DOI: 10.46765/2675-374X.2021v2n2p126

BRAZILIAN CONSENSUS GUIDELINES FOR HEMATOPOIETC STEM CELL TRANSPLANTATION - INBORNS ERRORS OF METABOLISM

Adriana Mello Rodrigues[1,2], Alessandra Gomes[3,4], Juliana Folloni Fernandes[4,5], Liane Daudt[6,7], Carmem Bonfim[1,2,8]

1- Hospital Infantil Pequeno Príncipe – Curitiba – PR
2- Hospital de Clínicas da Universidade Federal do Paraná – Curitiba – PR
3- Hospital Sírio-Libanês – São Paulo – SP
4- Instituto de Tratamento do Câncer Infantil (ITACI) – Instituto da Criança – Hospital das Clínicas da Universidade de São Paulo – São Paulo – SP
5- Hospital Israelita Albert Einstein – São Paulo – SP
6- Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul – Porto Alegre – RS
7- Hospital Moinhos de Vento – Porto Alegre - RS
8- Hospital Nossa Senhora das Graças – Curitiba - PR

Correspondence to: tmohpp@gmail.com

For the past three decades, hematopoietic stem cell transplantation (HSCT) has been used as an effective therapy for selected inborn errors of metabolism (IEM), mainly lysosomal storage diseases and peroxisomal disorders. The main rationale for HSCT in IEM is based on correcting the decreases enzymes by the donor cells within and outside the intravascular compartment. Instead, the success of enzyme replacement therapy (ERT) in patients with a moderate/good clinical condition generated interest in employing ERT prior to or during HCT in patients with a poor clinical condition. The goal of HSCT is to achieve normal or near-normal quality of life by preventing further neurologic and development deterioration[1].

MUCOPOLYSACCHARIDOSIS

The mucopolysaccharidosis (MPS) diseases are a group of lysosomal storage disorders caused by deficiency of degradative enzymes of glycosaminoglycans (GAGs). These GAGs are usually excreted in urine and can be detected by initial diagnostic screening tests. Lysosomal enzymes are present at elevated levels in serum and body fluids of affected patients. Metabolic correction of lysosomal storage diseases is due to the mannose-6-phosphate receptor-mediated endocytosis of secreted enzymes, or by direct transfer of enzymes from adjacent cells. All the MPS disorders are autosomal recessive in their inheritance, except for Hunter syndrome (MPS- II X-linked)[2-5].

Mucopolysaccharidosis type I (MPS-IH, Hurler Syndrome) is caused by deficient enzyme activity of alpha-L-iduronidase (IDUA). The severe form of the disease is characterized by a progressive systemic dysfunction, affecting heart, liver, eyes, bones, joints, respiratory system, facial appearance, and often the central nervous system (CNS)[2-5].

In mucopolysaccharidosis type II (MPS-II, Hunter Syndrome) there is a deficiency of the enzyme iduronate-2-sulfatase (IDS). The severe neuropathic form of the disease presents before the age of 3 years with profound neurocognitive and developmental delay and shares clinical features with MPS-IH[2-5].

The mucopolysaccharidosis type VI (MPS-VI, Maroteaux-Lamy Syndrome) is caused by deficient enzyme activity arylsulfatase B (N-acetylgalactosamine 4-sulfatase). The patient with the rapidly progressive form often presents with short stature, several skeletal and joint abnormalities, compromised pulmonary and cardiovascular function, ocular alterations, including blindness in some cases, and early mortality[2-5].

HSCT is indicated for types I and II, whereas for type VI only for those who do not respond to enzyme replacement therapy. HSCT should preferably be performed in children under two years of age or in older children who have minimum cognitive deficit. The performance of HSCT in the pre-symptomatic phase offers the best results and the success of HSCT is associated with the level of enzyme production and the percentage of chimerism in the

donor. Despite successful HSCT, the benefits may be limited in skeletal deformities, in progression of corneal clouding and in the mitral and aortic valve deformities, in some, this may lead to progressive valvular dysfunction[6].

It can be performed with related non-carriers and unrelated donors (preferably hematopoietic cell source: bone marrow). In the literature, the use of umbilical cord blood has shown superiority in achieving complete chimerism and adequate enzyme production compared to other cell sources, but there is a higher rate of engraftment failure and these results have not been reproduced in Brazilian scenario. A recent study has shown that the use of a reduced toxicity regimen with the addition of thiotepa improves engraftment and is related to a low transplant mortality[7]. The use of heterozygous donors is NOT recommended. The use of haploidentical donors should also be avoided, except for X-linked forms or proved non-carrier relatives, parents are obligated heterozygotes. Myeloablative conditioning regimens are recommended, based on Busulfan (with pharmacokinetics), fludarabine, and thymoglobulini[8-12].

Intense international collaboration during the last decade has identified predictors of clinical outcomes, including myeloablative conditioning, early timing of transplantation, and probably enzyme activity level in blood after HSCT. This has resulted in optimized transplantation protocols and 5-year survival rates > 90%[6, 10,11]. The Brazilian government has approved HSCT with related and unrelated donors for patients with MPS I and II.

X-LINKED ADRENOLEUKODYSTROPHY

X-linked adrenoleukodystrophy (X-ALD) is a peroxisomal disorder characterized by cerebral demyelination, adrenal insufficiency and progressive neurologic deterioration. The ALD gene encodes the ABCD1 protein which is involved in transport of fatty acyl coenzyme A substrates or their cofactors into peroxisomes. Its metabolic hallmark is the accumulation of very long chain fatty acids (VLCFA) in tissues and plasma, due to impaired transport and beta-oxidation of these fatty acids in peroxisomes. However, it has no effect in patients with established neurologic deficits, as brain levels of VLCFA are unchanged by the treatment[13].

Patients with X-Linked ADL may present with 6 forms of the disease. The cerebral form affects approximately 40-60% of patients and is characterized by cognitive deficits followed by progressive demyelination of the CNS and evolution to disability, dementia, neurovegetative state and death within a few months to several years from diagnosis. A complete evaluation of a boy with cerebral X-ALD includes a thorough neurologic examination, comprehensive neuropsychological assessment with IQ and an MRI of the brain with and without contrast (gadolinium) with MRI severity score determination, referred to as the Loes score. The predominant pattern of demyelination seen by brain MRI is posterior in 80-85% of cases. Although neurologic deterioration occurs in all boys with the cerebral form, 40% of female heterozygous carriers exhibit mild-to-moderate non-cerebral signs of the disease[13].

HSCT is indicated in the progressive cerebral form, at an early stage, aiming to prevent the progression of cerebral demyelination. The patient should undergo clinical assessment of neurological status (IQ >80) and MRI (Loes score >1 and <9) before the procedure. The neurologic benefits of HSCT in X-linked adrenoleukodystrophy are mediated by the replacement of brain microglial cells derived from donor bone marrow myeloid cells. HSCT can prevent the progression of neurological disease, but there is no improvement in other disease manifestations such as adrenal insufficiency and so far, there is no evidence that it prevents the development of adrenomyeloneuropathy[14-16].

HSCT can be performed with related non-carriers and unrelated donors (preferably hematopoietic cell source: bone marrow). The use of heterozygous carrier's donors is NOT recommended. There are case series using haploidentical (non-carrier) donors, but the experience is very limited and should be done in reference centers. Conditioning regimens are myeloablative and based on busulfan (recommended with pharmacokinetics), fludarabine, and thymoglobulin[14-16].

The Brazilian government has approved HSCT from related and unrelated donors for patients with X-linked ADL who have signs of cerebral disease (Loes score 1-9) and good performance.

GLOBOID CELL LEUKODYSTROPHY - KRABBE DISEASE

Krabbe Disease is a rare autosomal recessive lysosomal neurodegenerative disorder caused by deficiency of galactocerebrosidase (GALC). It is characterized by white matter degeneration in the CNS and peripheral nervous system, with large macrophages (globoid cells). There is progressive neurological deterioration, with loss of motor function, spasticity, cognitive deficit, auditory and visual deficit, seizures

are common, and the disease leads to early death[17,18]. There are 3 different presentations:

1. Classic or infantile form, with manifestations before 6 months and death before 2 years
2. Juvenile form, starting in childhood and dying in early adolescence.
3. Adult form, starting from late childhood to 5th. decade of life.

HSCT is indicated for patients with the infantile form if performed before the development of neurological symptoms, preferable in the first two months of life. In these cases, the diagnosis is usually made by family history or neonatal screening. It is also indicated for patients with juvenile and adult forms, with no or early neurologic symptoms. HSCT improves clinical outcomes in KD patients only if delivered pre-symptomatically or in oligosymptomatic. It can be performed with related non-carriers and unrelated donors (preferably hematopoietic cell source: bone marrow). The use of heterozygous carrier's donors is NOT recommended. Conditioning regimens are myeloablative and based on busulfan (with pharmacokinetics), fludarabine, and thymoglobulin[17,18].

METACHROMATIC LEUKODYSTROPHY

Metachromatic leukodystrophy is caused by arylsulfatase A (RSA) deficiency and is characterized by central and peripheral demyelination. Diagnosis is made by measuring the enzyme and urinary sulfatides[15,16]. The disease is classified according to the clinical presentation and age of symptom onset:

1. Late Infantile Form: The clinical presentation occurs before 30 months of life with rapid evolution and progressive motor dysfunction, walking difficulty, dysarthria, dysphagia, decerebration. Death occurs 2 to 4 years after the onset of manifestations.
2. Juvenile Form: Manifests between 2.5 and 16 years of age with postural abnormalities, behavioral changes, optic atrophy, spastic quadriparesis, language regression.
3. Adult form: It manifests after 16 years of age with psychiatric or intellectual symptoms, incontinence, spastic tetra paresis, cognitive regression. Progression tends to be slower than in other forms of the disease.

HSCT is not indicated in the late infantile form as it does not prevent the progression of the disease. In juvenile or adult forms, HSCT should be indicated in asymptomatic or mildly symptomatic patients. It can be performed with related non-carriers and unrelated donors (preferably hematopoietic cell source: bone marrow). The use of heterozygous carrier's donors is NOT recommended. Conditioning regimens are myeloablative and based on busulfan (with pharmacokinetics), fludarabine, and thymoglobulin[15,16].

GAUCHER DISEASE

Gaucher disease is the most common lysosomal storage disorder. It is autosomal recessive and characterized by deficient activity of the lysosomal enzyme glucocerebrosidase and as a result, the accumulation of glucocerebroside in the lysosomes. The pathophysiologic feature of Gaucher disease is the presence of Gaucher cells derived from the monocyte-macrophage system. Most Gaucher cells are found in the spleen, liver, bone marrow, and lymph nodes, causing enlargement and dysfunction of these organs and resulting in clinical manifestations. Bleeding due to thrombocytopenia, anemia, and hepatosplenomegaly are the common early features. Bone involvement is common, but it is not always associated with symptoms, when present, range from mild to severe bone pain crises.

The diagnosis can be made by measuring the glucocerebrosidase activity of peripheral blood leukocytes or by cultured skin.

There are three types of Gaucher disease:

Type 1: It is the most common form accounting for 90–95% of the cases, characterized by onset in adulthood and by the absence of primary CNS involvement.

Type 2: It is characterized by severe neurologic involvement, that include oculomotor apraxia, opisthotonos and bulbar signs, and an onset during infancy.

Type 3: It presents by the onset of neurologic disturbances later in the first decade of life.

Enzyme replacement therapy is the treatment of choice for type 1 Gaucher disease. However, since the pathophysiology of Gaucher disease is due to the accumulation of lipid-laden macrophages, HSCT is also considered a possible treatment choice, especially for those with matched unaffected related donors. The benefit of transplantation varies between organ systems. Hematologic and physical improvement is rapid and sustained. Reticuloendothelial organs, such as the liver and spleen, regress within a few months, and there is some evidence that the skeletal changes seen in Gaucher disease regress.

OSTEOPETROSIS

Osteopetrosis is a genetic disease characterized by skeletal sclerosis, resulting from the reduction or loss of osteoclasts function, consequently there is impairment of bone reabsorption. The severe form is an inherited autosomal recessive disease and is characterized by fractures, neurological symptoms and early spinal cord failure. These children rarely survive more than 2 years of life[19,20].

HSCT is indicated in the severe form (infantile malignancy), except in patients with neurodegeneration (OSTM1 mutation) and with mutations in RANKL. There is also a rare form of OP with CLCN7 mutation that presents with neurodegeneration, these cases may not be candidates for HSCT. HSCT can be performed with related or unrelated donors (preferably hematopoietic cell source: bone marrow) and, more recently, studies have shown satisfactory survival rates with haploidentical donors[21]. The use of unrelated umbilical cord is associated with a higher incidence of graft failure. Conditioning regimens should be myeloablative and based on busulfan (with pharmacokinetics), fludarabine, thymoglobulin and thiotepa. HSCT in osteopetrosis has high rates of engraftment failure (even with related sibling donors) and of a second transplant, in addition to a very high risk of sinusoidal obstruction syndrome[19,20,22].

GENERAL RECOMMENDATIONS FOR HSCT IN METABOLIC DISEASES

1. Do not use a carried donor.
2. Umbilical cord blood or bone marrow are the preferred stem cell source.
3. Most regimens are myeloablative and busulfan pharmacokinetics are strongly recommended.

MYELOABLATIVE CONDITIONING REGIMENS FOR METABOLIC DISEASES[23]:

Busulfan (weight based) mg/kg or recommended myeloablative AUC of 85-95 ng/ L x h.

TABLE 1 - Initial busulfan dose is based on weight:

Body weight	mg/kg/day
3 to 15kg	5,1
15 to 25kg	4,9
25 to 50kg	4,1
50 to 75kg	3,3
75 to 100kg	2,7

2. Fludarabine 160mg/m2
3. Rabbit ATG 7,5-10mg/kg

GVHD prophylaxis: with cyclosporine and mycophenolate mofetil or prednisone (1mg/Kg/day) for cord blood transplantations and cyclosporine and short course of methotrexate (Day +1, +3, +6, ± 11) for patients receiving bone marrow.

FINAL CONSIDERATIONS

HSCT corrects the enzymatic defect but does not modify the course of the disease in some organs. Due to the particularities of these diseases, it is recommended that these patients be transplanted in specialized centers. Even after the transplant, most patients will still need care from the multidisciplinary team (neurologists, cardiologists, orthopedists, ophthalmologists, endocrinologists, psychologists).

REFERENCES:

1. Rosenthal, J. Thomas' Hematopoietic Cell Transplantation, Fifth Edition. 2016 John Wiley & Sons, Ltd.; 885:909.

2. Chiesa R, Wynn R, Veys P. Haematopoietic Stem Cell Transplantation in Inborn Errors of Metabolism. Curr Opin Hematol. 2016;23(6):530-535.

3. Köse S, Aerts-Kaya F, Uçkan Çetinkaya D, Korkusuz P. Stem Cell Applications in Lysosomal Storage Disorders: Progress and Ongoing Challenges. Adv Exp Med Biol. 2021. Doi: 10.1007/5584_2021_639. Online ahead of print.

4. Tan EY, Boelens JJ, Jones AS, Wynn RF. Hematopoietic Stem Cell Transplantation in Inborn Errors of Metabolism. Front Pediat. 2019;7:433.

5. Protocolo Clínico e Diretrizes Terapêuticas para MPS I, II, IV – Ministério da Saúde, Portaria conjunta Nº 12 (11/04/2018), Portaria conjunta Nº 16 (24/05/2018), Portaria conjunta Nº 20 (05/12/2019).

6. Van Den Broek et al. Hurdles in treating Hurler disease: potential routes to achieve a "real" cure. Blood advances, 23 june 2020; 4(12): 2837-2849.

7. Vander Lugt et al. Reduced-intensity single-unit unrelated cord blood transplant with optiona;l immune boost for nonmalignant disorders. Blood advances. 2020; 4(13):3041-3052.

8. Neven B, Diana JS, Castelle M, Magnani A, Rosain J et al. Haploidentical Hematopoietic Stem Cell Transplantation with Post-Transplant Cyclophosphamide for primary immunodeficiencies and inherited disorders in children. Biol Blood Marrow Transplant. 2019;25(7):1363-1373.

9. Lum SH, Orchard PJ, Lund TC, Miller WP, Boelens JJ, Wynn R. Outcome After Cord Blood Transplantation Using Busulfan Pharmacokinetics-Targeted Myeloablative Conditioning for Hurler Syndrome. Transplant Cell Ther. 2021;27(1):91.e1-91.e4.

10. Guffon N, Pettazzoni M, et al. Long term disease burden post-transplantation: three decades of observations in 25 Hurler patients successfully treated with hematopoietic stem cell transplantation (HSCT). Orphanet J Rare Dis. 2021;16(1):60.

11. Aldenhoven M, Jones AS, Bonney D, Borrill RE, Boelens JJ et al. Hematopoietic cell transplantation for Mucopolysaccharidosis patients is safe and effective: results after implementation of international guidelines. Biol Blood Marrow Transplant. 2015;21:1106-1109.

12. Aldenhoven M, Wynn RF, Orchard PJ, O'Meara A, Veys P et al. Long-term outcome of Hurler syndrome patients after hematopoietic cell transplantation: an international multicenter study. Blood. 2015;125(13):2164-2172.

13. Raymond GV, Aubourg P, Paker A, Escolar M, Fischer A et al. Survival and Functional outcomes in boys with Cerebral Adrenoleukodystrophy with and without Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant. 2019;25(3):538-548.

14. Fernandes JF, Bonfim C, Kerbauy FR, Rodrigues M, Esteves I et al. Haploidentical bone marrow transplantation with post transplant cyclophosphamide for patients with X-linked adrenoleukodystrophy: a suitable choice in an urgent situation. Bone Marrow Transplant. 2018;53(4):392-399.

15. Van den Broek BTA, Page K, Paviglianiti A, Hol J, Allewelt H et al. Early and Late outcomes after cord blood transplantation for pediatric patients with inherited leukodystrophies. Blood Adv. 2018;2(1):49-60.

16. K.M. Page et al. Hematopoietic Stem Cell Transplantation to Treat Leukodystrophies: Clinical Practice Guidelines from the Hunter's Hope Leukodystrophy Care Network. Biol Blood Marrow Transplant. 2019;25(12):363-374.

17. Allewelt H, Taskindoust M, Troy J, Page K, Wood S et al. Long-term functional outcomes after Hematopoietic Stem Cell Transplant for Early Infantile Krabbe Disease. Biol Blood Marrow Transplant. 2018;24:2233-2238.

18. Weinstock NI et al. Brainstem development requires galactosylceramidase and is critical for pathogenesis in a model of Krabbe disease. Nat Commun. 2020;11(1):5356.

19. Wynn R and Schulz A. Inborn Errors of Metabolism and Osteopetrosis. In: The EBMT Handbook:

Hematopoietic Stem Cell Transplantation and Cellular Therapies. 7th edition.

20. Schulz AS, Moshous D, Steward CG, Villa A, Sobacch C. Osteopetrosis – Consensus guidelines for diagnosis, therapy and follow-up. Version 3. Avaible from: https://esid.org/content/download/15294/420706/file/00_OP_Guidelines_V3.pdf

21. Neven B, Diana JS, Castelle M, et al. Haploidentical Hematopoietic Stem Cell Transplantation with Post-Transplant Cyclophosphamide for Primary Immunodeficiencies and Inherited Disorders in Children. Biol Blood Marrow Transplant. 2019 Jul;25(7):1363-1373.

22. Orchard et al. Hematopoietic stem cell transplantation for infantile osteopetrosis. Blood. 2015;126(2):270-276.

23. I.H.Bartelink, JJ.Boelens et al. EBMT/ESID Guidelines for haematopoietic stem cell transplantation for primary immunodeficiencies. 2017.