CHAPTER 43

HSCT in the haemoglobinopathies

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1. Introduction

Although advances in iron chelation therapy, transfusion and supportive care have dramatically improved life expectancy in thalassaemia major and sickle cell disease (SCD), patients continue to suffer disabling symptoms, particularly in adulthood, and most die prematurely from complications of the disorders and/or their treatment. HSCT is the only proven cure, effecting both resolution of symptoms and freedom from life-long, emotionally- and physically-demanding treatment (1, 2). The decision to undergo HSCT is often difficult since these disorders are not usually immediately life-threatening.

2. Indications for HSCT in thalassaemia (Table 1)

All transfusion-dependent children with HLA-identical family members are eligible for HSCT, including the rare cases of α-thalassaemia major. For patients with HbE/β-thalassaemia or thalassaemia intermedia, treatment must be individually tailored, as these diseases are heterogeneous: severely affected patients are transfusion-dependent and can benefit from HSCT. Improving medical treatment and inferior outcome with unrelated donors and in adults means that HSCT for these patients should only be considered in carefully selected patients and the procedure carried out in centres experienced in management of haemoglobinopathies. We advise delaying HSCT until both patient and donor are ≥2 years.

Table 1: **Indications for HSCT in thalassaemias**
1. Definite indication for HSCT: - Transfusion-dependent α- or β-thalassaemia major; transfusion-dependent HbE/β-thalassaemia - Age ≤16 years - HLA-identical family donor
2. Candidates who may be considered for HSCT in special circumstances: - Transfusion-dependent thalassaemia major in adults aged 17–35 years - Thalassaemia relapsing after previous HSCT - Transfusion-dependent S-β^0 thalassaemia - Thalassaemia intermedia

3. Indications for HSCT in SCD (Table 2)

Most clinicians offer HSCT only to patients with specific complications of SCD which predict for a poor prognosis. Many also offer HSCT to families wishing to return to countries without reliable access to good medical care. Pre-HSCT assessment must include neurological assessment (MRI/MRA, transcranial Doppler studies, neurocognition) and may reveal unanticipated severe cerebral vasculopathy ("moya moya"), which increases TRM and morbidity; such cases must be discussed with experts in SCD before proceeding to HSCT.

Table 2: **Indications for BMT in sickle cell disease (SCD)**

1. Definite indication for HSCT:
- One or more of the following clinical complications:
  - SCD-related neurological deficit, stroke or subarachnoid haemorrhage
  - Recurrent acute sickle chest syndrome (>2 episodes) which has failed to respond to a trial of hydroxycarbamide of at least 6 months or where hydroxycarbamide is contraindicated
  - Recurrent, severe debilitating pain due to vaso-occlusive crises which has failed to respond to a trial of hydroxycarbamide of at least 6 months or where hydroxycarbamide is contraindicated
- Age ≤16 years
- HLA-matched family donor

2. Candidates who may be considered for HSCT in special circumstances:
- Problems relating to future medical care e.g. unavailability of adequately screened blood products
- SCD relapsing after previous HSCT
- Transfusion-dependent S-β^0 thalassaemia
- Adults aged 17–35 years (as part of clinical trial)

Modified from the British Paediatric Haematology Forum Criteria (Amrolia et al., 2003a)

4. Conditioning regimens for haemoglobinopathies (Table 3)

The most commonly employed myeloablative regimens use oral busulfan (14–16 mg/kg) and intravenous cyclophosphamide (200 mg/kg); thiotepa, fludarabine or melphalan may be added to reduce graft rejection but their role is unproven (1, 2). Some groups, including ours, add ATG or alemtuzumab to pre-HSCT conditioning to reduce graft rejection with encouraging results, although it is important not to employ the high doses used to prevent GvHD (3). Hypertransfusion (maintaining Hb >13 g/dL) for 6 weeks prior to and after HSCT also reduces graft rejection. Reduced cyclophosphamide (120 mg/kg) is recommended for Pesaro Class 3 patients (see "Prognostic factors") to avoid high TRM but must be combined with other measures to prevent graft rejection (e.g. ATG, red cell hypertransfusion, fludarabine). Most groups use cyclosporin/methotrexate as GvHD prophylaxis; many now use low-dose methotrexate (2 doses of 10 mg/m^2) as graft rejection is less (3, 4). Busulfan dose-adjustment via blood levels has no significant impact on OS or EFS. Methotrexate is generally omitted in cord blood transplants (CBT) due to increased risk of graft rejection (5).

Table 3: **Conditioning regimens for haemoglobinopathies**

Drug	Total dose	Schedule of administration	Alternatives
Busulfan	14–16 mg/kg	1 mg/kg orally per dose; usually given day -9 to -6	iv busulfan treosulfan
Cyclophosphamide	200 mg/kg	50 mg/kg iv per dose usually given day -5 to -2 Give Mesna (twice cyclophosphamide dose)/ Use lower dose (120–160 mg/kg) in Pesaro Class 3	-
Alemtuzumab	0.3 mg/kg	0.1 mg/kg iv per dose usually days -8 to -6	ATG fludarabine melphalan thiotepa

5. Results of HSCT for thalassaemias

5.1. Role of HSCT in thalassaemia

The aim of HSCT is to improve long-term survival and/or quality of life (QoL). There are no controlled survival or QoL trials of HSCT versus medical treatment in thalassaemia. However, recent data show that patients who comply with iron chelation, and have no cardiac or liver damage, survive into their fifth decade (6). Since TRM is 2–5% and the risk of graft failure is ≤5%, such patients have a predicted survival of around 90–95% to age 40 with either therapeutic approach and the decision to proceed to HSCT should be based on QoL, i.e. the perceived benefit of freedom from life-long transfusions, chelation and their long-term complications. By contrast, for patients with poor compliance, few survive to age 40 and for them HSCT offers not only improved QoL, but also increased long-term survival (6). However, it is often very difficult to predict which children will accumulate iron in their organs, sometimes despite adequate chelation, and the results of transplantation before significant iron accumulation and organ damage has occurred can assure long term cure.

5.2. Prognostic factors (Tables 4 and 5)

5.2.1. Pesaro class

Analysis of the first large series of patients undergoing HSCT for thalassaemia identified 3 independent prognostic factors for outcome in children (Table 4):

- Hepatomegaly

- Liver biopsy evidence of portal fibrosis
- Irregular compliance with chelation.

These factors form the basis of the Pesaro classification into good, intermediate and poor risk (Class 1, 2 and 3 respectively). Table 5 shows how Pesaro class predicted OS, thalassaemia-free survival and graft rejection (1). Even modest organ damage pre-HSCT increased TRM. Pesaro classification does not predict outcome in all centres- perhaps due to low TRM in many recent series. Nevertheless, it is useful for identifying high-risk patients who may not benefit from HSCT or who may need modified conditioning (4).

Table 4: **Pesaro Classification for predicting outcome of HSCT for thalassaemia major**

Risk factors	Class 1	Class 2*	Class 3
Hepatomegaly (>2 cm below costal margin)	No	Yes/no	Yes
Irregular chelation#	No	Yes/no	Yes
Portal fibrosis on liver biopsy	No	Yes/no	Yes

** One or two of any of the 3 risk factors; # Desferrioxamine started >18 months after regular transfusions commenced or desferrioxamine administered <8 hours/night on at least 5 nights per week*

Table 5: **Outcome of BMT for thalassaemia by Pesaro Risk Classification***

	Class 1	Class 2	Class 3#
Survival (%)	93	87	93
Thalassaemia-free survival (%)	90	84	85
Transplant-related mortality (%)	6	13	6
Graft rejection (%)	7	4	8

Data are mostly taken from Schrier and Angelucci, 2005 (1).
** See Table 4; # Data from Sodani et al., 2004 (4) using modified conditioning regimen*

5.2.2. Other factors

In children <17 years, age is not an independent predictor of outcome. However, adults consistently show inferior OS and EFS to children (64% OS; 62% EFS), even using reduced-intensity conditioning (RIC) (1, 7). Hepatitis B/C infection affects neither TRM nor EFS. Thalassaemia trait in the donor does not affect outcome.

5.3. Outcome of HSCT for thalassaemia using HLA-matched family donors (Table 5)

Most groups currently report OS of 90–95% and thalassaemia-free survival of 80–90% in children (1, 3). Acute GvHD and infections are the commonest causes of TRM. Severe chronic GvHD after sibling SCT is uncommon (2–5% of patients). Graft rejection (~10%) is more common and usually occurs within 6 months. Therefore, monthly donor/host chimerism (peripheral blood) should be monitored for the first 3–6 months; falling donor chimerism usually responds to manipulation of immune suppression. Anecdotal experience suggests DLI rarely reverses established rejection but may be successful if used early. Failure of primary engraftment with aplasia is rare and has a poor outcome even with second HSCT and autologous HSCT may be safer; therefore cryopreservation of autologous marrow prior to allogeneic HSCT may be advisable.

Most HSCT for thalassaemia use marrow from HLA-identical siblings; where there is consanguinity, other close relatives may be HLA-identical and outcome is not significantly different. Families without sibling donors often extend their families, with/without prenatal or pre-implantation genetic diagnosis. PBSC are not generally chosen for thalassaemia HSCT since most donors are young children (reluctance to use G-CSF or central venous catheters) and the largest series showed more severe GvHD in PBSC transplants (8).

5.4. Outcome and role of cord blood transplantation (CBT) for thalassaemia

CBT data from HLA-identical siblings are limited and show excellent OS (100%) but significant graft rejection (21%) which can be reduced by omitting methotrexate and including thiotepa in conditioning (4). Since graft rejection is significant, it is reasonable to use cord blood only where the total nucleated cell dose is >3 x 10^7/kg and to wait until the donor is ≥2 years of age so “back up” donor marrow is available.

5.5. Outcome and role of unrelated donor HSCT for thalassaemia

Experience of unrelated donor SCT for thalassaemia is limited to small numbers with a variety of conditioning regimens, age groups and donor types and relatively short follow up (9). Recent data confirm lower OS (79%) and thalassaemia-free survival (66%) after unrelated compared to HLA-identical family donors. At present the role of unrelated donor HSCT in thalassaemia remains to be established and is best investigated through well-designed clinical trials.

6. Results of HSCT for SCD

6.1. Role of HSCT in SCD

SCD is very heterogeneous. Although all patients have impaired QoL because of unpredictable pain and progressive organ damage, specific clinical features (e.g. recurrent chest syndrome, stroke and frequent severe painful crises) best identify SCD patients with a poor prognosis (2). For them HSCT offers both improved QoL and, since 50–60% of adults with SCD fail to reach their 50s, better prospects for long-term survival.

6.2. Prognostic and risk factors

The Pesaro classification does not apply to SCD and there is no equivalent prognostic score for SCD. However, careful evaluation of patients enrolled in transfusion programmes for CNS disease is recommended. Donor sickle cell trait does not affect outcome.

6.3. Outcome of HSCT for SCD using HLA-matched family donors (Table 6)

Approximately 250 patients have been transplanted worldwide, virtually all <16 years and most for complicated SCD, particularly SCD-related stroke (Table 6) (2, 10–12). OS is ~90%; SCD-free survival 82–86%; TRM 7–8% and graft rejection 8%. All patients with stable engraftment no longer had clinical manifestations of SCD. Commonest causes of TRM are GvHD and infections. The risk of neurological complications is increased in the peri-HSCT period (1/3 of patients), particularly seizures and intracranial haemorrhage. However, these neurological problems are reduced significantly by prophylactic anticonvulsants before HSCT continuing for at least 6 months; maintaining platelets >50 x 10^9/L; and rigorous control of cyclosporin, magnesium and blood pressure. Graft failure occurs in 10–18% almost always with autologous reconstitution/relapse of SCD. Mixed haematopoietic chimerism is usually stable but falling donor haematopoiesis has been successfully treated by DLI. Chimerism should be monitored monthly for the first 6 months.

Table 6: **Outcome of BMT for sickle cell disease**

	Walters et al. 2000 (n=50)	**Bernaudin et al. 1997 (n=26)**	**Vermylen et al. 1998 (n=50)**	**Panepinto et al. 2007 (n=67)**
Overall survival	94% (6 yr)	92% (8 yr)	93% (11 yr)	97% (5 yr)
Event free survival	84% (6 yr)	75% (8 yr)	82% (11 yr)	85% (5 yr)
Graft rejection*	10%	18%	10%	13%
Acute GvHD ≥ Grade 2	8%	23%	20%	10%
Chronic GvHD - extensive	4%	8%	6%	4%

* *All had autologous reconstitution with relapse of SCD*

6.4. Outcome and role of CBT for SCD

CBT data from HLA-identical sibling donors are limited and show excellent OS (100%) (4). Graft rejection occurs but numbers are too small for analysis of risk factors. Similar principles about the role of CBT apply in SCD as those in thalassaemia. Methotrexate should be omitted; thiotepa may be added to conditioning and cord blood should be used only where the total nucleated cell dose is >3 x 10^7/kg. It is recommended to wait until the donor is ≥2 years old so "back up" donor marrow is available.

6.5. Outcome and role of unrelated donor HSCT for SCD

Unrelated donor HSCT for SCD is not routinely recommended and experience is limited to occasional case reports.

7. Long-term effects of SCT for haemoglobinopathies: special features

Iron overload improves slowly post-HSCT but can be accelerated by regular phlebotomy or chelation beginning 9–12 months after HSCT until the total iron burden approaches normal (liver iron <5 mg/g DW; serum ferritin <700 ng/mL) (1). There are few data on fertility post-HSCT for thalassaemia and SCD although occasional pregnancies and paternities have been reported. Advances in cryopreservation of testicular and ovarian tissue show promise even for pre-pubertal children; available options should be discussed with families prior to HSCT.

8. Conclusions

HSCT remains the only cure for thalassaemia and SCD. Cure appears life-long and associated with acceptable long-term risks. Families and physicians must weigh up the risks, including TRM and graft failure, against expected survival and QoL with medical treatment. For thalassaemia outcome of HSCT is best in patients <16 years old who comply well with chelation and have no liver dysfunction. They can expect long-term survival of 95% and thalassaemia-free survival of 90%. Patients with poor risk features have a reduced chance of cure (56–82%) and higher TRM (up to 20%) but still have a long-term survival advantage over conventional medical management. SCD is more heterogeneous; the patients predicted to benefit most from HSCT are those with CNS disease or recurrent chest syndrome despite hydroxycarbamide. Long-term EFS after HSCT for SCD in childhood is 82–86%, almost identical to recent US data on survival in SCD with medical treatment. Future prospects include effective RIC regimens, which currently have unacceptably high rejection rates in haemoglobinopathies, and gene therapy (2).

References

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Mutiple Choice Questionnaire

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

1. The following are standard indications for HSCT in children with sickle cell disease:

a) Recurrent splenic sequestration if there is an HLA-matched family donor ☐

b) Stroke if there is an HLA-matched family donor ☐
c) Stroke if there any HLA-matched donor ☐
d) Severe growth and pubertal delay if there is an HLA-matched family donor ☐

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2. The following are prognostic factors in the Pesaro classification for outcome of HSCT for thalassaemia:

a) Hepatomegaly, portal fibrosis and cardiac dysfunction ☐
b) Hepatosplenomegaly, portal fibrosis and serum ferritin >2000 ng/mL ☐
c) Hepatosplenomegaly, hepatic cirrhosis and cardiac dysfunction ☐
d) Hepatomegaly, portal fibrosis and a history of irregular chelation ☐

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3. Overall survival in children after HSCT for thalassaemia from an HLA-identical family donor is:

a) 90-95% ☐
b) 80-85% ☐
c) 70-75% ☐
d) 75-80% ☐

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4. Most conditioning regimens for haemoglobinopathy use a combination of:

a) Cyclophosphamide and TBI ☐
b) Cyclophosphamide and busulfan ☐
c) Cyclophosphamide and ATG ☐
d) Cyclophosphamide and fludarabine ☐

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5. The following are common long-term complications of HSCT for haemoglobinopathies:

a) Growth delay ☐
b) Secondary malignancy ☐
c) Relapse ☐
d) Infertility ☐