

## Chapter 1

# Why hematopoietic stem cell transplantation and for whom?

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### Introduction

Transplantation of allogeneic and autologous hematopoietic stem cells has become an increasingly safe and effective procedure in recent years, and is now established as one of the most important curative strategies in patients with hematological malignancies. It also has an important role to play in the management of acquired marrow failure, hemoglobinopathies, congenital immunodeficiency and metabolic disease.

At first it was thought that HSCT cured patients because increased, myeloablative doses of chemo-/radiotherapy could be given while the risk of permanent marrow aplasia was avoided by giving HSC after the chemo-/radiotherapy. While this remains the sole mechanism of action in autologous transplants it is now clear that in patients transplanted with allogeneic stem cells there can be an additional, immunologically mediated graft-vs.-leukemia (GVL) effect. The growing realization of the potency of the GVL effect has led to:

- the development of reduced-intensity transplants whose curative potential is entirely dependent on the immunotherapeutic potential of the donor immune system;
- an increased interest in the possibility of using allogeneic transplants in the treatment of solid tumors or autoimmune disease

However, since the anti-tumor activity of the GVL effect is mediated by the donor immune system, it is therefore linked with the major complication of allogeneic transplantation: graft-vs.-host disease (GVHD). Thus, although there has been a major expansion in the numbers of patients considered eligible for allogeneic transplantation in the past

decade, this procedure still remains associated with major toxicity consequent upon immunosuppression and GVHD.

### Historical perspective

Hematopoietic stem cell transplantation has been used to treat humans for nearly 40 years; it was first given in 1968 for an infant with a severe combined immune deficiency who was unable to reject a graft and then a year later in 1969 for a patient with leukemia who had been given lethal total body irradiation. In both cases genetically HLA-identical siblings were used and gave bone marrow. Treatment in these early cases demonstrated that leukemia could be cured, that immune deficiency could be corrected, and that long-term survival was possible. However, problems with infections, graft-vs.-host disease, and graft failure meant that this was considered a very risky technique for many years. In the last 10 years HSCT has become much more successful because of the steady improvements across the field. These have included:

- better tissue type matching of donor and recipient using molecular DNA techniques;
- greater availability of matched unrelated donors;
- refinements in pre-transplant conditioning regimens;
- improved methods for early detection of infection;
- new anti-infective agents, ciclosporin and other immunosuppressive drugs to reduce the risk of graft-vs.-host disease;
- better supportive care, with protective isolation and improved techniques for nutritional support.

No single discovery led to this dramatic improvement in outcome; instead it is the summation of many smaller developments that together have led to very dramatic changes in outcome. For example, in pediatric practice success for transplantation for primary immunodeficiency has risen from 50% to approaching 90% in the last 25 years. This has meant that patients previously considered too ill, too damaged by infection, too old or to have a condition not amenable to transplant are now being considered for HSCT.

### Basic principles of hematopoietic stem cell transplantation

Two fundamental principles underpin the development of stem cell transplantation as an effective and relatively safe clinical procedure:

- a combination of drugs and/or radiotherapy are given before the infusion of stem cells, which may include antibodies such as antithymocyte globulin (ATG) that destroy lymphocytes, referred to as the conditioning or preparative regimen; it is essential for disease eradication and the creation of “space” within the marrow cavity to allow engraftment of allogeneic stem cells;
- transplantation of enough stem cell inoculum to ensure lifelong reconstitution of all hematopoietic lineages.

### Conditioning regimens

In autologous SCT where there is no genetic difference between the transplanted stem cells and the patient, the only role of the conditioning regimen is tumor eradication. In contrast, in patients transplanted with allogeneic stem cells, whether from a brother/sister or unrelated donor who share the same tissue types (HLA), a potent host-vs.-graft reaction will be generated directed against the transplanted stem cells unless the host immune system is suppressed. Therefore the conditioning regimen serves two purposes in patients undergoing an allogeneic transplant:

- host immunosuppression to prevent graft rejection;

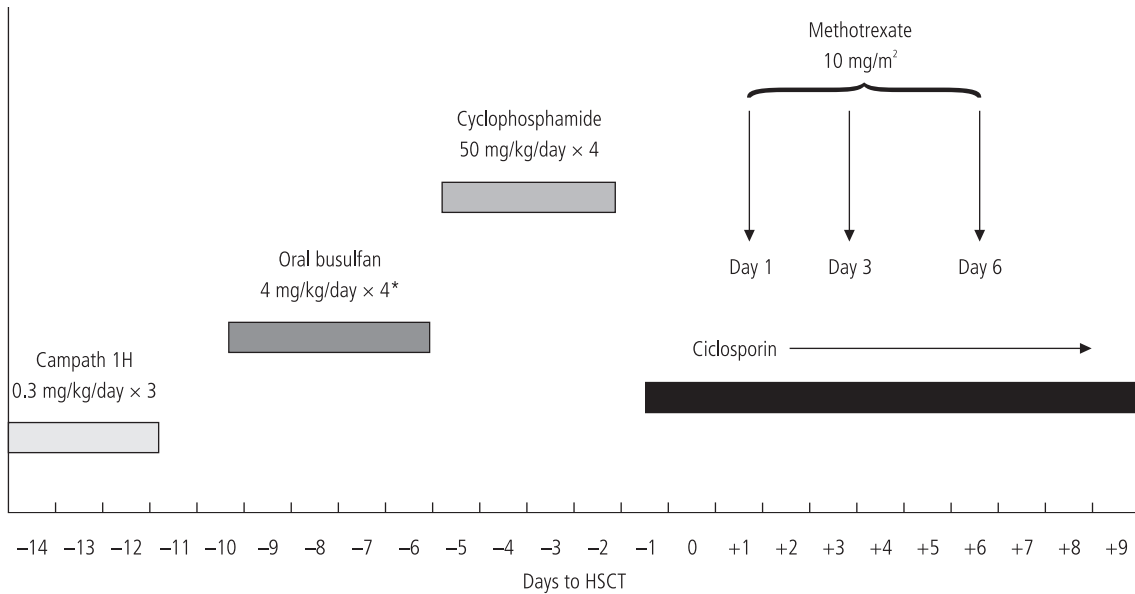
- host myeloablation in order to eradicate malignant hematopoiesis.

Until recently, all patients undergoing an allogeneic transplant received a myeloablative conditioning regimen. In order to achieve the maximum degree of tumor eradication, myeloablative regimens employ high doses of chemo- and/or radiotherapy and are associated with significant side effects (see Fig. 1.1). This means that, even when transplanting young patients with a well-matched donor, 10–20% will die of these side effects (so-called transplant-related mortality). However, the mortality of such intensive regimens rises to unacceptable levels in older patients (greater than 50–55 years old) and so, until recently, allogeneic transplantation has been considered too risky for older patients with leukemia. As hematological malignancies are much more common in older patients, this has profoundly limited the usefulness of allogeneic transplantation. However, the recent demonstration that durable donor engraftment can be reliably achieved using a nonmyeloablative preparative regimen, coupled with increased awareness of the potency of the GVL reaction, has led to the development of a range of reduced-intensity conditioning (RIC) regimens (often referred to as “mini”-transplants, see Fig. 1.2 ). These regimens are associated with markedly reduced transplant-related mortality (TRM) than would be seen after a myeloablative regimen. As a result, allogeneic transplantation can now be safely performed in many patients in whom it would previously have been contraindicated on the grounds of age or comorbidity. Very rarely for conditions such as severe combined immune deficiency (SCID), it is possible to achieve engraftment of selected cell lineages without the use of conditioning.

### Sources of stem cells for clinical transplantation

Sources for hematopoietic stem cells for transplantation include:

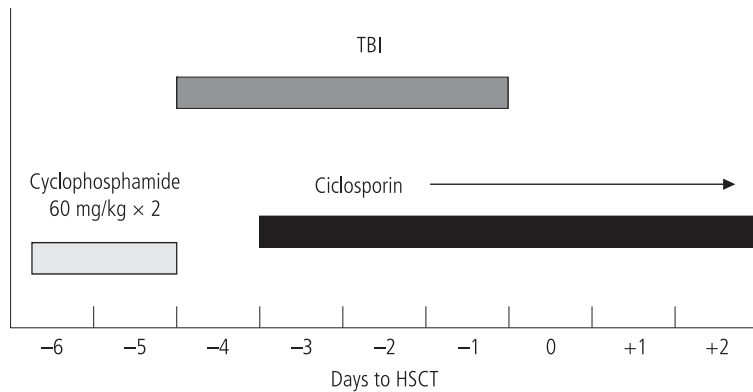
- bone marrow;
- peripheral blood stem cells (PBSC) – following mobilization from the bone marrow using granulocyte-colony stimulating factor (G-CSF);
- umbilical cord.



\*(or i.v. dose dependent on weight)

**Fig. 1.1** Example of standard conditioning regimen (for a child with combined immunodeficiency using whole marrow matched unrelated donor). © Children’s Bone Marrow Transplant Unit, Newcastle General Hospital, Newcastle upon Tyne, UK; redrawn with permission.

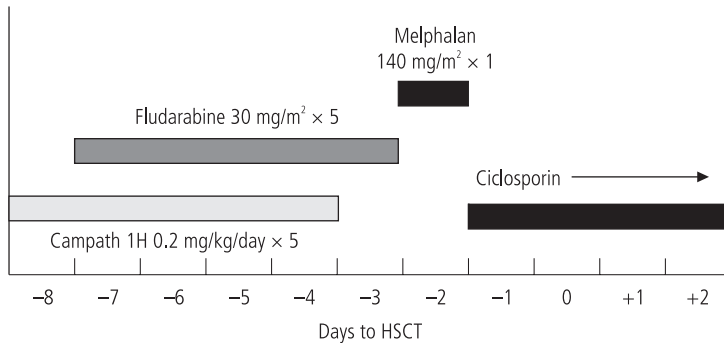
**Fig. 1.2** Example of conditioning regimen for HLA-matched sibling whole marrow transplant for ALL. © Children’s Bone Marrow Transplant Unit, Newcastle General Hospital, Newcastle upon Tyne, UK; redrawn with permission.



The safe delivery of myeloablative therapy and the genesis of a GVL effect is dependent on the transplantation of long-term reconstituting cells (LTRCs). These cells are defined by their capacity for self-renewal as well as their ability to mature into all hematopoietic lineages; LTRCs differ from more mature hematopoietic progenitors, which have limited ability to self-replicate and are already committed to develop into a specific lineage. LTRCs are rare, however, occurring with a frequency of  $1 : 10^4$  or  $1 : 10^5$  mononuclear cells in

the bone marrow. One of the major determinants of successful stem cell engraftment is the number of stem cells transplanted.

Originally stem cells were obtained from bone marrow by direct puncture and aspiration of bone marrow and the cells obtained were infused intravenously. In recent years stem cells have also been harvested from the peripheral blood and from umbilical cord blood. The term hematopoietic stem cell transplantation (HSCT) is therefore now replacing the term bone marrow transplanta-



**Fig. 1.3** Example of low-intensity conditioning regimen. © Children's Bone Marrow Transplant Unit, Newcastle General Hospital, Newcastle upon Tyne, UK; redrawn with permission.

tion. HSCs are harvested from peripheral blood by giving the donor daily injections of G-CSF for 5 days. The cells are then harvested using a filtration technique called apheresis, which has transformed both autologous and allogeneic SCT (Fig. 1.3 shows a patient undergoing plasmapheresis). The use of G-CSF-mobilized peripheral blood stem cells (PBSCs) makes it possible to transplant significantly higher stem cell doses than is possible if harvested bone marrow is used. Consequently PBSC now play a critical role in optimizing engraftment whether the donor and recipient are HLA tissue type matched or mismatched and where graft enhancing donor T cells have to be removed to prevent GVHD. Incorporating these principles into clinical practice has markedly reduced the risk of graft failure.

Durable engraftment of allogeneic stem cells is also helped by graft-facilitating donor T cells, which usually overcome any residual HVG response generated by host T cells that have survived the conditioning regimen. Thus the major factors determining engraftment are the intensity of host immunosuppression delivered by the conditioning regimen, the numbers of donor T cells in the stem cell inoculum and the degree of genetic disparity between donor and host.

The use of PBSCs is associated with earlier neutrophil and platelet engraftment and in patients with advanced leukemia this may translate into a lower TRM. However, transplantation of PBSC results in an increased incidence of chronic GVHD, reflecting the five- to tenfold greater dose of T cells transplanted if mobilized cells are used in preference to bone marrow-harvested cells. Thus the

use of PBSC has become commonplace in patients being allografted for advanced leukemia where TRM is a major cause of treatment failure, but bone marrow is still preferred in diseases such as aplastic anemia where chronic GVHD is an important cause of treatment failure. The increasing use of PBSC has obvious implications for allogeneic stem cell donors as the G-CSF in the doses used for stem cell mobilization may cause bone pains and splenomegaly.

In the absence of a HVG reaction, graft failure is very rarely observed in autologous transplants providing an adequate stem cell dose is used. Because of their ease of procurement coupled with an increased stem cell dose, PBSCs are now almost universally used in preference to bone marrow harvests in autologous transplants.

Umbilical cord blood (CB) cells, harvested at the time of delivery, have been used as a source of allogeneic stem cells. CB is rich in LTRC and hematopoietic progenitors, and durable engraftment can be reliably obtained in infants and children. Moreover, the incidence of severe GVHD is significantly lower with mismatched CB than would be expected using a comparable unrelated marrow or PBSC donor. It is theoretically possible that the lower numbers of T cells and their naive phenotype contained in CB collections will be associated with a reduced GVL effect, but no increase in relapse risk has yet been reported in CB transplants. Given the difficulties that can be experienced obtaining stem cell collections from unrelated donors, the relative ease of access to CB banks has resulted in this becoming an increasingly important stem cell source in pediatric transplantation. However, in

older patients delayed engraftment is commonly observed because of the lower cell doses (per kg body weight) transplanted and this has limited their use in adults. Therefore approaches that improve engraftment, such as *ex vivo* expansion of hematopoietic progenitors, will be needed before CB is widely used in adult transplantation.

### Principles of donor choice

Potential donors:

- Autologous (the patient)
- Allogeneic (another person)
  - HLA-identical (matched) sibling
  - Other related donor (RD)
    - HLA-matched
    - HLA-mismatched, including haploidentical (half matched, usually a parent)
  - Unrelated donor (URD)
    - HLA-matched (often termed matched unrelated donor, MUD)
    - HLA-mismatched

### Currently accepted indications for hematopoietic stem cell transplantation

Both autologous and allogeneic SCT are now firmly established as important treatments for hematological malignancies. The use of peripheral blood stem cell progenitors, coupled with improvements in supportive care, has reduced the mortality of autografting to below 5% (similar to that of a major surgical procedure) and allowed its extension to patients up to 70 years of age. By contrast, allogeneic SCT remains associated with substantial morbidity and mortality, consequent mainly upon the toxicity of the conditioning regimen and the risk of GVHD, which currently precludes its extension to patients beyond the age of 55. However, this is often outweighed by the increased anti-leukemic effect of an allograft and consequently the decision in any individual patient whether to autograft, allograft or employ chemotherapy alone is often complex and dependent on a range of host and donor factors.

### Chronic myeloid leukemia (CML)

Although CML can only be cured by allogeneic SCT, and the long-term disease-free survival rate after HSCT is now in excess of 70% in patients fortunate enough to have an HLA-identical sibling, the encouraging data using the tyrosine kinase inhibitor imatinib has relegated allogeneic transplantation to a second-line option in adults. Nonetheless, a number of patients still wish to proceed immediately to an allograft; a careful analysis of a range of pre-transplant patient and donor details and their influence on HSCT outcome should lead to the best calculated treatment option.

### Acute leukemia

The precise role of allogeneic transplantation in patients with AML in first complete remission (1st CR) has been hard to establish. When carrying out studies of the results of HSCT it has proved hard to prevent bias when randomizing patients to HSCT or non-HSCT treatment groups. Furthermore, in many studies the HSCT and non-HSCT groups have not contained the same number of high-risk patients. It is generally accepted that allografting substantially decreases the risk of relapse but whether this benefit outweighs the attendant transplant-related mortality remains controversial. Most groups, however, would consider allogeneic transplantation in all patients in first CR apart from those with good-risk disease (with chromosome markers  $t : 15 : 17$ ,  $inv 16$  and  $t : 8 : 21$ ) in whom outcome with conventional chemotherapy is good. There is general agreement that allogeneic SCT is the only curative option in 2nd CR and, in the absence of an HLA-identical sibling, the use of unrelated donor (URD) should be considered.

Allogeneic SCT is also best in patients with myelodysplasia where the outcome after HSCT using a sibling or unrelated donor is better than after conventional chemotherapy. Results are improved if transplantation is performed early in the course of the disease and a number of scoring systems have been used to determine the natural history in order to assist the difficult decision of when to submit an otherwise healthy patient to a life-threatening but potentially curative procedure.

Autologous SCT has been investigated as a method of dose escalation in AML by many groups. Results of the recent MRC study confirmed that autografting using bone marrow cells harvested in remission reduces the risk of relapse in patients with standard risk disease in 1st CR, compared with conventional chemotherapy. However, this effect was blunted by a higher-than-expected transplant-related mortality and current studies are therefore investigating whether the use of peripheral blood stem cells or earlier transplantation will improve outcome.

Most studies indicate that allogeneic HSCT should be considered in all adults with acute lymphoblastic leukemia (ALL) in 1st CR, with the possible exception of those with good-risk disease as defined by white cell count and immunophenotype. In patients with Philadelphia positive ALL and the 4:11 chromosome translocation this is effectively the only curative option and unrelated donor transplantation is now indicated in patients in whom an HLA-identical sibling cannot be identified. The role of autologous SCT in the management of patients with ALL remains unclear and is the subject of ongoing randomized studies.

### **Non-Hodgkin's lymphoma**

The superiority of autologous HSCT over salvage chemotherapy in patients with chemosensitive relapses of high-grade non-Hodgkin's disease was confirmed by a recent randomized study. Although it might be expected that dose intensification would benefit patients with poor prognostic features during 1st CR, this has yet to be confirmed by a large randomized study. No randomized studies have examined whether the benefit of autografting extends to patients with follicular NHL, although this is suggested by data from single-center studies. The role of allogeneic transplantation remains controversial. The biology of follicular lymphoma, coupled with the uncertainty surrounding the ability of autologous HSCT to effect a cure, makes allogeneic HSCT using a reduced-intensity conditioning regimen an attractive option and there are encouraging preliminary data in support of this approach.

### **Hodgkin's disease**

Comparison with historic controls suggests that autologous HSCT is superior to conventional chemotherapy in patients with relapsed or refractory Hodgkin's disease. Pilot studies also support the use of autologous HSCT in patients with "high-risk" disease while they remain in 1st CR, and this is the subject of a number of ongoing studies. Allogeneic HSCT using a myeloablative conditioning regimen is usually associated with unacceptably high transplant-related mortality, mostly due to pulmonary complications, and currently has only a limited role although this may change with the advent of reduced-intensity conditioning regimens.

### **Multiple myeloma**

Allogeneic transplantation remains the only curative therapy in multiple myeloma and is capable of producing molecular remissions in up to 30% of patients transplanted. However, the particularly high transplant-related mortality in myeloma and the rarity of the disease in patients under 50 have led to pessimism as to whether it is possible to exploit the undoubted graft-vs.-myeloma experience observed after allogeneic HSCT in more than a small minority of patients with this disease. However, it appears that modifications to the conditioning regimen coupled with improvements in supportive care can substantially reduce the TRM and the age limit in which allografting is considered is currently being extended. By contrast, autologous SCT can be safely performed in patients up to the age of 70 and, although not apparently curative, has been shown to improve both overall and disease-free survival. Best results are obtained in patients with chemosensitive disease, a low presentation betaroglobulin and a normal karyotype. Whether a double autograft is of benefit to patients is currently under investigation, although it appears that such an approach is technically feasible in the majority of patients under 65.

### **Solid tumors**

The role of autologous SCT in the management of advanced breast cancer remains controversial. An

early study that suggested benefit in metastatic disease is now discredited and a randomized study of this therapy has failed to show a benefit. The question remains as to whether a subgroup of patients will benefit and the results of a number of ongoing studies are eagerly awaited. There are encouraging data from a number of centers showing that dose intensification with autologous stem cell support improves survival in patients with disseminated germ cell tumors, although this requires confirma-

tion. The possibility of exploiting a graft-vs.-tumor effect in malignancies such as renal cell carcinoma or breast carcinoma is supported by anecdotal reports of responses after allogeneic SCT or donor lymphocyte infusion (DLI) and raises the possibility of extending the benefit of allografting, possibly using a non-myeloablative conditioning regimen, to non-hematological malignancies. Tables 1.1, 1.2, 1.3, 1.4 and 1.5 indicate the types of conditions for which HSCT is used.

**Table 1.1** Indications for bone marrow transplantation in children

<i>Malignant conditions</i>	<i>Nonmalignant conditions</i>
<p><i>Acute leukemia</i></p> <ul style="list-style-type: none"> <li>• Acute lymphoblastic leukemia (ALL)                             <ul style="list-style-type: none"> <li>• high-risk ALL in 1st CR</li> <li>• high- and intermediate-risk relapsed ALL in 2nd CR</li> <li>• ALL in <math>\geq</math>3rd CR</li> </ul> </li> <li>• Acute myeloid leukemia (AML)                             <ul style="list-style-type: none"> <li>• poor risk AML in 1st CR</li> <li>• AML in 2nd CR<sup>†</sup></li> </ul> </li> </ul> <p>Chronic myeloid leukemia</p> <p>Myelodysplasia, including juvenile myelomonocytic leukemia</p> <p>Non-Hodgkin's lymphoma (NHL)</p> <ul style="list-style-type: none"> <li>• relapsed Burkitt's NHL*</li> <li>• relapsed diffuse large cell NHL*</li> <li>• relapsed anaplastic large-cell lymphoma</li> <li>• relapsed T-cell lymphoblastic NHL</li> </ul> <p>Hodgkin's disease (HD)</p> <ul style="list-style-type: none"> <li>• relapsed/refractory HD (adolescents)*</li> <li>• ?multiply relapsed HD</li> </ul> <p>High-risk solid tumors*</p> <ul style="list-style-type: none"> <li>• stage 4 (or other high risk) neuroblastoma</li> <li>• high-risk Ewing's sarcoma</li> <li>• high-risk or relapsed medulloblastoma</li> <li>• selected patients (in the context of clinical trials) with relapsed or refractory                             <ul style="list-style-type: none"> <li>• Wilms' tumor</li> <li>• germ cell tumor</li> </ul> </li> </ul>	<p><i>Bone marrow failure (including inherited monocytopenia)</i></p> <ul style="list-style-type: none"> <li>• Aplastic anemia</li> <li>• Fanconi anemia</li> <li>• Other constitutional bone marrow failure syndromes                             <ul style="list-style-type: none"> <li>• dyskeratosis congenita</li> <li>• congenital amegakaryocytic thrombocytopenia</li> <li>• Schwachman–Diamond syndrome</li> <li>• Diamond–Blackfan anemia</li> </ul> </li> <li>• Kostmann syndrome</li> </ul> <p>Hemoglobinopathy</p> <ul style="list-style-type: none"> <li>• Thalassemia (selected patients)</li> <li>• Sickle cell anemia (selected patients)</li> </ul> <ul style="list-style-type: none"> <li>• Primary Immunodeficiency</li> <li>• Osteopetrosis</li> <li>• Certain metabolic storage diseases</li> </ul>

Allogeneic HSCT unless indicated otherwise:

\* Autologous HSCT

<sup>†</sup> Autologous HSCT may be indicated in some patients with late relapse (>1 year from initial diagnosis)

**Table 1.2** Types of stem cell transplantation

Autologous (autograft)	The patient's own stem cells are harvested and reinfused after the patient has received chemotherapy to kill malignant cells. Used in leukemias, lymphomas and some solid tumors. Also used for immunomodulatory effect in some autoimmune disorders
Allogeneic (allograft)	Stem cells from another individual are infused after the patient's own bone marrow has been destroyed by chemotherapy and/or radiotherapy. Potential allogeneic donors may include: <ul style="list-style-type: none"> <li>• HLA-identical (matched) sibling</li> <li>• Other related donor (RD) <ul style="list-style-type: none"> <li>• HLA-matched</li> <li>• HLA-mismatched, including haploidentical (half matched, usually a parent)</li> </ul> </li> <li>• Unrelated donor (URD) <ul style="list-style-type: none"> <li>• HLA-matched (often termed matched unrelated donor, MUD)</li> <li>• HLA-mismatched</li> </ul> </li> </ul>

**Table 1.3** Immunodeficiencies suitable for transplantation

SCID  
Wiskott–Aldrich syndrome  
CD40 ligand deficiency  
Other T-cell immune deficiencies  
Chronic granulomatous disease  
Leukocyte adhesion deficiency  
Hemophagocytic syndromes

**Table 1.4** Diseases for which allogeneic transplant is used (adapted from Duncombe 1997)

## (a) Adults

<i>Sole chance of cure</i>	<i>Improved disease-free survival over conventional treatment</i>
Primary immunodeficiency syndromes	Acute myeloid leukemia (AML) (first or second remission)
Aplastic anemia	Acute lymphoblastic leukemia (ALL) (first or second remission adults only)
Thalassemia	Myelodysplasia
Sickle cell disease	Multiple myeloma
Inborn errors of metabolism	
Chronic myeloid leukemia (CML)	

## (b) Children

<i>Sole chance of cure</i>	<i>Anticipation of improved disease-free survival compared to conventional treatment</i>	<i>Prospect of definitive cure in contrast to "disease control"</i>
Chronic myeloid leukemia (CML)	Selected patients with acute lymphoblastic leukemia (ALL)	Selected patients with thalassemia
Myelodysplasia (most patients)	Acute myeloid leukemia (AML)	Sickle cell disease
Juvenile myelomonocytic leukemia (JMML)	Non-Hodgkin's lymphoma	
Fanconi anemia	Hodgkin's disease	
Other constitutional bone marrow failure syndromes		



**Table 1.5** Diseases for which autologous transplant is used (adapted from Duncombe 1997)

(a) Adults		
<i>Proven benefit in RCT</i>	<i>Probable benefit</i>	<i>Possible benefit</i>
Non-Hodgkin's lymphoma	Relapsed Hodgkin's lymphoma	Chronic myeloid leukemia
Acute myeloid leukemia	Acute lymphoblastic leukemia	Disseminated breast cancer
Multiple myeloma	Relapsed testicular cancer	Disseminated lung cancer
		Other solid tumors
		Severe autoimmune disease
(b) Children		
<i>Proven benefit in RCT</i>	<i>Probable benefit</i>	<i>Possible benefit</i>
Stage 4 neuroblastoma	Relapsed/refractory Hodgkin's disease (adolescents)	Relapsed or refractory
	Relapsed Burkitt's NHL	• Wilms' tumor
	Relapsed diffuse large-cell NHL	• Germ cell tumor
	Other high-risk neuroblastoma	
	High-risk Ewing's sarcoma	
	High-risk or relapsed medulloblastoma	

## Children

### Hematological malignancy

#### *Acute lymphoblastic leukemia (ALL)*

Allogeneic HSCT is appropriate in certain groups of children with higher-risk ALL provided that they are in remission at the time of HSCT (high-risk ALL in 1st CR). Some patients with high-risk ALL are transplanted in 1st CR. Ideally an HLA-matched RD or URD should be used, but some centers will accept other closely but not fully matched donors (e.g. one antigen mismatch). High-risk ALL is defined by the following criteria:

- Philadelphia positive (BCR-ABL genetic rearrangement);
- presence of >5% blasts in bone marrow after 4 weeks of induction treatment in children with:
  - near haploid karyotype ( $\leq 44$  chromosomes in leukemic blasts);
  - MLL gene rearrangement;
- failure to enter remission (i.e. presence of >25% blasts in bone marrow) after 4 weeks of induction treatment.

Allogeneic HSCT is indicated in most children with ALL in 2nd CR, using an HLA-matched or closely matched RD or URD. Three risk groups of relapsed ALL may be defined, based on:

- timing;
- immunophenotype;
- site of relapse.

The risk groups are currently treated according to a risk-stratified approach, as follows.

#### *Standard risk*

- *Definition:* late (>6 months after completion of chemotherapy) isolated extramedullary (central nervous system [CNS] or testicular) relapse.
- *Treatment:* chemotherapy and local (testicular or cranial) radiotherapy.

#### *Intermediate risk*

- *Definition:*
  - late marrow or combined (i.e. marrow and extramedullary) relapse of non-T-cell ALL; or
  - early (>18 months after initial diagnosis but <6 months after stopping chemotherapy) isolated extramedullary or combined relapse of non-T-cell ALL; or
  - early extramedullary relapse of T-cell ALL.
- *Treatment:* it remains unclear whether chemotherapy (plus local radiotherapy for extramedullary disease) or HSCT is superior in these patients.

*High risk*• *Definition:*

- any very early relapse (<18 months from initial diagnosis of ALL);
- any marrow or combined relapse of T-cell ALL;
- early marrow relapse of non-T-cell ALL.

• *Treatment:* HSCT

Although HSCT has often been performed in 1st CR in infants (<12 months of age at diagnosis), in view of the poorer prognosis in comparison to that in older children with ALL, there is no definite evidence that this improves survival. Currently, HSCT in 1st CR is recommended only for high-risk infantile ALL:

- <6 months old at diagnosis;
- MLL gene rearrangement;
- presenting white cell count  $>300 \times 10^9/L$ .

Autologous HSCT is very rarely performed in children with ALL.

*Acute myeloid leukemia (AML)*

A meta-analysis of six prospective cohort studies demonstrated statistically significant reductions in relapse risk and improvements in overall and disease-free survival in children with AML in 1st CR undergoing HLA-identical sibling allogeneic HSCT compared to the use of autologous HSCT or chemotherapy alone. However, as the prognosis of children with good- and standard-risk AML treated with intensive chemotherapy protocols has improved greatly, allogeneic HSCT using an HLA-matched donor (RD or URD) is now recommended for AML in 1st CR only in children with poor-risk disease as defined by:

- adverse cytogenetic features (e.g. monosomy 7); or
- resistant disease (>15% blasts in bone marrow) after first course of intensive chemotherapy.

Children with good-risk (favorable cytogenetic abnormalities) or standard-risk AML (not in either good- or poor-risk group) are given intensive chemotherapy only.

Allogeneic HSCT is recommended in most children with AML in 2nd CR who have not had a previous transplant, and the use of mismatched donors may be considered as the prognosis with chemotherapy alone is poor.

Autologous transplants are now performed very rarely in children with AML in the UK, as they probably offer no advantage over intensive chemotherapy.

*Chronic myeloid leukemia (CML)*

Despite the increasing use of imatinib in the initial treatment of CML in adults, HSCT with an HLA-matched RD or URD is still considered to be the treatment of choice in children in:

- chronic phase (after initial disease control with hydroxyurea);
- advanced phase;
- blast crisis (after initial chemotherapy).

The use of mismatched donors may be appropriate in advanced-phase CML or blast crisis.

*Myelodysplasia (MDS)*

Although some sub-types of pediatric MDS (e.g. refractory cytopenia) may be relatively indolent, with stable blood counts during prolonged follow-up, others may progress rapidly to AML. Juvenile myelomonocytic leukemia (JMML) is a very rare disease unique to childhood with features of both MDS and myeloproliferative disease. HSCT is generally considered to be the best or even only chance of cure for most children with MDS, especially those with JMML. HLA-matched RDs or URDs may be suitable, and in higher risk MDS (e.g. JMML) the use of mismatched URDs or haploidentical RDs is appropriate.

*Non-Hodgkin's lymphoma (NHL)*

Autologous HSCT may be appropriate in children with relapsed Burkitt's lymphoma or diffuse large-cell NHL. There are early but promising data about the efficacy of allogeneic HSCT (RD or URD) in relapsed anaplastic large-cell NHL. Children with relapsed T-cell lymphoblastic lymphoma may benefit from allogeneic HSCT, but in practice it is often very difficult to achieve 2nd CR and hence perform a transplant in these patients.

*Hodgkin's disease (HD)*

Adolescents with relapsed or refractory HD are

usually treated with autologous HSCT, but this is seldom done in younger children as it offers little additional benefit beyond conventional relapse chemotherapy. As in adults, interest is growing in the possible role of reduced-intensity allogeneic HSCT in children and adolescents with multiply relapsed HD.

#### *Non-hematological malignancy*

Autologous HSCT, usually with PBSC, is indicated to rescue children from high-dose chemotherapy (occasionally with additional radiotherapy) given for certain relapsed or poor-prognosis solid tumors:

- stage 4 (or other high risk) neuroblastoma;
- high risk Ewing's sarcoma;
- high risk or relapsed medulloblastoma;
- selected patients (in the context of clinical trials) with relapsed or refractory
  - Wilms' tumor;
  - germ cell tumor.

#### *Aplastic anemia, etc.*

Allogeneic HSCT is indicated for children with severe or very severe aplastic anemia if an HLA-ID sibling donor is available; if not, intensive immunosuppressive treatment is usually performed initially since URD or mismatched RD HSCT is associated with a relatively high risk of graft rejection or severe GVHD; such transplants are indicated after failure to respond to two courses of immunosuppressive treatment in view of the otherwise very poor prognosis of these patients.

#### *Fanconi anemia (FA)*

At present HSCT is the only curative treatment for FA and is indicated when the patient starts to become transfusion dependent, or in the presence of myelodysplastic or leukemic transformation. Until recent years, the results of HLA-identical sibling HSCT were much better than those of URD HSCT due to graft failure and GVHD. However, the introduction of more immunosuppressive conditioning protocols has increased greatly the success rate of alternative-donor HSCTs.

#### **Other constitutional bone marrow failure syndromes**

Several inherited bone marrow failure syndromes may be treated by HSCT, including:

- *dyskeratosis congenita* (DKC):
  - HSCT (RD preferred to URD) is the only curative treatment, but is associated with considerable pulmonary and other organ toxicity, necessitating careful choice of conditioning regimen;
- *congenital amegakaryocytic thrombocytopenia* (CAMT):
  - HSCT (RD preferred to URD), usually performed with a standard conditioning regimen, is the only cure;
- *Schwachman–Diamond syndrome* (SDS):
  - HSCT (RD preferred to URD) may cure the hematological but not the other manifestations of SDS, and may be associated with considerable toxicity;
- *Diamond–Blackfan anemia* (DBA):
  - HLA-identical sibling HSCT may cure uncomplicated DBA (i.e. anemia only), but URD HSCT is not recommended;
  - it may be appropriate to consider use of an HLA-matched URD HSCT in DBA complicated by bone marrow failure when no RD is available.

#### **Kostmann's disease (severe congenital neutropenia, SCN)**

Although >90% of children with SCN respond satisfactorily to G-CSF, HSCT is the only treatment available for those who fail to respond and who continue to suffer from severe, life-threatening bacterial and fungal infections, and for the minority of patients who develop myelodysplastic or leukemic transformation. Although most HSCTs performed to date have employed HLA-identical sibling donors, there is an increasing number of reports of successful alternative-donor transplants.

#### **Thalassemia**

Better transfusion and iron chelation therapy have improved the prognosis for children with thalassemia given optimal treatment from infancy, so an improvement in their quality of life (by avoiding

the need for regular blood transfusions and chelation therapy) is the main benefit of HSCT. Therefore the decision as to whether to perform HSCT is complex. Ideally a transplant should be performed in early childhood, when the risk of organ damage due to iron overload from multiple blood transfusions is low. The results of alternative-donor (e.g. URD) HSCT in thalassemia are relatively poor, although this may be considered for carefully selected patients. There is increasing interest in the use of umbilical cord blood as a stem cell source, but a high cell dose is essential.

### Sickle cell disease

HLA-identical sibling donor HSCT may benefit patients with high-risk SCD, as suggested by the presence of at least one of the following:

- previous history of:
  - cerebrovascular accident;
  - acute chest syndrome (if hydroxyurea has failed);
- recurrent vaso-occlusive crises (if hydroxyurea has failed).

The following features (unless present in conjunction with the indications above) are no longer considered in the UK to constitute an indication for HSCT in SCD:

- impaired neuropsychological function and abnormal cranial MRI scan;
- sickle nephropathy;
- sickle lung disease;
- bilateral proliferative retinopathy and significant unilateral or bilateral visual impairment;
- osteonecrosis (multiple joints);
- alloimmunization to red cell antigens.

HSCT usually stabilizes and in some cases improves the complications of sickle cell disease, but the high risk of neurological complications (30%) means that this treatment is generally best undertaken in centers with experience in the management of SCID.

### Primary immunodeficiencies and metabolic storage disorders

Primary immune deficiency disorders and metabolic storage disorders all arise because of defects

in cells derived from the pluripotent hematopoietic stem cell. For this reason they ought to be amenable to cure by HSCT.

Severe combined immune deficiency, the most severe form of primary immune deficiency, from which untreated infants usually die in the first year of life, was one of the first conditions to be successfully treated by HSCT. It was also found that some forms of this condition were amenable to T-cell-depleted mismatched HSCT, even without pre-transplant conditioning. Initially only 50% of HSCTs were successful but particularly in the last 5 years success rates have now risen to approaching 90%. In the light of this success other primary immune deficiencies, which although not immediately lethal in the first months of life still cause serious illness and reduced life expectancy, are now treated by HSCT. The cumulative risk of serious ill health and death during childhood, adolescence and early adult life is now considerably greater than the relatively small risk of HSCT. Indeed, latest data suggest an overall success rate of 80–90% using matched sibling or unrelated donor. Immune deficiencies treated include Wiskott–Aldrich syndrome, chronic granulomatous disease, Chediak Higashi syndrome and hemophagocytic lymphohistiocytosis, as well as less well-defined combined immune deficiencies (Table 1.3).

HSCT has not been as successful with metabolic disorders, although results are improving. In infantile osteopetrosis, HSCT can certainly be very successful but the risk of complications including graft rejection are higher. Subtypes of osteopetrosis with neuroretinal degeneration are not amenable to HSCT, however, as although the bone defect is corrected, neuroretinal degeneration progresses inexorably. HSCT has been attempted for many metabolic storage disorders but patients need to be evaluated very carefully, particularly those with neurological involvement, as although there may be successful engraftment and correction of some features of the disorder, the child may still deteriorate and die from the neurological complications. Of all of the metabolic storage diseases the greatest success has been with Hurler's syndrome (mucopolysaccharidosis type I).

### Autoimmune disease

The observation that a patient with severe autoimmune disease improved considerably after HSCT carried out for another reason has led to the development of HSCT for various forms of autoimmune disease. Initially autologous HSCT was performed where the patient's bone marrow was taken, T cells purged (as these are thought to be largely responsible for provoking the manifestations of autoimmune disease) and then the patient's own T-cell-depleted bone marrow returned after conditioning therapy. This has been particularly successful in children with juvenile idiopathic arthritis, most having long periods of disease-free remission, although after some years perhaps up to a third relapse to a greater or lesser extent. More recently, allogeneic transplantation has been attempted and this looks likely to be an important area for future development.

### Further reading

- Antoine, C. *et al.* (2003) Long term survival in transplantation of haemopoietic stem cells for immunodeficiencies. Report to the European Experience 1968–1999. *Lancet* **361**:553–560.
- Ball, S.E. (2000) The modern management of severe aplastic anaemia. *Br J Haematol* **110**: 41–53.
- Bleakley, M., Lau, L., Shaw, P.J., Kaufman, A. (2002) Bone marrow transplantation for paediatric AML in first remission: a systematic review and meta-analysis. *Bone Marrow Transplant*. **29**: 843–852.
- Brodsky, R.A., Smith, D.A. (1999) *Curr Opin Oncol*.
- Chessells, J.M. (2001) The role of bone marrow transplantation in first remission of paediatric ALL. *Front Biosci* **6**: G38–42.
- Craddock, C., Chakraverty, R. (2005) Stem cell transplantation. In Hoffbrand, A.V., Catovsky, D., Tuddenham, E. (eds), *Postgraduate Haematology*, 5th edition. Oxford: Blackwell Publishing, pp. 419–435.
- Cwynarski, K., Roberts, I.A.G., Iacobelli, S. *et al.* (2003) Stem cell transplantation for chronic myeloid leukaemia in children. *Blood* **102**: 1224–1231.
- Gahrton, G. (2005) Progress in hematopoietic stem cell transplantation in multiple myeloma. *Curr Opin Hematol* **12**: 463–470.
- Gibson, B.E.S., Wheatley, K., Hann, I.M. *et al.* (2005) Treatment strategy and long-term results in paediatric patients treated in consecutive UK AML trials. *Leukemia* **19**: 2130–2138.
- Goldman, J.M., Melo, J.V. (2003) Chronic myeloid leukemia – advances in biology and new approaches to treatment. *N Engl J Med* **349**:1451–1464.
- Harrison, G., Richards, S., Lawson, S. *et al.* (2000) Comparison of allogeneic transplant versus chemotherapy for relapsed childhood acute lymphoblastic leukaemia in the MRC UKALL R1 trial. *Ann Oncol* **11**: 999–1006.
- Ljungman, P., Urbano-Ispizua, A., Cavazzana-Calvo, M. *et al.* (2006) Allogeneic and autologous transplantation for haematological diseases, solid tumours and immune disorders: definitions and current practice in Europe. *Bone Marrow Transplant* **37**: 439–449.
- Locatelli, F., De Stefano, P. (2004) New insights into haematopoietic stem cell transplantation for patients with haemoglobinopathies. *Br J Haematol* **125**: 3–11.
- Locatelli, F., Nollke, P., Zecca, M. *et al.* (2005) Hematopoietic stem cell transplantation (HSCT) in children with juvenile myelomonocytic leukemia (JMML): results of the EWOG-MDS/EBMT trial. *Blood* **105**: 410–419.
- Peggs, K.S., Hunter, A., Chopra, R. *et al.* (2005) Clinical evidence of a graft-versus-Hodgkin's-lymphoma effect after reduced-intensity allogeneic transplantation. *Lancet* **365**: 1934–1941.
- Peggs, K.S., Mackinnon, S., Linch, D.C. (2005) The role of allogeneic transplantation in non-Hodgkin's lymphoma. *Br J Haematol* **128**: 153–168.
- Peters, C., Stewart, C.G. (2003) Hematopoietic cell transplantation for inherited metabolic diseases: an overview of outcomes and practice guidelines. *Bone Marrow Transplant* **31**: 229–239.
- Pritchard, J., Cotterill, S.J., Germond, S.M., Imeson, J., de Kraker, J., Jones, D.R. *et al.* (2005) High dose melphalan in the treatment of advanced neuroblastoma: Results of a randomized trial (ENSG-1) by the European Neuroblastoma Study Group. *Pediatr Blood Cancer* **44**: 348–357.
- Steward, C.G., Jarisch, A. (2005) Haemopoietic stem cell transplantation for genetic disorders. *Arch Dis Child* **90**: 1259–1263.
- Yusuf, U., Frangoul, H.A., Gooley, T.A. *et al.* (2004) Allogeneic bone marrow transplantation in children with myelodysplastic syndrome or juvenile myelomonocytic leukemia: the Seattle experience. *Bone Marrow Transplant* **33**: 805–814.