CHAPTER 14

Haematopoietic stem cell transplantation

14.1

For patients with thalassaemia

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1. Introduction
The β-thalassaemias are congenital haemolytic anaemias which are due to mutations that either reduce or abolish the production of the β-globin chain of adult haemoglobin (HbA, α₂β₂). Caused by over 200 different mutations, the β-thalassaemias are amongst the most common inherited blood disorders worldwide. Allogeneic haematopoietic stem cell transplantation (HSCT) still remains the only potentially curative treatment for patients with thalassaemia (1). Since the first successful allogeneic HSCT, performed in Seattle more than 20 years ago by Thomas and colleagues on an Italian child (2), hundreds of patients with thalassaemia have been cured of their original disorder after receiving an allograft, in most cases from an HLA-identical family donor (3-5). In view of this result, allogeneic HSCT represents a most attractive therapeutic alternative, especially for those patients, and their families who do not accept the prospective of a lifelong disease requiring continuing treatment with blood transfusion and drugs (5).

2. HLA-identical sibling transplant

2.1 Transplant outcome and prognostic factors
The extensive experience accumulated in the field of HSCT from an HLA-identical sibling for patients with thalassaemia has allowed the identification of clinical parameters influencing post-transplantation outcome, thus permitting more refined prognostic counselling for patients considering the option of HSCT or their parents (3-7). In particular, the risk of dying of transplantation-related complications has been clearly shown to be mainly dependent on patient age, iron overload and infection with hepatitis viruses. Adults, especially when affected by chronic active hepatitis, have a worse outcome than children, the probability of survival with transfusion independence having been reported to be 58% (7). Among children below the age of 17, three classes of risk have been identified, on the basis of regularity of previous iron chelation, liver enlargement and presence of portal fibrosis (see also Table 1) (3). In the most recent update of the Pesaro group’s experience, the probability of thalassaemia-free survival for patients younger than 17 years at time of HSCT, who received the allograft from an HLA-identical relative, was 87% and 85%, respectively, in patients belonging to class I and II (8). Worse results have been reported in paediatric patients who had low compliance with iron chelation, especially those in class III, favouring the occurrence of iron-induced organ damage; in these patients the probability of thalassaemia-free survival was initially reported to be 53%, mainly due to transplantation-related mortality. By reducing the dosage of cyclophosphamide, used together with busulfan in the preparative
regimen of these patients, it has been possible to document a lower incidence of transplantation-related mortality for children in class III, in the order of 25% (6). A most recent survey, reporting on a limited number of class III patients, mainly from Middle-East Countries, has suggested that the adoption, during the 2 months preceding HSCT, of a hypertransfusion regimen, intended to reduce the expansion pressure on the erythron, together with the use of azathioprine and hydroxyurea to suppress haematopoiesis and fludarabine for reducing the risk of rejection, may lower the probability of treatment failures and improve post-transplant outcome in this subgroup of patients (9). These encouraging preliminary results need to be confirmed in larger cohorts of patients, including those of Caucasian origin. The results obtained by the Pesaro team in patients transplanted from an HLA-compatible relative have been substantially reproduced by other groups, whose studies have confirmed that the majority of patients with thalassaemia given HSCT from an HLA-identical sibling can be cured of their disease and that both an heavy iron overload and old age unfavourably affect post-transplant outcome (10, 11).

### 2.2 Reasons for treatment failure

Both transplant-related mortality (TRM) and lack of sustained donor engraftment contribute to treatment failure in patients with haemoglobinopathies. In particular, the incidence of graft rejection in patients given HSCT for thalassaemia is considerably higher than that observed in patients transplanted for leukaemia (6, 8). Several factors may explain the high incidence of graft failure after an allograft in patients with haemoglobinopathies, including previous sensitisation to alloantigens through repeated transfusions, no chemotherapy treatment before HSCT and large spleen size.

<table>
<thead>
<tr>
<th>Table 1: Stratification of patients with thalassaemia under the age of 17 undergoing haematopoietic stem cell transplantation in 3 different classes of risk according to the presence or absence of regular iron chelation therapy, portal fibrosis and hepatomegaly</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I</strong></td>
</tr>
<tr>
<td>No hepatomegaly</td>
</tr>
<tr>
<td>No portal fibrosis at liver biopsy</td>
</tr>
<tr>
<td>History of regular iron chelation therapy</td>
</tr>
<tr>
<td><strong>Class II</strong></td>
</tr>
<tr>
<td>One or two of the risk factors</td>
</tr>
<tr>
<td><strong>Class III</strong></td>
</tr>
<tr>
<td>Hepatomegaly (&gt;2 cm below the costal margin)</td>
</tr>
<tr>
<td>Portal fibrosis at liver biopsy</td>
</tr>
<tr>
<td>History of irregular iron chelation therapy</td>
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</tbody>
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especially in older patients. Notably, in patients transplanted from an HLA-identical sibling, the incidence of rejection is directly correlated with the patient’s class of risk, an incidence of 4%, 8% and 12% being observed in patients belonging to risk class I, II and III, respectively (6, 8).

Stable mixed chimerism is also not uncommon among patients transplanted for thalassaemia from a compatible sibling (12), as seen also in patients with acquired aplastic anaemia following HSCT. Patients with thalassaemia developing stable chimerism, even with a low percentage of donor marrow progenitors (20-30%), have been reported to experience marked enrichment of donor cells in the mature red blood cell compartment, which makes them transfusion-independent (12). However, a not negligible proportion of thalassaemia patients given HSCT with mixed chimerism develop secondary graft failure, in particular when increasing proportions of recipient’s cells are observed in serial monitoring.

### 2.3 Reduced intensity allografts

The observation that sustained mixed chimerism is frequently observed in thalassaemia patients has provided a strong biological and clinical rationale for considering the use of reduced-intensity preparative regimens in patients with thalassaemia. This novel approach has been extensively investigated for the treatment of patients with malignancies who are not eligible for an allograft using standard conditioning regimens, either because of age or poor medical condition (14, 15). In fact, non-myeloablative conditioning regimens, mainly based on the use of purine analogues like fludarabine, can reduce or eliminate toxic effects associated with conventional HSCT allowing a wider applicability of the procedure. In the context of non-malignant disorders, the use of a reduced intensity preparative regimen could also allow engraftment of donor cells. Once T and NK cells of the donor have engrafted, they can either completely eliminate residual host cells, or favour the induction of a state of stable mixed chimerism, which, as mentioned before, may be sufficient to cure the patient. Post-transplant donor lymphocyte infusion (DLI) may help eradicate host residual host haematopoiesis. Thalassaemia patients with liver/heart damage could represent the ideal candidates for well-controlled, clinical trials of less toxic conditioning regimens carried out in centres experienced in HSCT. Such regimens may also help reduce the incidence of late effects, in particular those concerning growth and fertility, resulting from high-dose chemotherapy used for conventional HSCT) for treating patients with haemoglobinopathies (16-18). So far, only a few reports have demonstrated the feasibility of using reduced-intensity preparative regimens. Although transplant-related toxicity was mild in all cases reported, a significant proportion of these patients did not have sustained engraftment of donor erythropoiesis. This finding indicates that, stable donor
Engraftment is more difficult to achieve with non-myeloablative strategies in patients with haemoglobinopathies than in adults with malignancy, and it does not encourage the use of this approach in young and fit patients who can tolerate more intensive myeloablative treatment. Reduced intensity preparative regimens may find more appropriate application in older patients or in those with poor performance status and/or organ dysfunction, predicting a high risk of life-threatening complications if a fully myeloablative regimen is employed. In the perspective of identifying conditioning regimens displaying both immune-suppression and myelo-suppression, able to prevent host-versus-graft reaction and promote engraftment, while devoid of relevant extra-medullary toxicity, a recent study has reported encouraging results (19). In this phase I-II trial, a novel conditioning regimen including thiotepa, treosulfan and fludarabine was utilised in patients with thalassaemia given an allogeneic HSCT; it was associated mild extra-medullary toxicity, and proved to be effective. Indeed, in 20 patients with thalassaemia given an allogeneic HSCT, 9 of whom were adults or belonged to the class III of the Pesaro classification, the 2-year probability of survival and thalassaemia-free survival was 95% and 85%, respectively. An update of this study, analysing 32 patients, substantially confirms the results obtained in the initial cohort of patients (see also Figure 1 for details). Altogether, these results render the use of a treosulfan-based preparative regimen attractive in patients with thalassaemia eligible for an allograft, in order to reduce the risk of life-threatening complications and increase the number of patients successfully cured. In particular, treosulfan-based myeloablation might find elective application in adult patients or in those with poor performance status and/or organ dysfunction, all predicting a high risk of life-threatening complications if busulfan is employed.

It is possible that in order to increase the chance of successful transplantation when reduced-intensity regimens are employed, stem cell doses higher than those attainable with marrow harvest may be needed. This means a preferential use of cytokine-mobilised, peripheral blood haematopoietic stem cells, a practice which raises concerns for the donor when the donor is a minor, and for the recipient because of the increased risk of chronic graft-versus-host disease (GvHD) suggested by some studies (20). Also the use of DLI for obtaining a stable chimerism may trigger the development of severe, life-threatening or invalidating, GvHD.

2.4 Complications of HSCT
Chronic GvHD is considered one of the most severe and feared complications of HSCT; it has been reported to occur in between 8% and 27% of patients with thalassaemia, given HSCT from a compatible relative (11, 21). In fact, although only a minority of patients with chronic GvHD have the extensive form of the disease, the quality
of life of patients with extensive chronic GvHD may be certainly worse than that of patients with thalassaemia treated with supportive therapy (i.e. regular erythrocyte transfusions and iron-chelating drugs). Thus, the most effective strategy of pharmacological prophylaxis must be employed to reduce the incidence of both acute and chronic GvHD in patients with thalassaemia.

In terms of long-term side effects associated with HSCT in patients with thalassaemia, available data (22, 23) suggest that HSCT probably does not lead to more adverse endocrine consequences (i.e. growth impairment, delayed puberty, hypothyroidism) than conservative therapy, with the exception perhaps of patients who maintain an excellent compliance with iron chelation for the crucial years before and around puberty. Effects on fertility are more worrying as, despite anecdotal report of successful pregnancy after transplantation (24), the vast majority of patients given standard preparative regimens (namely those containing busulfan) before HSCT lose fertility, whereas a significant number of successful pregnancies in women with

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**Figure 1:** Treosulfan as conditioning regimen

Survival and thalassaemia-free survival. Two-year Kaplan-Meier estimates of the overall survival (---) and survival with transfusion independence (............) in 32 patients with thalassaemia transplanted after a conditioning regimen including thiotepa, treosulfan and fludarabine.
thalassaemia treated with conservative therapy have been reported in recent years (25, 26). Due to the recent introduction of regimens including treosulfan instead of busulfan, it is still unknown whether treosulfan-based conditioning may be associated with a greater chance of preserving patient’s fertility. As liver fibrosis, cirrhosis and cardiac failure are well-known complications of iron overload in thalassaemia patients, a program of serial phlebotomies post-transplantation is employed in many centres to reduce iron overload in patients who have successfully undergone HSCT and it has been demonstrated that through regular phlebotomy or even chelation therapy, it is possible to prevent or reverse organ damage due to pre-existing iron overload in the liver (27). Likewise, regarding cardiac function, a recent report documented that subclinical left ventricular diastolic dysfunction and impaired left ventricular contractility in transplanted thalassaemia patients with may be reversed with an effective regimen of iron reduction such as phlebotomy (28). A phlebotomy programme can be started even

Figure 2: Kaplan-Meier estimates

Kaplan-Meier estimates of the overall survival (——) and survival with transfusion independence (-----) in 50 paediatric patients belonging to the class I and II of the Pesaro classification transplanted from an unrelated volunteer. Additional estimation of survival with transfusion independence was performed considering patients with graft rejection and subsequent sustained engraftment after second transplantation from the same donor as non-failures (-----).
in the first months after HSCT, whenever the patient reaches a sustained haemoglobin value greater than 10.5 g/dL.

3. Cord blood transplantation for patients with thalassaemia

Over the past decade, cord blood haematopoietic stem cells have been used increasingly, in place of bone marrow progenitors, for transplanting paediatric patients with either malignant or non-malignant disorders (29). In comparison with BMT, the main clinical advantage associated with cord blood transplantation (CBT) from an HLA-identical sibling is the lower risk of both grade II-IV acute and chronic GvHD (29-31). The low incidence of GvHD in CBT recipients renders this type of transplant particularly appealing for patients with thalassaemia, also for other patients affected by a non-malignant disorder. After a few anecdotal reports of successful CBT for patients with thalassaemia (32, 33), a study from the Eurocord cooperative group has analysed the outcome of 33 patients with thalassaemia, belonging to class I and class II in the Pesaro classification, given CBT from a sibling, HLA-identical in 30 cases and with a single HLA-disparity in the 3 remaining donor/recipient pairs (34). No patient died for transplant-related complications, suggesting that related CBT for haemoglobinopathies is a safe procedure (34). Seven out of these 33 patients did not have sustained engraftment of donor cells, although two of them obtained sustained engraftment after subsequent BMT from the same donor. A better probability of thalassaemia-free survival was observed in patients belonging to class I as compared to those assigned to class II of the Pesaro classification, (89% vs. 62%, respectively, p=0.05). Patients who did not receive methotrexate as part of GvHD prophylaxis and who were given thiotepa during the preparative regimen had a remarkably better outcome, this indicating that, in optimal conditions, CBT offers a probability of success at least as good as that of BMT. A recent update of this analysis on 38 patients confirmed the absence of transplant-related mortality, with a thalassaemia-free survival in the order of 80% (Locatelli F, unpublished results). A recent report addressed the issue of donor/recipient chimerism in patients with thalassaemia given CBT from an HLA-identical relative in a longitudinal study (35). The study showed that mixed chimerism sustained over time in circulating leukocytes was found in a large proportion of these patients, without, however, predicting the occurrence of graft failure (35). In particular, at time of haematological engraftment, all 27 children given CBT, who were studied, displayed mixed chimerism, with co-existence of donor and host haematopoietic cells. Subsequently, 13 of them converted to full donor chimerism, while the remaining 14 children are maintaining a stable mixed chimerism after a median follow-up time of 42 months. This study also demonstrates that mixed chimerism
is associated with a favorable transplantation outcome, as all the 27 patients investigated are alive and transfusion independent, without having experienced neither acute nor chronic GvHD (35). The possibility of using cord blood cells for curing thalassaemia may tempt a couple who has an affected child to conceive a new compatible, healthy sibling. This raises some bioethical issues (36). Pre-natal diagnosis of thalassaemia is widely available and, besides determining whether a foetus is healthy, makes it possible also to evaluate HLA-compatibility with the affected child. Pre-natal knowledge of lack of HLA-compatibility between the affected child and the foetus might induce the parents to decide to terminate the pregnancy also in the case the foetus results to be healthy, an attitude that is questionable from an ethical standpoint. Moreover, the recent demonstration that \textit{in vitro} fertilisation and pre-implantation selection of compatible, healthy embryos is feasible (37) may encourage a couple with an affected child to initiate a pregnancy with the certainty that a source of stem cells will be available for transplantation (36). Reduced to its essential ethical-bioethical problematic issues, this attitude of selecting the “HLA compatible and not sick” embryo entails weighing the desirable saving of a life (with optimum quality of success) against the choice of discarding other (equally not sick) embryos just because they are not HLA-compatible with the candidate recipient (thus, not “usable” for transplantation purposes) (36). Discussing \textit{in utero} HLA typing performed early in the pregnancy offers also the opportunity to mention that there is another, more innovative, way to perform genetic counselling for beta thalassaemia: in fact, it has been recently reported that couples at risk diagnosed with an affected embryo may decide against termination of the pregnancy if the prospect of BMT from a family member (namely an HLA-identical living sibling) is available (38).

4. A strategy to increase the applicability of HSCT: the use of unrelated volunteers

Only 25-30% of patients with diseases potentially curable by HSCT have a suitable HLA-compatible sibling. Thus, the vast majority of patients who can benefit from an allograft lack a family donor. During the past 15 years, with the establishment of bone marrow donor registries, which now include more than 12 million volunteers world-wide, many patients who need allogeneic HSCT have been able to locate a suitable unrelated donor. However, mainly because of HLA polymorphism and the limitations of serological techniques for HLA-typing, increased difficulties with engraftment and augmented incidence of both acute and chronic GvHD have been reported in recipients of an unrelated donor allograft (39, 40). Recently, it has been
demonstrated that more precise characterisation of HLA alleles using high-resolution typing for both class I and class II molecules can reduce the risk of developing immune-mediated complications and fatal events after transplantation (41). These achievements have provided the rationale for considering the possibility of performing HSCT from unrelated volunteers in patients with haemoglobinopathies. Thus, it has been hypothesised that with accurate selection of the donor, the outcome of patients given an allograft from an unrelated volunteer could become comparable to that of patients transplanted from an HLA-identical family donor. Some anecdotal reports have initially shown that unrelated donor HSCT is able to cure patients with thalassaemia major (42, 43). The Italian co-operative group for BMT (GITMO) activated a protocol of transplantation from an unrelated donor for patients with thalassaemia major, the results of which have been published in different reports (44-46). In all cases, the unrelated volunteer donor was selected using high-resolution molecular typing for both HLA class I and II loci and stringent criteria of compatibility in the donor recipient pair (namely allelic identity for HLA loci A, B, C and DRB1 or single allelic disparity for class I loci). Altogether, the results obtained with this protocol in the different classes of risk for paediatric patients (44, 45), as well as in adults (46), demonstrate that, when donor selection is based on stringent compatibility criteria, it is possible to reproduce the results already reported using a compatible family donor. As an example, Figure 2 shows the Kaplan-Meier estimates of survival and of survival with transfusion-independence in 50 children with thalassaemia belonging to the class I and II of the Pesaro classification. In the same cohort of patients, the cumulative incidences of transplant-related mortality and of extensive chronic GvHD were 6% and 7%, respectively.

Thus, the experience of transplantation using unrelated volunteer shows that both the risk of death and that of developing severe chronic GvHD are limited and do not exceed the level already largely accepted when using a family donor provided that stringent criteria of compatibility be employed for selecting the donor. The main limitation of the Italian experience is that, using such criteria, approximately only one third of thalassaemia patients who started the search found a suitable donor in a median time of 3-4 months. In order to further widen the applicability of HSCT, it is theoretically possible to select the donor according to less strict matching criteria and to use some sort of in vivo serotherapy, which has recently been proven to reduce the incidence of both acute and chronic GvHD in a dose-dependent manner, after an allograft from an unrelated donor (47). However, it remains to be proved whether the results achievable with HSCT from unrelated donors selected using less stringent criteria of compatibility with the recipients can favourably compare with those reported using an HLA-identical sibling as donor.
This concern is highlighted by an analysis on the role of DPB1 disparity between donor and recipient in the Italian cohort of patients with thalassaemia transplanted from an unrelated volunteer (48). In that study, in fact, the risk of graft rejection was found to be significantly increased in patients with a non-permissive disparity (defined according to the rules of functional immunogenetics) at locus DPB1 in the host-versus-graft direction. Other relevant immunogenetic aspects influencing the outcome of thalassaemia patients transplanted from an unrelated donor refer to the role played by the 14-basepair (bp) deletion-insertion polymorphism located in the 3’-untranslated region of the HLA-G gene and to the interaction between killer immunoglobulin-like receptors (KIRs) and their ligands. Indeed, a recent study has demonstrated that thalassaemia patients given BMT from an unrelated donor who were homozygous for the 14-bp deletion had a significantly higher risk of developing acute GvHD as compared to patients homozygous or heterozygous for the 14-bp insertion (49). As far as the interaction between KIRs and their HLA ligands, another report has suggested that patient HLA C1/C2 heterozygosity may favour the development of donor alloreactivity and thereby increase the risk of GvHD. Conversely, HLA C1/C1 and C2/C2 homozygosity of the patient seems to reduce the risk of GvHD, but may increase the incidence of graft rejection (50). The data deriving from these studies (49, 50) may be helpful in tailoring the intensity of GvHD prophylaxis and conditioning regimens in thalassaemia patients receiving HSCT from an HLA-identical volunteer donor.

Finally, it must be mentioned that, for the time being, the use of T-cell depleted HSCT from an HLA-partially matched relative is not routinely advisable for patients with thalassaemia, due to the high risk of serious, often fatal, infectious complications. Haploidentical, T-cell depleted HSCT can be considered in extreme situations, such as that of a patient completely not compliant with any type of chelation therapy and/or with immunisation to allogeneic or autologous erythrocyte antigens that renders transfusion either impossible or life-threatening.

5. The choice between transplantation and conventional treatment
Safe blood transfusion and effective iron-chelating drugs have dramatically improved both survival and quality of life of patients with thalassaemia over the last two decades, and have changed a previously fatal disease with early death, to a chronic, although progressive, disease compatible with prolonged survival. In the developed world, the life expectancy of patients with thalassaemia is now in the order of 40-55 years, mainly depending on compliance with medical treatment (1, 51-53). In fact, when compliance with chelation therapy is good and consistent, 90% of patients survive well into their 30s, whereas, where compliance is poor, fewer than 10% will reach their 40th birthday (54). In the developing world, by contrast, most children
with this disease die before the age of 20 years because of the unavailability of safe blood products in adequate amounts and/or of expensive iron-chelating drugs. In view of all these considerations the evaluation of the benefit/risk balance of what HSCT can offer profoundly differs for patients with thalassaemia living in different socio-economic contexts. As mentioned before, HSCT has the great appeal of being the only treatment able to definitively cure thalassaemia, although it is associated with a consistent risk of complications that can dramatically shorten the life duration of some patients. The best results can be obtained in younger patients with limited iron overload and without severe organ damage. These patients are the “ideal” candidates for an allograft, whereas older, heavily iron-overloaded patients, especially when affected by liver complications, run a considerable risk of transplant-related, life-threatening complications. It is possible, however, that the latter patients, whenever the transplant is successful, are those who receive the maximum benefit from it, given the much reduced life expectancy, associated, in thalassaemia, with continuing transfusions in the presence of reduced compliance with iron chelation.

Looking at the option of HSCT for treating thalassaemia from the point of view of a health system will show that this procedure for thalassaemia is highly cost effective. In fact the cost of medical treatment for this disease is considerable: recent calculations estimated the lifetime treatment cost in the UK at £803,002, whereas the cost of HSCT ranges between approximately £50,000 and £100,000, depending on the country in which it is performed. In view of this finding, there is no doubt that, for countries with limited economic resources, HSCT can be a convenient option, provided that the resources needed for performing the transplant are immediately available.

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**Multiple Choice Questionnaire**

To find the correct answer, go to [http://www.esh.org/iron-handbook2009answers.htm](http://www.esh.org/iron-handbook2009answers.htm)

1. Which are the “ideal” thalassaemia patient candidates for an allograft?
   a) Older, heavily iron-overloaded patient ........................................... □
   b) Patients affected by liver complications ..................................... □
   c) Young patients with limited iron overload and without severe organ damage .......................................................... □
   d) Young patients with heavy iron overload .................................... □

2. Which of the following explains the high incidence of graft failure after an allograft in patients with haemoglobinopathies:
   a) Previous sensitisation to alloantigens through repeated transfusions .... □
   b) No chemotherapy treatment before HSCT ..................................... □
   c) Large spleen size ........................................................................ □
   d) All the above ........................................................................... □

3. Which of the following measures have been recently reported to be capable of lowering the probability of treatment failures and improving post-transplant outcome in thalassaemia patients from Middle-Eastern countries?
   a) A hypertransfusion regimen during the 2 months preceding HSCT .... □
   b) The use of azathioprine and hydroxyurea before HSCT ................. □
c) The use of fludarabine as part of the preparative regimen

d) All of the above

4. **What is the main clinical advantage associated with cord blood transplantation (CBT) from an HLA-identical sibling, in comparison with BMT, for patients with thalassaemia:**
   
a) Lower risk of both grade II-IV acute and chronic GvHD
   
b) Absence of risks for the donor
   
c) Reduced risk of transmitting infections
   
d) Rapid availability of the cryopreserved cells

5. **When safe blood transfusion is applied and compliance with chelation therapy is good, what is the proportion of thalassaemia patients who at present can survive well into their 30s?**
   
a) 50% of patients
   
b) 30% of patients
   
c) 90% of patients
   
d) 100% of patients