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Cord blood is the optimal graft source for the treatment of pediatric patients with lysosomal storage diseases: clinical outcomes and future directions

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Abstract

Initially used as an alternative hematopoietic stem cell source for patients without a human leukocyte antigen–matched bone marrow or peripheral blood stem cell donor, unrelated cord blood (UCB) is now the preferred donor source when hematopoietic stem cell transplantation (HSCT) is used to treat patients with lysosomal storage disorders (LSD). Without transplantation, these patients have serious progressive multi-system deterioration and premature death. UCB transplantation favorably alters the natural history of these diseases and prolongs survival. It primarily works through cellular enzyme replacement by healthy engrafted donor cells providing a continuous endogenous supply of enzyme throughout the body and, thorough engraftment of donor-derived microgial cells, in the central nervous system. HSCT in LSD, the majority performed in patients with mucopolysaccharidoses and leukodystrophies, is associated with remarkably high rates of engraftment and survival. Importantly, recipients of UCB, as compared with other donor sources, more often achieve full-donor chimerism and normalization of enzyme levels, which has been associated with superior long-term clinical prognosis. Additionally, UCB units are readily available, reducing time to transplantation and thereby providing access to transplant at young ages, another highly important predictor for long-term neuro-developmental function. For these reasons, UCB grafts are nowadays considered to be the optimal graft source for HSCT in patients with LSD.

Key Words: *hematopoietic stem cell transplantation, leukodystrophies, lysosomal storage disorders, mucopolysaccharidoses, unrelated cord blood*

Introduction

Since the first successful case of unrelated cord blood transplantation (UCBT) in a patient with Fanconi anemia 26 years ago [1], the use of UCB as a hematopoietic stem cell (HSC) source has become a routine practice. To date, more than 35,000 unrelated donor cord blood transplants have been performed worldwide. Hundreds of public and private cord blood banks have been established, storing inventories of >700,000 and >4,000,000 units, respectively.

The potential alternative option of UCB as a hematopoietic graft source is increasingly being used in patients with lysosomal storage disorders (LSD) and disease involvement in the central nervous system (CNS), for which hematopoietic stem cell transplantation (HSCT) is currently the only curative treatment option. UCB can be successfully transplanted without full human leukocyte antigen (HLA) matching between the donor and recipient, significantly increasing the possibility of identifying a suitable unrelated donor in a short time frame and without increasing the risk of acute or chronic graft-versus-host disease (GVHD). When UCB donors are used, screening of donor enzyme levels will allow for the selection of a donor with high normal levels of endogenous enzyme production. In addition, the use of UCB as the donor for HSCT holds several additional biological advantages for patients with LSD. This review will highlight these benefits and will also focus on the results of UCBT in LSD, with particular emphasis on the mucopolysaccharidoses (MPS) and the more common leukodystrophies, because these disorders account for the vast majority of HSCT in LSD (Figure 1) [2].

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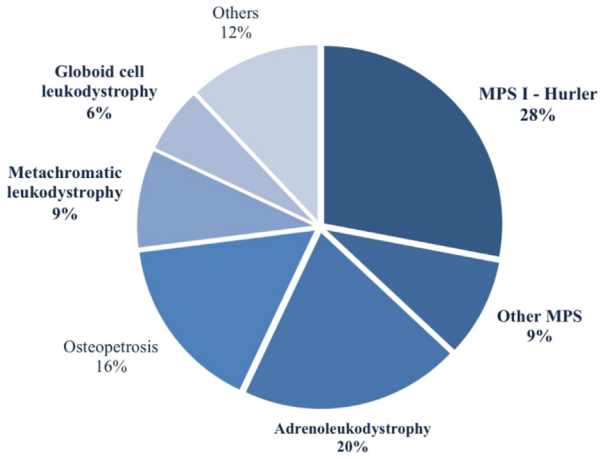

Figure 1. Hematopoietic stem cell transplantation in inborn errors of metabolism: frequencies reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) from 2000 to 2013 (n = 1293) [2]. Mucopolysaccharidoses type I–Hurler syndrome (MPS I–Hurler) represents the most transplanted inherited metabolic disorder, with 28% of the HSC transplantations performed between 2000 and 2013. "Other MPS" (9%) include mainly type II (Hunter syndrome, 2%), type III (Sanfilippo syndrome, 2%) and type VI (Maroteaux-Lamy syndrome, 2%). HSCT in the leukodystrophies is also frequently performed, including adrenoleukodystrophy (20%), metachromatic leukodystrophy (9%) and Globoid cell leukodystrophy (including Krabbe disease, 6%). "Others" include mainly I-cell disease (2%), mannosidosis (2%), Niemann-Pick disease (1%), Gaucher disease (1%) and Wolman disease (1%).

HSCT in LSD

LSD comprise a group of heterogeneous disorders caused by the deficiency of a lysosomal enzyme or a disturbance of other lysosomal functions. The disrupted lysosomal function results in incomplete breakdown and subsequent widespread and progressive accumulation of macromolecules (eg, proteins, polysaccharides and lipids) in the lysosomes of various tissues. As these macromolecules accumulate, the lysosomes enlarge and secondary processes are triggered, leading to cell death and tissue and organ dysfunction, ultimately resulting in fatal progressive multi-system disease [3,4]. The subset of LSD typically treated with HSCT involves the CNS as a primary target, leading to neuro-inflammation, neuro-degeneration, demyelination and severe clinical neurofunctional impairment. The estimated prevalence of the group LSD as a whole has been reported to be approximately 1 in 7000 live births [5,6]. Considering these figures, many doctors are likely to encounter a patient with an LSD during their career.

After successful HSCT, the engrafted donor-derived HSCs provide a continuous endogenous source of the missing enzyme throughout the body, including the peripheral tissues as well as the CNS, for cross-correction of the defective metabolism [7,8]. It has been observed that the donor-derived macrophages cross the blood-brain barrier with subsequent differentiation into microglia, secreting the deficient enzyme for recapture by the surrounding neurons [9]. The timing of migration to and engraftment of donor-derived microglial cells after HSCT is not known, but, on the basis of clinical observations, probably is months after hematologic engraftment. It is also possible that donor cells exert anti-inflammatory and pro-neurogenic effects through paracrine signaling.

Although enzyme replacement therapy (ERT) has become available for certain LSD, this treatment is incapable of crossing the blood-brain barrier and therefore is not able to prevent or treat cerebral signs and symptoms. For several LSD with CNS involvement, usually the more severe LSD subtypes, HSCT is therefore still the only treatment available [10].

ERT is also being used, primarily before HSCT, to improve the clinical condition of the patient. Although ERT might be of value for patients with significant pulmonary or cardiac disease manifestations, placing them at higher risk for proceeding to HSCT, delaying the HSCT should be avoided as much as possible [10].

UCBT in MPS

The MPS represent approximately 35% of all LSD and are characterized by a progressive lysosomal accumulation of incompletely degraded glycosaminoglycans, previously termed mucopolysaccharides [3]. Seven distinct clinical types have been identified, with a wide spectrum of clinical manifestations varying among the different MPS types (Table I) [3,4,11]. Even within the various MPS types, subtypes are acknowledged (eg, MPS type I–Hurler, Hurler-Scheie or Scheie), mainly on the basis of age of onset, rate of disease progression and/or CNS involvement. Although genotype-phenotype correlations do not always hold, some mutations (such as a nonsense mutation on both involved alleles in MPS type I) are associated with a complete lack of residual enzyme activity, causing an early onset of clinical manifestations and rapid disease progression, including psychomotor deterioration [10].

Although the MPS types and subtypes differ clinically, a shared phenomenon is that most patients have a period of normal development followed by a progressive physical and/or cognitive deterioration as the accumulation increases. Frequently observed manifestations include psychomotor retardation (not in MPS I–Scheie, MPS IIB, MPS IV and MPS VI), musculoskeletal manifestations, vision and hearing impairment and life-threatening cardiopulmonary failure (Table I) [3]. All MPS types are inherited in an autosomal recessive manner, except for MPS