

* CHAPTER 41

HSCT for inborn errors of metabolism

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1. Introduction

For the past two decades, HSCT has been used as an effective therapy for selected inborn errors of metabolism (IEM). This group of conditions consists of several lysosomal storage diseases (LSDs) and peroxisomal disorders, osteopetrosis and a variety of rare miscellaneous disorders (e.g. purine nucleoside phosphorylase- and adenosine deaminase deficiency, mevalonic aciduria).

Frantantoni and Neufeld laid the foundation for our understanding of transferable lysosomal enzymes by demonstrating cross-correction of metabolic defects in co-cultures of fibroblasts from Hurler and Hunter syndrome patients. These results provided the rationale for Hobbs to trial HSCT in a Hurler patient in the early eighties (1). Dramatic improvement in the clinical phenotype of this first patient resulted in over 1000 HSCTs for various IEM (>20 diseases/disorders) worldwide. Unfortunately, for unknown reasons not all LSDs benefit from HSCT, and therefore careful evaluation of the effect of HSCT is important to make clear guidelines on indications for HSCT. In addition, success has been limited by high rates of graft-failure (15–75%), transplant-related-mortality and absence of instant availability of unrelated donors for rapidly progressive diseases (2, 3). Risk-factor analyses and improved transplantation techniques including the rapid availability of umbilical cord blood (UCB) have resulted in less graft-failure and less transplant-related mortality. In osteopetrosis HSCT can correct the disease by providing haematopoietic stem cells as well as osteoclasts. Success is dependent on timing of the procedure, and possibly also depends on stem cell source as well as on the underlying genetic defect. In this Chapter, indications for HSCT are discussed and current guidelines of HSCT for IEM are summarised.

2. Lysosomal storage diseases and peroxisomal disorders

2.1. Indications

Despite the fact that HSCT for IEM have been performed for more than 25 years, series of considerable size are only present for Hurler's syndrome, infantile Krabbe Disease and X-ALD. In other disorders the effects and outcome of HSCT are difficult to assess because of the limited number of cases, wide range of clinical heterogeneity and the absence of a good functioning registry for proper long-term follow-up. If damage to the central nervous system (CNS) is present, this is irreversible and therefore a contra-indication for HSCT in all candidate diseases (4, 5). The indications and contra-indications are listed in [Table 1](#). This guideline however should be interpreted in the context of progress in transplantation.

2.2. Results

Quality of life in successfully transplanted patients for certain indications, like Hurler's syndrome (HS), seems encouraging. However the relatively high rates of graft-failure (15–75%) and transplant-related toxicity limits its success (2, 6). Since HS is the most frequent indication for HSCT within the LSD-group of IEM, HSCT for HS serves as a model for a risk factor analysis for graft failure. In multivariate analysis (n=146 HS-patients, transplanted between 1994–2004), T-cell depletion and reduced intensity conditioning were found to be serious risk-factors for graft failure (6). Busulfan-targeting (Therapeutic-Drug-Monitoring) on the other hand protected against graft failure. No difference in graft failure was noted between the different cell sources used (BM, PBSC or UCB). However, significantly (p=0.037) more patients receiving cord-blood achieved full-donor chimerism. This is in line with other studies (4, 7) using UCB in IEM and was once again observed in a recent 'EUROCORD-EBMT Working Party Inborn Errors' survey (n=42): the EFS after 2001, was 84% using UCB, similar to that found in the same period using BM or PBSC. All UCB recipients however (except two with a donor chimerism of 90 and 94%) had full-donor chimerism and all had normal enzyme levels, in comparison to 60% in the BM/PBSC matched controls from the same period (publication pending).

Although no large studies have examined the effect of lower enzyme levels after HSCT

Table 1: Guideline for indications (Peters et al. (2); Boelens et al. (3))

Disease	Indication
Mucopolysaccharidoses (MPS)	
<i>MPS I</i>	Yes
- Hurler	No **
- Hurler-Scheie	
<i>MPS VI; Maroteaux-Lamy</i>	
- Severe phenotypes	No **
<i>MPS VII; Sly</i>	Yes
<i>Other MPS</i>	No
Leukodystrophy	
<i>X-linked adrenoleukodystrophy</i>	
- Cerebral	Yes
<i>Metachromatic leukodystrophy</i>	
- Juvenile subtype	In development***
- "Late subtype"	Yes
<i>Globoid leukodystrophy</i>	
- Early infantile subtype (Krabbe's disease)	Yes
- Late onset type	Yes

continue

Disease	Indication
Other inborn errors of metabolism	
<i>Fucosidosis</i>	In development***
<i>α-mannosidosis</i>	Yes
<i>Aspartylglucosaminuria</i>	In development***
<i>Farber's lipogranulomatosis</i>	In development***
<i>Gangliosidosis</i>	
- GM1	In development***
- GM2	No
<i>Gaucher</i>	
- Type I	No **
- Type III	No/ Yes *
<i>Mucopolipidosis I</i>	In development***
<i>Neuronal ceroid lipofuscinosis (NCL)</i>	
- NCL 1	No
- NCL 2	No
<i>Niemann-Pick</i>	
- Type B	Yes
- Type A and C	In development***
<i>Osteopetrosis</i>	
Exclude neuronopathic osteopetrosis (e.g. in OSTM1) and carbonic anhydrase type II deficiency. Be cautious in case of mild or transient phenotype: discuss with experts	
- Malignant infantile subtype	Yes *
- Wolmans disease	Yes
<i>Adenosine-deaminase-deficiency</i>	Yes
<i>Purine-nucleoside-phosphatase-deficiency</i>	Yes
<i>Mevalonic aciduria</i>	In development***

*ERT: enzyme replacement therapy, MPS: Mucopolysaccharidosis. * No/Yes: depending on clinical phenotype, ** No: SCT is not indicated because of ERT, *** In development: not a clear indication, but is being evaluated in clinical and pre-clinical studies or single cases suggest efficacy. This guideline is applicable for patients who do not have any central nervous system (CNS) involvement or those who are only slightly affected. Advanced disease is always a contra-indication for HSCT. Since intravenous enzyme replacement therapy (ERT) does not cross the blood-brain-barrier, ERT is not a treatment option where there is CNS involvement. Donor derived monocytes do cross the blood brain barrier. This table is mainly based on patients receiving bone marrow or peripheral blood stem cells. Emerging stem cell sources, such as umbilical cord blood, as well as improvement of transplantation techniques, may in future extend the list*

on long-term outcome parameters, there are recent suggestions that it does influence the neuro-cognitive outcome. Since cord-blood appeared to increase the likelihood of sustained engraftment resulting in full-donor chimerism and normal enzyme levels, cord-blood should be considered as a preferential stem cell source. Because the enzyme level is reduced in heterozygous family donors – and further reduced again if there is mixed donor chimerism after the transplant when using BM/PBSC, carrier donors will produce lower enzyme levels making them a less preferable donor, despite HLA-

Table 2: Donor hierarchy and conditioning**a. Hierarchy of preferred stem cell source:**

1. SIB/MFD (not carriers)
2. UD (10/10 allel match)* or unrelated cord blood (UCB: 6/6)
3. UCB (5/6 Ag match)
4. UCB (4/6 Ag match) or mismatched-UD (non-T-depleted)
5. UCB (3/6 Ag match) or HAPLO

Notes:

- UD (10/10) may be bypassed depending on institutional preference or because of time
- For UD: either BM or PBSC ($>10 \times 10^6/\text{kg}$) could be chosen
- Cell dose for UCB: 5-6/6 match: $>3.0 \times 10^7$ NC/kg and/or 2×10^5 CD34+/kg, 4/6-match $>5 \times 10^7$ NC/kg and/or $>3 \times 10^5$ CD34+/kg. Matching according to intermediate resolution criteria (low resolution on A and B, high resolution on DR)
- Unrelated donors are regarded as non-carriers of the mutation
- In case of osteopetrosis: currently no preference for unrelated marrow, cord blood or haploidentical transplant can be advised. Minimum cord blood stem cell dose as defined above should be used.

b. Pretransplant immunosuppression:

- SIB: no
- UD/UCB: either Campath-1H 3×0.3 mg (day -9 to -7)
or ATG-SangStat 4×2.5 mg/kg (day -4 to -1)

c. Conditioning:

- SIB/UCB/UD: Busulfan 480 mg/m^2 total dose (IV: day -9 to -6)
with therapeutic drug monitoring AUC $20000 \mu\text{g} \times \text{h/L}$ (cumulative per day)
Cyclophosphamide 200 mg/kg total dose (day -5 to -2)
- HAPLO: Bu/Cy + fludarabine 160 mg/m^2 (4×40 mg)

Note:

For osteopetrosis the WP-IE of the EBMT is currently writing a protocol. The conditioning regimen will probably be busulfan (IV), fludarabine, +/- thiotepa based.

d. GvHD-prophylaxis:

- SIB: CsA (+ MTX: 10 mg/m^2 ; day +3, +6 and +11)
 - UD (BM):
 - with Campath-1H: CsA
 - with ATG: CsA + MTX (10 mg/m^2 ; day +3, +6 and +11)
 - UD (PBSC) UD/Mismatched-UD (BM): CsA + MMF (30 mg/kg ; stop day +28 if no GvHD)
 - UCB: CsA + prednisolone 1 mg/kg (until day +28, taper in 2wks)
- In all cases aim for a CsA-trough level: $200 \mu\text{g/L}$*

Tapering CsA-prophylaxis:

- SIB/UD: CsA until day +50. Then taper 20% per week
- UCB: CsA until + 6 months. Then taper over 3 months

SIB: HLA matched sibling; MFD: matched family donor; HAPLO: haploidentical donor; UD: unrelated donor

matching (see guidelines EBMT: www.EBMT.org; [Table 2](#)). A study on the long-term outcome and the influence of mixed-chimerism/enzyme levels within the European series began in summer 2007.

The observation of less mixed-chimerism in patients receiving UCB is intriguing. Possible factors contributing to this higher level of donor engraftment include better graft-versus-marrow (GvM) effect because of the greater mismatch, the greater proliferative potential of cord blood stem cells and the presence of mesenchymal cells in the cord blood that favourably influence engraftment.

2.3. Risk factors/morbidity

In the early reports on HSCT of IEM (mainly HS) high rates of GvHD and idiopathic pneumonia syndrome (IPS) were reported. Within the EBMT study the incidence of GvHD and pulmonary complications was considerably lower, 16 and 8%, respectively. The incidence of chronic GvHD was only 5–15%. Since graft failure was common until recently second transplants were performed quite often. Survival after second transplant in the EBMT-series in Hurler's syndrome (n=33) was over 80%.

2.4. Enzyme replacement therapy and SCT

Enzyme replacement therapy (ERT) has become available for various indications (e.g. Gaucher, MPS-1, MPS-2, MPS-6). However for diseases with CNS involvement, like Hurler's syndrome, HSCT remains the treatment of choice. In a study analysing the effects of ERT on EFS and transplant-related morbidity, patients receiving HSCT + ERT were compared with those receiving HSCT alone. Neither a positive nor a negative effect on EFS after receiving ERT prior to HSCT was noted, as compared to a historic cohort. However, in those patients in a poor clinical condition (e.g. cardiomyopathy, severe respiratory problems) prior to HSCT, ERT can be considered to improve the general clinical condition making them eligible for HSCT (8).

2.5. The future

More detailed long term follow up outcome should be measured in this group of patients to define better guidelines regarding selection of patients eligible for transplantation as well as better guidelines for transplantation techniques. For Hurler's syndrome such a study has been initiated recently. More than 150 successfully transplanted patients will be analysed for predefined long-term outcome parameters within the upcoming years.

Neonatal screening might also influence the outcome. Early detection and transplantation might further influence the effect of HSCT, since HSCT in pre-symptomatic infants is safer than in symptomatic patients with organ damage.

3. Osteopetrosis

3.1. Indications and results

A study has recently been published proving the principle that TCIRG1 based osteopetrosis in mice can be corrected by introducing the gene in haematopoietic stem cells (9). Clinically, the largest series of HSCT for osteopetrosis reported to date is described by Driessen et al. (n=122: Transplants between 1980–2001) (10). The majority of patients (n=40) were transplanted with an HLA-identical sibling donor, resulting in a 5 yr DFS of 73%. For unrelated donor and haplo-identical transplants the DFS was less impressive, 40% and 24%, respectively. However, haploidentical-transplants performed in experienced centres show a clear improvement over time. UCB appears to be a good alternative stem cell source: a recent EUROCORD-study on the outcome of UCB-transplantation (n=25) showed an “alive and engrafted”-rate of about 50% (Bierings et al., EBMT abstract 2007). For indications and contra-indications in different geno- and phenotypes of the disease see Table 1. Functional outcome and the impact of various genetic subtypes have not been assessed successfully so far.

3.2. Risk factors and morbidity

Transplant toxicity in HSCT for osteopetrosis is mainly caused by graft-failure, pulmonary complications and veno-occlusive disease (VOD). VOD can successfully be prevented by defibrotide (11). Pulmonary arterial hypertension is mainly seen in the first 3 months after HSCT, while outcome of treatment for pulmonary hypertension is generally poor.

3.3. The future

Careful evaluation of long-term follow-up is of utmost importance. An analysis of the impact of different genotypes on outcome is currently ongoing. A new IV busulfan – fludarabine ± thiotepa regimen is being discussed within the EBMT-WP-IE.

4. Miscellaneous IEM

In addition to the IEM discussed above, some miscellaneous IEM will profit from HSCT. These indications include adenosine deaminase (ADA) and purine-nucleoside-phosphorylase deficiencies (PNP) resulting in a (severe) combined immunodeficiency due to storage of toxic metabolites in lymphocytes, leading to profound lymphopenia. For ADA-SCID more treatment options are available: PEG-ADA and gene-therapy. ADA and PNP are discussed in more detail in Chapter 40. Recently, a successful transplantation has been performed in mevalonic aciduria refractory to steroid and

therapeutic monoclonal antibody. After successful sibling transplantation, HSCT resulted in almost normalisation of the excretion of mevalonic acid and in a long-term complete remission of the disease without any immunosuppressive medication.

5. Conclusion

HSCT is an effective procedure for selected IEM. The procedure has become much safer with EFS rate of more than 80% in a-symptomatic/slightly affected LSD patients in recent years.

Clear guidelines for indications, donor selections and conditioning regimens have been made recently. Umbilical cord blood has become the cell source of preference for several indications. Guidelines should be interpreted in the context of transplantation progress. Improvement of transplantation techniques and alternative therapies may change the recommended indications and contraindications for IEM.

References

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Mutiple Choice Questionnaire

To find the correct answer, go to <http://www.esh.org/ebmt-handbook2008answers.htm>

1. There are no treatment options for patients with an IEM:

- a) Correct statement.....
- b) HSCT is an effective treatment for all IEM.....
- c) HSCT is a treatment option for a selected group of IEM.....
- d) HSCT is only effective in Hurler syndrome patients.....

2. Which of the following statements about enzyme replacement therapy (ERT) is correct?

- a) ERT is a safer and more effective treatment option for IEM than HSCT...
- b) ERT is only effective in IEM without neurological involvement, since ERT does not cross the "blood brain barrier".....
- c) ERT is necessary pre-transplant to prevent transplantation related mortality and graft failure.....
- d) ERT + HSCT is the most effective treatment for IEM for all indications...

3. Which of the following statements about graft failure in HSCT for IEM is correct?

- a) Historically, high graft failure rates were reported mainly associated with T-cell depleted grafts and "reduced intensity conditioning".....
- b) Graft failure has never been a problem in HSCT for IEM.....
- c) Not graft failure but TRM is the major problem in HSCT for IEM.....
- d) Less graft failure is reported using unrelated cord blood as stem cell source.....

4. The period between diagnosis and HSCT is not important, the outcome depends on the degree of donor matching:

- a) No, the shorter the period between diagnosis and HSCT, the better the outcome
- b) Correct, you should not use mismatched grafts in IEM
- c) Correct, do not use unrelated cord blood
- d) Correct, even neonatal screening will not improve outcome

5. For every genotype of osteopetrosis HSCT is a potentially curative treatment option:

- a) Correct statement
- b) HSCT is not a treatment option for any genotype
- c) HSCT is only a treatment option for selected genotypes
- d) Not HSCT but ERT is currently the state of the art treatment for all genotypes of osteopetrosis