

LETTER TO THE EDITOR

Eighteen-year follow-up of the first Italian MPSI patient treated with bone marrow transplantation

Bone Marrow Transplantation (2008) **41**, 905–906;
doi:10.1038/sj.bmt.1705988; published online 18 February 2008

Mucopolysaccharidosis I (MPSI) is a lysosomal storage disease caused by the deficiency of the enzyme α -L-iduronidase. This genetic disorder leads to the widespread accumulation of the glycosaminoglycans (GAGs) heparan and dermatan sulphate in all organs and tissues and manifests itself with a wide spectrum of clinical symptoms, defining the disease in three major phenotypes: MPSI H (Hurler syndrome), MPSI HS (Hurler–Scheie syndrome) or MPSI S (Scheie syndrome). MPSI H is characterized by cardiac disease, obstructive airway disease causing sleep apnoea, joint stiffness, skeletal abnormalities, corneal clouding, hepatosplenomegaly, inguinal or umbilical hernia, and a severe and rapidly progressive central nervous system involvement, which is not present in MPSI HS. MPSI S is the most attenuated form, which is sometimes diagnosed late or even not recognized.¹

The first attempt at treatment took place in the 1980s, when a 1-year-old boy affected by MPSI underwent bone marrow transplantation (BMT), as described by Hobbs *et al.*² Despite the high transplant-related mortality at that time, BMT was the only therapeutic choice for two decades. A unanimous consensus on the use of this procedure in children below 3 years of age with an IQ above 70 was achieved in 2003.³ Since the advent of enzyme replacement therapy in the year 2000 (Aldurazyme; recombinant human α -L-iduronidase laronidase; Genzyme Corporation, Cambridge, MA, USA; BioMarin Pharmaceuticals Inc., Novato, CA, USA), there has been another therapeutic option for the long-term treatment of the non-neurological phenotype of MPSI.⁴ Here, we describe the first Italian transplanted patient affected by Hurler–Scheie syndrome, at 18 years post transplant.

The patient was born in 1978 and was diagnosed with MPSI syndrome at the age of 3 years after elevated urinary GAG assay (30.9 mg/mmol creatinine; normal value: 14.5 ± 3.4 mg/mmol creatinine) and null leukocyte α -L-iduronidase activity determination (0.2 nmol/h/mg of protein). Owing to the progression of the disease and the identification of a matched sibling, a carrier for the disease, the patient underwent BMT in 1989. Conditioning regimen included busulphan (16 mg/kg for 4 days) and cyclophosphamide (50 mg/kg for 4 days). The graft-versus-host disease (GvHD) prophylaxis consisted of cyclosporin A (3 mg/kg, i.v. and then 10 mg/kg orally for 6 months). Bone

marrow engraftment and full-donor chimaerism were achieved. The patient developed overall acute grade II GvHD that was resolved with concomitant steroid therapy. Two months after the procedure all the biochemical signs of the underlying disease disappeared and have been absent since then. α -L-iduronidase activity reached normal levels (84.18 nmol/h/mg of protein), and urinary GAG levels normalized to 16.9 mg/mmol creatinine. Liver biopsy showed a clearance of GAGs 6 months post BMT. Preexisting mild cardiac disease was shown by echocardiography and revealed mitral valve thickening with mild left ventricular insufficiency, with ejection fraction of 65%. Six- and 16-year follow-up show that BMT was able to maintain cardiac function and stopped the progression of valve thickening and heart insufficiency. Moreover, respiratory function is normal.

Despite the improvement of somatic disease, the patient needed the following surgical interventions: tendon elongation at the age of 14 years, stabilization of the lumbar column at the age of 16 years and carpal tunnel reduction twice on each side at the ages of 23 and 24 years. Bilateral corneal transplantation was required at the age of 22 and 23 years, respectively.

However, linear growth improved and the patient gained 26 cm and is now 137.7 cm tall (normal value 160 cm) and sexual maturity was reached at the age of 19 years with ongoing regular menses. The patient's perception of quality of life improved significantly and at the moment she works regularly.

In summary, we showed that BMT was successful in modifying the progression of the disease and inducing substantial clinical improvement of somatic disease. In contrast, BMT was not able to ameliorate the skeletal, ocular and peripheral neurological disease. Thus, early diagnosis is mandatory to perform BMT or haematopoietic stem cell transplantation under the age of 2 years to exploit organ plasticity.³

C Messina, A Rampazzo, S Cesaro, C Monciotti,
N Gasparotto, R Tomanin and M Scarpa
*Department of Pediatrics, University of Padova,
Padova, Italy*
E-mail: maurizio.scarpa@unipd.it

References

- 1 Neufeld EF, Muenzer J. The Mucopolysaccharidoses. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds). *The Metabolic*

- and *Molecular Bases of Inherited Disease*, 8th edn, vol. III. McGraw-Hill: New York, 2001, pp 3421–3452.
- 2 Hobbs JR, Hugh-Jones K, Barrett AJ, Byrom N, Chambers D, Henry K *et al.* Reversal of clinical features of Hurler's disease and biochemical improvement after treatment by bone-marrow transplantation. *Lancet* 1981; **2**: 709–712.
 - 3 Peters C, Steward CG. Hematopoietic cell transplantation for inherited metabolic diseases: an overview of outcomes and practice guidelines. *Bone Marrow Transplant* 2003; **31**: 229–239.
 - 4 Wraith JE. The first 5 years of clinical experience with laronidase enzyme replacement therapy for mucopolysaccharidosis I. *Expert Opin Pharmacother* 2005; **6**: 489–506.