

BONE MARROW TRANSPLANTATION IN PATIENTS WITH STORAGE DISEASES

A developing country experience

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ABSTRACT - Bone marrow transplantation (BMT) is a therapeutic option for patients with genetic storage diseases. Between 1979 and 2002, eight patients, four females and four males (1 to 13 years old) were submitted to this procedure in our center. Six patients had mucopolysaccharidosis (MPS I in 3; MPS III in one and MPS VI in 2), one had adrenoleukodystrophy (ALD) and one had Gaucher disease. Five patients had related and three unrelated BMT donor. Three patients developed graft versus host disease (two MPS I and one MPS VI) and died between 37 and 151 days after transplantation. Five patients survived 4 to 16 years after transplantation. Three patients improved (one MPS I; one MPS VI and the Gaucher disease patient), one patient had no disease progression (ALD) and in one patient this procedure did not change the natural course of the disease (MPS III).

KEY WORDS: storage diseases, bone marrow transplantation, genetic neurological diseases, mucopolysaccharidosis, adrenoleukodystrophy, Gaucher disease.

Transplante de medula óssea em pacientes com doença de acúmulo: experiência de um país em desenvolvimento

RESUMO - O transplante de medula óssea é uma opção terapêutica para os pacientes com doenças de acúmulo. Entre 1979 e 2002, oito pacientes, quatro femininos e quatro masculinos (entre um e 13 anos de idade) foram submetidos a este procedimento em nosso centro. Seis pacientes apresentavam mucopolissacaridose (MPS I em 3; MPS III em um e MPS VI em 2), um paciente apresentava adrenoleucodistrofia e um apresentava doença de Gaucher. Cinco pacientes receberam o transplante de doador aparentado e três de doador não aparentado. Três pacientes desenvolveram doença do enxerto versus hospedeiro (dois com MPS I e um com MPS VI) e faleceram entre 37 e 151 dias após o transplante. Cinco pacientes sobreviveram entre 4 e 16 anos após o transplante. Três tiveram melhora clínica (um MPS I, um MPS VI e o paciente com doença de Gaucher), um paciente não apresentou progressão da doença (adrenoleucodistrofia) e um paciente não teve alteração da história natural da doença (MPS III).

PALAVRAS-CHAVE: doenças de acúmulo, transplante de medula óssea, doenças neurológicas genéticas, mucopolissacaridose, adrenoleucodistrofia, doença de Gaucher.

Bone marrow transplantation (BMT) is the intravenous infusion of hematopoietic progenitor cells to reestablish marrow function in a patient with damaged or defective bone marrow¹. It is widely used in a number of genetic and acquired, neoplastic and non-neoplastic diseases, including severe combined immunodeficiency, Wiskott-Aldrich syndrome, hyper IGM syndrome, Chediak-Higashi disease, hereditary

lymphohistiocytosis, thalassemia, sickle cell disease and in autoimmune diseases such as systemic sclerosis, systemic lupus erythematosus and multiple sclerosis^{2,3}. Since 1980, it has been advocated for storage diseases' treatment, when the first transplantation in a Hurler syndrome (MPS I) patient was done⁴. This therapy can be effective for selected inherited metabolic diseases including mucopolysaccharidosis (MPS)

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syndromes (Hurler, Maroteaux-Lamy and Sly syndromes), leukodystrophies (childhood-onset cerebral X-linked adrenoleukodystrophy (ALD), globoid-cell adrenoleukodystrophy, metachromatic leukodystrophy), fucosidosis, alpha-mannosidosis, Gaucher disease, Niemann-Pick type B, osteogenesis imperfecta, primary amyloidosis and malignant infantile osteopetrosis^{2,5-7}.

BMT provides a clinically practical method for permanently replacing deficient enzyme activity in patients with storage diseases. This is consequence of enzymatic activation in the new monocyte/macrophage system of the recipient derived from the donor, occurring also in the central nervous system (CNS)^{5,8}. The production of normal enzymatic activity occurs as a result of continuous marrow turnover. These newly derived marrow cells continue to proliferate and replace the recipient deficiencies⁸.

In this article, we describe the results of BMT in eight patients with storage diseases treated in a single institution.

METHOD

From October 1979 to May 2002 we performed 1337 BMT in Hospital de Clínicas of the Universidade Federal do Paraná, Curitiba - Brazil. In this group, we have eight patients with storage diseases submitted to transplantation

between 1988 and 2000. There were four boys and four girls and at the moment of BMT they had a medium age of 5 years old (1 to 13 years old). The source of stem cells was the bone marrow for all patients.

Six patients had mucopolysaccharidosis (MPS), three with MPS I, one with MPS III (Sanfilippo syndrome) and two with MPS VI (Maroteaux-Lamy syndrome). All of them received a combination of busulfan (16-20 mg/kg) + cyclophosphamide (120 mg/kg) for the preparatory regimen and cyclosporine and a short course of methotrexate for graft versus host disease (GVHD) prophylaxis. In this group, three patients were male and three were female. There were four related donor and two unrelated donor.

A thirteen years old boy with childhood-onset cerebral adrenoleukodystrophy (COALD) (magnetic resonance imaging (MRI) severity score or loes score: 8 and performance intellectual quotient (IQ) > 80) was submitted to an unrelated bone marrow transplant (one mismatch in locus B) in June 2000. The preparatory regimen consisted of cyclophosphamide 120 mg/kg, anti-lymphocytic globulin and hyperfractionated total body irradiation (with cranial sparing) and the GVHD prophylaxis was done with cyclosporine and partial T cell depletion.

The last patient was a three years old girl who had type 1 Gaucher disease and received BMT in November 1991 from an HLA identical sibling. The preparatory regimen consisted of busulfan 16 mg/kg and cyclophosphamide 120 mg/kg and GVHD prophylaxis with cyclosporine and short course of methotrexate.

Table. Patients submitted to BMT and clinical progression.

Case	Age (years)	Gender	Disease	Donor type	Preparatory regimen	GVHD prophylaxis	GVHD	Outcome*
1	2	M	MPS I	Related	Busulfan + Cyclophosphamide	Cyclosporine + Methotrexate	Absent	Improvement
2	4	F	MPS I	Unrelated	Busulfan + Cyclophosphamide	Cyclosporine + Methotrexate	Severe	Death at +37
3	3	M	MPS I	Related	Busulfan + Cyclophosphamide	Cyclosporine + Methotrexate	Severe	Death at +70
4	6	F	MPS III	Related	Busulfan + Cyclophosphamide	Cyclosporine + Methotrexate	Absent	Unaltered
5	2	M	MPS VI	Related	Busulfan + Cyclophosphamide	Cyclosporine + Methotrexate	Absent	Improvement
6	7	F	MPS VI	Unrelated	Busulfan + Cyclophosphamide	Cyclosporine + Methotrexate	Severe	Death at +151
7	13	M	ALD	Unrelated	Cyclophosphamide + ALG + TBI	Cyclosporine + partial T cell depletion	Absent	No progression
8	3	F	Gaucher	Related	Busulfan + Cyclophosphamide	Cyclosporine + Methotrexate	Absent	Improvement

* comparing with the natural history; BMT, bone marrow transplantation; Age, age at BMT; GVHD, graft versus host disease; MPS, mucopolysaccharidosis; ALD, Adrenoleukodystrophy; M, male; F, female; ALG, anti-lymphocytic globulin; TBI, total body irradiation.

RESULTS

Five patients are alive between 1146 to 5170 days after transplant and all but one (MPS III) had improvement or no progression. Three patients with MPS developed acute GVHD grade III to IV and one patient had extensive chronic GVHD. All of them died, two MPS I (37 and 70 days after BMT) and one MPS VI after 151 days of transplantation. These patients received a BMT from unrelated donors (2 patients) or a phenotypically identical donor (the mother of one patient) and the leading cause of death in all of them was the severe GVHD. The surviving patient with MPS I had no improvement in his bone disease or ophthalmic manifestations (Table).

The ALD patient did not develop any severe complication after transplant and persisted with adrenal insufficiency and steroid replacement. More than 2 years after transplant he still does not show any signs of neurological deterioration (Table).

The Gaucher disease patient had no severe complications and she is alive and well 3806 days post-BMT (Table).

DISCUSSION

Mortality in patients submitted to BMT to non-malignant disorders is 19%⁹. Peters et al. in a cohort of 40 patients receiving unrelated BMT for Hurler syndrome had a mortality rate about 50% within 2 years of follow-up, mainly of extensive chronic GVHD, that is the leading cause of death in these patients¹⁰⁻¹². In our study there is a mortality rate of 37% in the entire group and 50% in MPS.

In the MPS group, BMT was able to improve clinical symptoms in two patients (MPS I and MPS VI). All deaths occurred in MPS patients due to severe GVHD.

In MPS I, engraftment extends survival until the third decade of life after transplantation, compared with 5 to 10 years survival in patients untreated^{5,8}. A decision to transplant in MPS I therefore requires extremely careful patient assessment and family counseling especially where alternative donors are to be used. It is critical to perform the transplant as early as possible, ideally before 18 months of age, while intellectual function is relatively well preserved. Also, ongoing intensive physical, occupational and speech therapy are essential to optimizing development before, during, and after BMT⁶. Patients with MPS I may continue to progress with neurological deterioration because the microglial kinetics repopulation after transplantation is slower than that in peripheral macrophages¹¹. BMT had no impact over ophthalmic or

skeletal manifestations, and these observations are in accordance with previous reports⁶.

Our patient with MPS III according to the literature, despite the successful transplantation performed early in the disease did not have any significant neuropsychological improvement⁶.

MPS VI transplanted patients had improvement of clinical symptoms and in quality of life^{8,13}. The recommendation is to transplant as early as possible because life-limiting disabilities in these patients are very important⁸. All phenotypes of MPS VI are associated with reduced life expectancy and should therefore be considered candidates for BMT⁶. The BMT improves the general condition, cardiomyopathy and facial features, but skeletal benefit is limited¹³.

In ALD, the BMT is usually performed for the childhood-onset cerebral adrenoleukodystrophy (CO-CALD)^{6,8}. Patients with increase MRI severity score on initial analysis, posterior involvement and age less than 10 years are particularly prone to have rapid loss of function and should be considered for immediate transplantation¹⁴. Their five-year survival is 62% compared with nil in patients with MRI abnormalities without transplantation⁵. Unfortunately, the transplantation and disease-specific outcomes in a typical boy with occipital demyelination who is diagnosed due to clinical symptomatology plus MRI severity score over than 7 have been very discouraging because many patients die of disease progression. For survivors, there are permanent, severe neurological and neuropsychological sequelae, with compromised quality of life⁶. A recently published study shows that a baseline neurological and neuropsychological function, degree of disability and neuroradiological status predicts outcomes after BMT and patients with score less than 9 had a superior survival¹⁵. In this group of patients, a good indication for BMT seems to be a maintained intellectual quotient (IQ) level, preferably higher than 80, since it seems to be difficult to normalize IQ level after BMT. Identification of pre-symptomatic boys, serial and careful follow-up by neuropsychological and neuroradiological studies, and prompt arrangement of transplantation are essential to improve the results of BMT for ALD¹⁶.

In Gaucher disease, BMT greatly reduces the skeletal problems in type 1 disease⁶. Because of the selective involvement of bone marrow derived cells, type 1 Gaucher disease remains the prototype of the bone marrow therapy since successful engraftment cures the disease. On the other hand, there is little evidence that BMT has an effect on the neurological abnor-

malities in chronic neuronopathic Gaucher disease¹³. Nowadays, the treatment of choice for Gaucher disease is enzyme replacement therapy^{12,13}.

Patient selection is fundamental for a successful treatment, since engraftment is not always related to neurological improvement but just with a better quality of life. Timing is of great importance, as in the case of Hurler syndrome, since very mild or advanced diseases are less likely to benefit from treatment^{17,18}. ALD patients with performance IQ scores over 80 should be preferentially indicated for BMT. If marked cognitive decline develops, little benefit is attained from transplantation¹⁶.

Future developments in neonatal screening techniques and BMT methods may allow for a very early diagnosis and a safer transplantation, in order to avoid development of symptoms and obtain long lasting engraftment¹⁹.

In patients with Gaucher disease, enzyme replacement is the treatment of choice and despite its cost, it is currently available for most patients. Unfortunately for MPS I and VI, enzyme replacement is usually possible only in clinical trials⁶. Recently unrelated donor cord-blood transplant was done in a group of MPS I patients with improved neurocognitive performance and decreased somatic features²⁰. In the future the gene therapy could help these patients.

To increase the likelihood of a good outcome, complex, multidisciplinary decision-making regarding whether to recommend BMT, when to do so, and how to provide optimal peri- and post-transplantation care is essential. It has led to favorable outcomes for many but not for all disorders. Improvements in BMT techniques and the development of novel stem cells will significantly impact the safety and efficacy of therapy as well as expand the list of candidate diseases⁶.

The success of BMT depends on the specific enzyme deficiency and the stage of the disease. Generally, visceral symptoms can be improved, whereas skeletal lesions remain relatively unaffected. Early transplantation is the goal so that enzyme replacement may occur before extensive central nervous system injury becomes evident²¹.

In this study, it was not possible to perform a statistical analysis due to our number of patients, which although limited, represents the largest experience of BMT in storage diseases in Latin America. It is important to refer these patients early in the course of their disease so that they will be able to benefit from this high-risk procedure. Stem cell transplantation

can reduce and even stop disease progression in selected patients and that is why early diagnosis and immediate treatment are essential.

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