising, longer follow-up is needed, and only half of patients achieved supranormal enzyme levels.[31]

In conclusion, CBT in patients with LD showed promising early and late outcomes, especially for those who are presymptomatic before CBT and those who received adequately dosed grafts. Early identification and treatment appear to be important predictors of outcomes, which suggests that NBS may further improve outcomes. Furthermore, fast referral to a specialized center after diagnosis is necessary. For symptomatic patients transplanted with a low performance score (<60 and 60-80), only 5% and 12%, respectively, of these patients were alive with improved performance at last known follow-up. Counseling of these patients and parents is of extreme importance. As life expectancy for patients with LSDs increases after CBT, international collaboration is of utmost importance to further optimize therapies, including CBT, to improve outcomes for these patients. Moreover, prospective trials comparing new (gene) therapies to the standard therapies are needed.

Authorship

Contribution: J.J.B. and J.K. designed and supervised the study; B.T.A.v.d.B., K.P., A.P., F.V., J.K., and J.J.B. drafted and revised the manuscript; B.T.A.v.d.B., J.J.B., A.P., A.R., J.H., F.V., P.M.v.H., K.P., and J.K. performed statistical analyses and analyzed and interpreted the data; J.H., H.A., F.V., G.M., M.A.D., V.B., T.O., P.J.S., C.K., A.A.-S., P.M.v.H., A.R.G., E.G., V.R., and A.R. contributed to the critical revision of the manuscript; B.T.A.v.d.B., K.P., A.P., J.H., H.A., F.V., G.M., M.A.D., V.B., T.O., P.J.S., C.K., A.A.-S., P.M.v.H., A.R.G., E.G., V.R., A.R., J.K., and J.J.B. contributed to the acquisition of the data. All authors approved the final manuscript as submitted.

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