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Hematopoietic Stem Cell Transplantation in the Leukodystrophies: A Systematic Review of the Literature

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Abstract

Objective—The objective of this study is to systematically review the literature on worldwide numbers of leukodystrophy patients undergoing hematopoietic stem cell transplantation (HSCT) as well as the safety and efficacy of the procedure in this patient population.

Materials and Methods—A PubMed and EMBASE search up to June 2012 was conducted with a manual search of references from relevant articles. Selected studies were evaluated using internationally accepted criteria. The effect estimates of HSCT upon survival in early-stage disease versus late-stage disease were compared.

Results—One hundred and fifty-two studies qualified for inclusion and reported on a total of 689 patients. Study quality ranged from *poor* to *good*; no study was rated excellent. Small sample sizes limited most studies. Meta-analysis in a subset of larger studies indicates that transplantation in earlier stages of disease fairs better than in the late stages. Beyond survival, little longitudinal data on functional outcome is reported and neurological outcome is sparse.

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Author Contributions

Articles were independently selected and reviewed by F.E., J.P., and A.P., and consensus on disagreements was reached between P.M., F.E., and A.P., F.E., P.M., and C.D. drafted the manuscript. Critical review and editing was performed by C.D., T.L., and M.E.

Disclosure

Florian Eichler and Asif Paker have served as consultants to Bluebird Bio (Cambridge, Massachusetts, United States). Florian Eichler and Christine Duncan are both coinvesti-gators of a clinical trial of gene therapy for X-linked ALD sponsored by Bluebird Bio.

Conflict of Interest

The authors have reported no conflicts of interest.

Conclusion—Further studies are needed to determine the neurological outcome following HSCT in the leukodystrophies. HSCT in the early stages of cerebral disease is still recommended for select leukodystrophies.

Keywords

leukodystrophy; bone marrow transplantation; white matter diseases

Leukodystrophies are heritable disorders affecting the white matter of the central nervous system (CNS). They can affect multiple functional domains over time, and are often progressive, resulting in significant disability and impaired quality of life. Hematopoietic stem cell transplantation (HSCT) has been employed to arrest disease progression for more than 20 years. Yet, the number of leukodystrophy patients transplanted worldwide, the optimal timing for transplant, the selection criteria, and outcome remain largely unknown. We systematically reviewed studies reporting HSCT performed in leukodystrophy patients.

Materials and Methods

Consensus Definition

On the basis of a definition of leukodystrophies arrived at by consensus among 13 investigators using a Delphi method, an interactive method based on a structured communication among a panel of experts (Adeline Vanderver, MD, personal written communication, January 11, 2013).

Research Questions

What have been the numbers of leukodystrophy patients reported worldwide and what is known about the safety and efficacy of the procedure? How does outcome in patients at early stages of cerebral disease compare with those transplanted in advanced cerebral disease?

Search Strategy

A literature review of PubMed and EMBASE from 1990 to 2012 was performed. The search terms (leukodystrophy and transplant) were based on the consensus definition mentioned above. Data extraction was performed by two blinded investigators excluding animal studies, review articles, and duplicates.

Inclusion and Exclusion Criteria

For the purpose of outcome analysis, peer-reviewed original articles written in English with a sample size of more than 10 patients that reported on the outcome after HSCT intervention were included. No relevant systematic reviews or meta-analysis were identified. Patients were categorized as late-stage versus early-stage at the time of transplant based on symptoms or magnetic resonance imaging (MRI) (e.g., the cut-off for Loes Score of 9 for adrenoleukodystrophy [ALD]) unless otherwise specified. The principle outcome for this review was defined as survival after having the transplant. To include the outcome for all the included patients, no time limit was considered for the analysis.

Data Analysis

The level and quality of evidence were determined by the study design, sample size, potential bias, statistical analysis, use of controls, and data collection strategy. Potential conflicts of interest were noted but were not included in the quality assessment. Articles were independently selected and reviewed by F.E. and A.P., and consensus on disagreements was reached between P.M., F.E., and A.P. Articles were assessed regarding the comparison of HSCT in early-stage and late-stage leukodystrophies. Discerning measures for early-stage versus late-stage disease as well as neurological outcome measures were extracted.

Standard Protocol Approvals, Registrations, and Patient Consents

Published data were used for this systematic review; hence, no ethical approval was sought.

Results

Search Results

PubMed yielded 1,381 hits and an additional 233 hits in EMBASE, with 536 unique citations identified. After excluding animal studies, review articles and duplicates, 152 studies qualified for inclusion, reporting on a total of 689 patients. Fig. 1 shows the numbers of transplanted leukodystrophy patients across continents. Two articles were collaborative international efforts (see, Peters et al[7] and Shapiro et al[8]). The majority of cases were ALD patients (461). Most studies included small numbers ($n < 5$) and only 10 articles reported on more than 10 patients of a specific disorder. Of these, only six articles reported survival events for both groups and only one reported on transplanted versus nontransplanted leukodystrophy patients. Transplantation occurred mostly in pediatric but was also reported in adult-onset leukodystrophies: 6 ALD, 13 metachromatic leukodystrophy (MLD), and 2 globoid leukodystrophy (GLD).

Donor Source for Transplantation

In most reported cases, the donor was unrelated (Table 1). However, in up to half of cases with MLD and GLD, and up to one-third of cases of ALD, the donor was not reported. The source of donor was most often bone marrow for ALD and MLD patients (31 and 36%, respectively) and most often umbilical cord blood (UCB) for GLD patients (32%). A small minority of cases had peripheral blood stem cell as donor source.

Transplant-Related Complications

On the majority of patients, there was no information regarding complications (Table 2). A third or fewer studies reported explicitly on transplant-related complications. Graft-versus-host (GvHD) was the most commonly reported complication followed by infection and graft failure. The type (acute or chronic) and severity of GvHD were inconsistently reported. This was true for ALD, MLD, and GLD.

Neurological Outcome and Survival

Approximately 67 to 80% of articles reported functional outcome, but up to half of the articles only listed “death” or “deterioration” as outcome measure. Only 20 to 25% of the articles made a reference to neuroimaging outcome. The subset of articles that listed more than 10 patients and neurological outcome were assessed for quality and nine articles judged as “good” or “fair” used for further analysis (see Table 3).[1–9] All but one of the articles employed neurological outcome measures that allowed for a comparison of HSCT in early-stage and late-stage leukodystrophies (see Table 4).

Discussion

Transplantations for leukodystrophies occur worldwide and have been reported from all continents apart from Africa. Most reported cases come from North America and Europe, although a publication bias may favor English-speaking countries.

Small samples sizes limited most studies. A systematic review in a subset of larger studies confirms that patients transplanted earlier in the process of neurologic decline fair better than those in advanced stages. This appears true for both ALD and GLD, and likely applies to other leukodystrophies as well. The difference may be based on the degree of normal brain that can be preserved. However, little longitudinal data or functional outcome is reported. Often the reason for “death” is unclear. Only rarely is brain imaging commented on and only a few images are shown.

Despite the commonalities among the leukodystrophies, important differences in the management of individual leukodystrophies remain. The crucial decision for the pediatric neurologist is at what stage to recommend transplantation. In ALD, mutation status does not predict the conversion to the cerebral form of the disease. However, MRI is an exquisitely sensitive marker of brain involvement—particularly, the presence of contrast enhancement—that can be used to determine who will develop progressive brain disease.[10,11] In GLD and MLD, on the contrary, concordance rates among siblings are usually high and progression of cerebral disease is more predictable, allowing for transplantation to be performed in presymptomatic or minimally symptomatic patients based on firm biochemical and genetic testing. A recent article on the neurodevelopmental outcome of UCB transplantation in MLD emphasizes this point.[12] Overall, conventional imaging in GLD and MLD correlates less well with disease severity compared with ALD, but advanced MRI in these disorders adds prognostic power.[11,13]

Despite improvements with early transplantation reported in the majority of large studies, it is still unclear whether these are sustained. There are reports on deterioration of peripheral nerve conduction velocities after initial improvements.[9] Reasons for this may include long-term toxicity from chemotherapy as well as defective remyelination by mutant Schwann cells. These findings are likely not related to the peripheral nerve alone but may apply to the CNS as well.

There is limited experience on the overall long-term neurological development and outcome of children after bone marrow transplantation in the leukodystrophies. The vast majority of

studies have not reported on neurological outcome. We know that pediatric patients who receive HSCT for hematologic malignancies have neurocognitive deficiencies that can be both acute and chronic.[14,15] The challenge in assessing leukodystrophies is separating residual toxic effects of myeloablation versus that of the disease itself.

There is heterogeneous and inconsistent reporting of HSCT complications and transplant-related mortality in the literature. However, we found the rate and nature of complications, including GvHD and infection, in children with leukodystrophies to be comparable to that of other inherited metabolic disorders cited in the literature.[16] Graft failure appears to be greater in this population than in HSCT for childhood malignancy. However, as graft failure is not well-described, conclusions cannot be drawn from the published literature. Overall, complication rates may be underestimated as poor outcomes are generally under-reported. Hemorrhagic cystitis and septicemia are among the most common infections reported.

Fully myeloablative conditioning regimens are used in the large majority of transplants in the literature. Over the years, effort has been made to use reduced intensity conditioning (RIC) regimens. There are case reports and small series of RIC in this population. However, there are no large, published prospective trials of RIC in childrenwith leukodystrophies. In some cases, this has come at the risk of engraftment problems (personal experience). We anticipate that in future, RIC may lead to improved transplant-related morbidity/mortality, more rapid engraftment, lessened neurotoxicity, and fewer late effects of transplant.

Several limitations to our systematic review exist. We cannot exclude that the difference in survival between patients transplanted with early-stage versus late-stage leukodystrophies is partially explained by lead-time bias. Furthermore, a formal meta-analysis was not possible because of heterogeneity in reported outcome measures.

In our review, we found that most articles on HSCT for leukodystrophies report on either transplant measures alone and do not include neurological or brain imaging scales or report neurologic outcomes with little detail about transplant complication or toxicity.

Prospective studies of the role and efficacy in HSCT for leukodystrophies are needed that include both transplant and neurologic clinical outcome measures and imaging scoring systems. Although scales have been developed for some diseases such as ALD, this yet has to be done for most of the other leukodystrophies.

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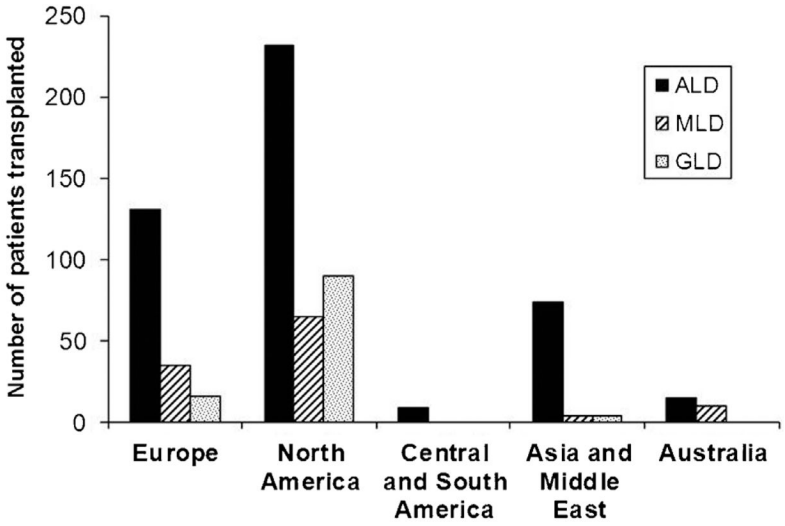

Fig. 1.

Hematopoietic stem cell transplantation in leukodystrophy patients reported across continents from 1999 to 2011 (number of articles, 152; number of patients, 689). The two international collaborative efforts account for 104 adrenoleukodystrophy patients and have been equally divided among European, North American, and Asian columns.

Table 1

Summary of donor source reported

	Source of donor			
	Bone marrow, *n* (%)	**Umbilical cord blood, *n* (%)**	**Peripheral blood stem cell, *n* (%)**	**Unknown, *n* (%)**
ALD (*n* = 461)	145 (31)	77 (17)	21 (5)	218 (47)
MLD (*n* = 114)	41 (36)	16 (14)	2 (2)	55 (48)
GLD (*n* = 110)	16 (15)	35 (32)	1 (1)	58 (53)
	Relation to donor			
	Related to donor, *n* (%)	**Unrelated to donor, *n* (%)**	**Unknown, *n* (%)**	
ALD (*n* = 461)	126 (27)	195 (42)	140 (30)	
MLD (*n* = 114)	19 (17)	34 (30)	61 (54)	
GLD (*n* = 110)	8 (7)	44 (40)	58 (53)	

Abbreviations: ALD, adrenoleukodystrophy; GLD, globoid leukodystrophy; MLD, metachromatic leukodystrophy.

Table 2

Summary of complications reported

	Reported presence of complications, *n* (%)	**Reported absence of complications, *n* (%)**	**Unknown, *n* (%)**	
ALD (*n* = 461)	79 (17)	9 (2)	373 (81)	
MLD (*n* = 114)	34 (30)	4 (4)	76 (67)	
GLD (*n* = 110)	27 (25)	4 (4)	79 (72)	
	GvHD, *n* (%)	**Infection, *n* (%)**	**Graft failure, *n* (%)**	**Other, *n* (%)**
ALD (*n* = 88)	44 (50)	23 (26)	14 (16)	13 (15)
MLD (*n* = 38)	27 (71)	8 (21)	6 (16)	8 (21)
GLD (*n* = 31)	28 (90)	2 (6)	0 (0)	6 (19)

Abbreviations: ALD, adrenoleukodystrophy; GLD, globoid leukodystrophy; MLD, metachromatic leukodystrophy.

Table 3

Summary of unique studies examining hematopoietic stem cell transplantation in the leukodystrophies[a]

Country (publication year)	Study design	Target population (numbers of patients)	Source of HSCT	Comparison	Neurological outcome measure
Germany (Baumann et al, 2003)	Prospective cohort	ALD (*n* = 12)	BM (*n* = 10), PBSC (*n* = 2)	Early vs. late transplant	Brain MRI
United States (Beam et al, 2007)	Prospective cohort	ALD (*n* = 12)	UCB (*n* = 12)	Early vs. late transplant	Survival, neurodevelopmental outcome
United States (Escolar et al, 2005)	Prospective cohort	GLD (*n* = 25)	UCB (*n* = 25)	asymptomatic vs. symptomatic	Survival, neurodevelopmental outcome
United States (Martin et al, 2005)	Prospective cohort	ALD (*n* = 8), MLD (*n* = 6), GLD (*n* = 16)	UCB (*n* = 20)	2 different transplant regimens	None
United States (Mahmood et al, 2007)	Retrospective cohort	ALD (*n* = 19)	BM (*n* = 19)	Early vs. late transplant, transplanted vs. nontransplanted	Survival
United States (Miller et al, 2011)	Retrospective cohort	ALD (*n* = 60)	BM (*n* = 60)	Early vs. late transplant	Survival, neurological outcome, brain MRI
International (Peters et al, 2004)	Retrospective cohort	ALD (*n* = 94)	BMC or UBC	Early vs. late transplant	Survival
International (Shapiro et al, 2000)	Prospective cohort	ALD (*n* = 12)	BM (*n* = 12)	Early vs. late transplant	Survival, neurological outcome, brain MRI
Canada (Siddiqi et al, 2006)	Prospective cohort	GLD (*n* = 12)	Not listed	Early vs. late transplant	Neurophysiology

Abbreviations: ALD, adrenoleukodystrophy; BM, bone marrow; GLD, globoid leukodystrophy; HSCT, hematopoietic stem cell transplantation; MLD, metachromatic leukodystrophy; MRI, magnetic resonance imaging; PBSC, peripheral blood stem cells; UCB, umbilical cord blood.

[a] Studies reporting on more than 10 patients.

Note: All but one of the articles employed neurological outcome measures that allowed for a comparison of HSCT in early-stage and late-stage leukodystrophies.

Table 4

Comparative measures and outcome in early-stage versus late-stage leukodystrophies

Country (publication year)	Target population (numbers of patients)	Discerning measure	Outcome measure	Outcome in advanced patients	Outcome in early patients
Germany (Baumann et al, 2003)	ALD (*n* = 12)	MRI Score (Loes) ≤ 9 vs. > 9	Clinical reporting	3 deteriorated, 1 stable	3 deteriorated, 5 stable
United States (Beam et al, 2007)	ALD (*n* = 12)	MRI Score (Loes) ≤ 9 vs. > 9	Event-free survival	3 long-term survival (> 800 d), 2 early death (< 200 d)	5 long-term survival (> 800 d), 2 early death (< 200 d)
United States (Escolar et al, 2005)	GLD (*n* = 25)	Neurodevelopmental, MRI, and neurophysiology assessment	Clinical reporting	Minimal neurologic improvement	Progressive central myelination, appropriate cognitive function
United States (Mahmood et al, 2007)	ALD (*n* = 19)	Compares early transplant to no transplant	5-year survival	51%	61%
United States (Miller et al, 2011)	ALD (*n* = 60)	MRI Score (Loes) < 10 vs. ≥ 10	5-year survival	60%	89%
International (Peters et al, 2004)	ALD (*n* = 94)	MRI Score (Loes) ≤ 9 vs. > 9	5-year survival	45%	92%
International (Shapiro et al, 2000)	ALD (*n* = 12)	MRI Score (Loes) ≤ 9 vs. > 9	Cognitive evaluation	2 deteriorated, 1 stabilized	5 improved, 3 stable, 1 deteriorated
Canada (Siddiqi et al, 2006)	GLD (*n* = 12)	age at transplant (first month vs. later in first year)	Nerve conduction velocities	Motor conduction velocity improved by 3 m/sec	Motor conduction velocity improved by 13 m/sec

Abbreviations: ALD, adrenoleukodystrophy; GLD, globoid leukodystrophy; MLD, metachromatic leukodystrophy; MRI, magnetic resonance imaging.