

# Hematopoietic cell transplantation activity in Europe for inherited metabolic diseases: open issues and future directions

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## Summary:

**For the past two decades, hematopoietic cell transplantation (HCT) has been used as effective therapy for selected inherited metabolic diseases (IMD). The primary goals of this therapy have been to promote long-term survival with donor-derived engraftment and to optimize quality of life. Careful, multidisciplinary decision-making regarding whether to recommend HCT and how to provide optimal peri- and post-HCT care has proven essential to increase the likelihood of a good outcome. Guidelines for HCT and monitoring have recently been provided in this journal. Here we report data on transplant activity for IMD in Europe and briefly discuss future directions. It is imperative that data collection for these procedures becomes as routine as that for patients undergoing HCT for malignancy and that follow-up is performed in a systematic manner. Large clinical trials have never been performed in this transplant field. Fortunately, accreditation procedures and improvements in information technology can now provide a firm foundation for such trials, which are urgently needed.**

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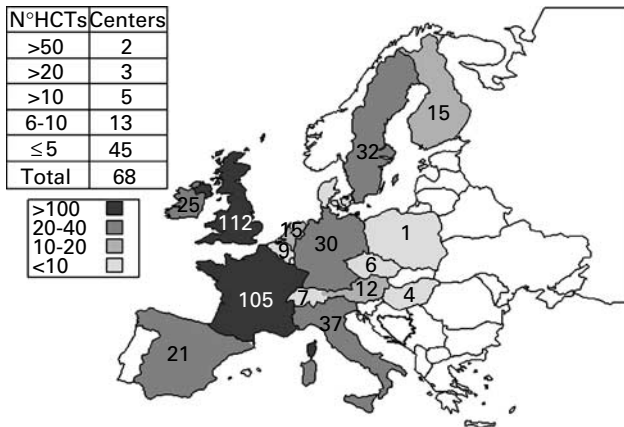
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Inherited metabolic diseases (IMD) comprise over 40 characterized genetic conditions with an aggregate estimated incidence approaching one in 7000 live births. In the last two decades, hematopoietic cell transplantation (HCT), enzyme replacement therapy (ERT) and, to a lesser extent, substrate reduction therapy (SRT) have been shown to be effective treatment strategies for these disorders. HCT provides highly effective therapy for selected patients with mucopolysaccharidosis type I (MPS I) and type VI, childhood onset cerebral X-linked adrenoleukodystrophy (ALD), globoid cell leukodystrophy, metachromatic

leukodystrophy (MLD), alpha-mannosidosis, osteopetrosis and a few other very rare conditions. The primary goals of HCT have been to promote long-term survival with donor-derived engraftment and to optimize the quality of life in selected patients with IMD. Current results and indications for the commoner diseases transplanted have been recently summarized.<sup>1</sup> Results have been particularly impressive for MPS I–H and ALD, although prolonged follow-up has been required to fully evaluate benefits. IMD are now at the convergence of many basic scientific discoveries and clinical trials of experimental treatments, which will modify the role of HCT. However, despite 20 years of HCT activity in this field, hundreds of transplants and papers, too many aspects of HCT remain unclarified. Some of the most relevant reasons are that data collection for these procedures has never become as routine as for patients undergoing transplantation for malignancies, follow-up has not been performed in a systematic manner and cooperative trials for such rare diseases have been lacking.

Since 1970, the European Bone Marrow Transplantation (EBMT) Group has been collecting data concerning patients transplanted in Europe. The first patient with IMD was registered in 1982. From 1982 to 2003, 468 HCTs for IMD were reported (Figure 1 and Table 1) by 68 centers. Unfortunately, in the EBMT Megafile, another 124 HCTs attributed to inborn errors have an unspecified diagnosis (although most are likely to be immunodeficiency disorders). Nearly half of the 468 transplants were performed in two countries, France and the United Kingdom, while other countries with large populations reported a far lower activity. This is best exemplified by the figures for MPS I transplants shown in Table 2. Comparative data about incidence and genetics among different European populations are lacking, but it is quite unlikely that this variation can explain such a discrepancy between European countries. Another possible explanation concerns problems in data collection and data flow. In some countries, HCT data are collected by National Registries and then passed on to the EBMT Registry. However, some registries do not use classification compatible with the EBMT Disease Classification Sheet No. 5, which allows for the subclassification of IMD. So it is possible that mistakes may occur and some information be lost between collection and final registration. However, problems with registration or communication between registries cannot be the sole explanation for the difference in numbers between

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**Figure 1** Distribution of HCTs for inherited metabolic diseases by country. Data from EBMT Registry 1982–2003,  $n = 468$  including Israel  $n = 24$ , Australia  $n = 4$ , Turkey  $n = 1$ , South Africa  $n = 1$ .

**Table 1** Distribution of HCTs by disease (data from EBMT Registry 1982–2003)

<i>Mucopolysaccharidoses</i>	276
MPS I	174
Others	36
Unspecified	66
<i>Sphingolipidoses</i>	75
Metachromatic leukodystrophy	35
Gaucher	13
Others	11
Unspecified	16
Adrenoleukodystrophy	83
Other	30
Unspecified	6
Total	468

**Table 2** Distribution by country of HCTs performed for mucopolysaccharidoses (MPS) (data from EBMT Registry 1982–2003)

Country	MPS type I	Other MPS	Unspecified MPS	Total no. of HCTs
United Kingdom	65	12	1	78
France	36	10	31	77
Ireland	23	1	1	25
Italy	8	8	9	25
Sweden	7	—	6	13
Austria	5	—	2	7
Israel	7	—	—	7
Spain	2	1	4	7
Belgium	4	—	2	6
Germany	1	—	5	6
Switzerland	5	—	1	6
Other seven countries	11	4	4	19
Total	174	36	66	276

countries. Sadly, our main conclusion is that there are real differences in current practice, thereby highlighting the need for standardization of practice across Europe. For

example, it is now possible to draw an algorithm for the clinical management of the different phenotypes of MPS I (Hurler, Hurler–Scheie, Scheie) incorporating the most relevant application of ERT and HCT.

The number of HCTs has been increasing with time. In most cases, the source of stem cells has been bone marrow, from either related or unrelated donors. In total, 70 HCTs have been performed with peripheral stem cells, mostly from unrelated donors. Only 17 used haploidentical donors. One would expect a higher number of cord blood transplants (CBT) in recent years considering that patients are often young and low in weight, but CBT comprised only 24 procedures, of which 16 were from unrelated donors. The role of CBT in patients with more severe disease phenotypes, which would allow rapid transplantation, has yet to be explored.

Unfortunately, the mechanisms of therapeutic benefit are generally not well understood (especially in ALD), nor are the lack of efficacy in some diseases that would be expected to benefit (eg Sanfilippo syndrome). The data indicate that a transplant for Sanfilippo syndrome has not been performed in Europe since 1996, but occasionally, patients with Hunter syndrome or progressing leukodystrophies are still transplanted despite available data, which suggests that HCT is contraindicated in these cases. Results in late-infantile MLD are still controversial and there is a critical need for retrospective review. There is often a lag period of 6–24 months before IMD stabilizes after HCT, making it necessary to extrapolate the likely condition of the patient at that future stage before deciding eligibility for transplantation. This lag is thought to be due to slow replacement of fixed tissue macrophages/histiocytes and microglial cells with cells of donor origin, together with the washout period of accumulated toxic metabolites. It is vital to collect information about the genotype, the specific organ damage and above all, the neuropsychological status at HCT to correctly evaluate the results. With the exception of few diseases (MPS I and ALD), most published data in this field are single case reports with short follow-up. A minimum set of data is included in the IBMTR and NMDP forms for IMD, but none of the European organizations collects data useful to define the long-term effect of HCT in these patients.

Historically, the overall survival after HCT for IMD patients otherwise fated to premature death has been reported in the largest series ranging from 50 to 85% according to the disease and type of transplant, with a transplant-related mortality (TRM) of approximately 10–15%. However, comprehensive data from recent years, when increased survival and reduced TRM should be expected, is lacking. The greatest challenge in this area of transplantation remains the high frequency of primary and secondary graft rejection and incomplete donor chimerism.<sup>2–6</sup> Initial engraftment has been reported to occur in 63–85% of MPS I–H patients, according to donor type and other transplant factors. Second graft procedures are needed in many patients, even where sibling donors have been used, increasing the risk of transplant-related morbidity and mortality. For example, a second transplant has been performed in 18% of MPS I patients reported to the EBMT Registry. Insufficiency of the myeloablative regimen

and immunosuppression has been considered the possible cause of such a high rate of rejection. A relevant number of patients (at least one-third of those transplanted in Europe) had a T-cell depleted graft because of concerns about the potential for GvHD to aggravate the inflammatory components of leukodystrophy, but the role of T-depletion has never been clarified. It has been suggested that earlier achievement of more complete donor chimerism by increasing cyclophosphamide doses may enhance long-term outcome after HCT for MPS I (Dr O'Meara, Dublin), and early results are encouraging. However, increasing regimen potency could enhance toxicity to fragile organ systems with pathological accumulation. Surprisingly, a remarkably low incidence of graft rejection and GvHD with favorable outcome has been reported by the Lyon group in France using a conventional BuCy regimen without *ex vivo* T-cell depletion.

Metabolic transplant procedures have relied mostly on a backbone of busulfan and cyclophosphamide conditioning. More recently there has been experimentation with increased immunosuppression, the addition of alternative agents such as melphalan, fludarabine and thiopeta, use of high stem cell doses and additional donor leukocyte infusions, but controlled data is lacking. It is generally believed that incomplete donor chimerism does not affect outcome since it is likely that as little as 10% of normal enzyme levels are required for full therapeutic effect. This supposition should be considered with care, particularly because of the lag phase to clinical stability. Many sibling donors will be carriers with approximately half of normal enzyme levels. When added to slow ingress of microglial cells and protracted washout of toxic metabolites, it seems likely that partial chimerism can only compromise the long-term benefit to the CNS of the transplant procedure.

A decade after the successful introduction of ERT for Gaucher diseases, this form of therapy has now been widened to other lysosomal storage diseases (Fabry disease, MPS I and VI, Pompe disease) and is under development for others (MPS II and IV, Niemann-Pick type B disease). However, the blood-brain barrier (BBB) prevents passage of potentially therapeutic drugs, including recombinant human enzymes. As examples, (a) in the neuronopathic form of Gaucher disease, ERT has been demonstrated to be clinically ineffective and (b) studies have already shown that laronidase (the synthesized form of alpha-L-iduronidase) does not appreciably cross the BBB and sequesters within the brain capillary endothelium in MPS I animals. Different techniques are under study to increase BBB permeability, but they are far from any clinical trial and the role of ERT seems limited to non-neuronopathic IMD. However, a further area of interest is the potential for pre-transplant ERT to reduce treatment-related mortality and to enhance engraftment and long-term outcome in IMD. Experimental protocols with laronidase pre- and post-HCT are under way in MPS I-H patients. Antibody levels to laronidase do not appear to reduce the efficacy of ERT,<sup>7</sup> but there are no data in the complex immunological setting of HCT about the possible role of ERT in favoring reactivity against the donor-derived enzyme. Pros and cons of combined (ERT + HCT) treatment therefore need careful elucidation by specific studies.

In the future it will be important to establish the correct place for transplant procedures alongside emerging therapies and new technology. Better understanding of genomics and proteomics may allow more accurate prognostication of disease severity: important both for patient selection for HCT and for gauging the impact of the procedure on the natural history of the disease. ERT is likely to supplant transplantation for some patients with milder forms of their diseases. Gene therapy (if therapeutic genes can be introduced in a large proportion of CNS target cells, with stable and integrated expression and a lack of significant toxicity) is an attractive approach to treat IMD and may render transplantation obsolete. The most striking results have been reported in animal models of MPS VII and MLD.<sup>8,9</sup> The greatest hope currently centers on the use of injectable lentiviral vectors that are currently undergoing initial trials. However, it seems unlikely that these therapies will be available to patients within a few years. Other current areas of interest are the use of mesenchymal stem cell infusions,<sup>10-12</sup> identification and expansion of neural stem cells and investigation of factors that can enhance neural repair.

For such rare diseases, it is imperative that data collection for these procedures becomes as routine as it has for patients undergoing transplantation for malignancy and that follow-up is performed in a systematic and standardized manner. A greater uniformity of protocols is crucial for proper studies. A critical review of various conditioning therapies used around the world is to be carried out by the Inborn Errors Group of the EBMT in November 2004; following this, recommended protocols for sibling and alternative donor transplants will be published on the EBMT site. Large clinical trials covering – as a minimum – all patients in Europe, will become necessary not only to clarify the many uncertain aspects of HCT in this field, but also to redesign the role of HCT as new therapies emerge. Fortunately, accreditation procedures (JACIE) and improvements in information technology can now provide a firm foundation for such trials.

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### References

- 1 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.
- 2 Peters C, Balthazor M, Shapiro EG *et al.* Outcome of unrelated donor bone marrow transplantation in 40 children with Hurler syndrome. *Blood* 1996; **87**: 4894–4902.
- 3 Peters C, Shapiro EG, Anderson J *et al.* Hurler syndrome: II. Outcome of HLA-genotypically identical sibling and

- HLA-haploidentical related donor bone marrow transplantation in fifty-four children. *Blood* 1998; **91**: 2601–2608.
- 4 Souillet G, Guffon N, Maire I *et al.* Outcome of 27 patients with Hurler's syndrome transplanted from either related or unrelated haematopoietic stem cell sources. *Bone marrow Transplant* 2003; **31**: 1105–1117.
  - 5 Peters C, Charnas LR, Tan Y, Ziegler RS *et al.* Cerebral X-linked adrenoleukodystrophy: the international hematopoietic cell transplantation experience from 1982 to 1999. *Blood* 2004; **104**: 881–888.
  - 6 Grewal SS, Krivit W, Defor TE *et al.* Outcome of second hematopoietic cell transplantation in Hurler syndrome. *Bone marrow Transplant* 2002; **29**: 491–496.
  - 7 Wraith JE, Clarke LA, Beck M, Kolodny EH *et al.* Enzyme replacement therapy for mucopolysaccharidosis. I: A randomized, double-blinded, placebo-controlled, multinational study of recombinant human alpha-L-iduronidase (laronidase). *J Pediatr* 2004; **144**: 581–588.
  - 8 Ellinwood NM, Vite CH, Haskins ME. Gene therapy for lysosomal storage diseases: the lessons and promise of animal models. *J Gene Med* 2004; **6**: 481–506.
  - 9 Biffi A, De Palma M, Quattrini A *et al.* Correction of metachromatic leukodystrophy in the mouse model by transplantation of genetically modified hematopoietic stem cells. *J Clin Invest* 2004; **113**: 1118–1129.
  - 10 Herzog EL, Chai L, Krause DS. Plasticity of marrow-derived stem cells. *Blood* 2003; **102**: 3483–3493.
  - 11 O'Malley K, Scott EW. Stem cell fusion confusion. *Exp Hematol* 2004; **32**: 131–134.
  - 12 Koc ON, Day J, Nieder M *et al.* Allogeneic mesenchymal stem cell infusion for treatment of metachromatic leukodystrophy (MLD) and Hurler syndrome (MPS-IH). *Bone Marrow Transplant* 2002; **30**: 215–222.