HSCT: How Does It Work?

2

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Abstract

The HSCT (haematopoietic stem cell transplant) is a particular treatment for many haematological and non-haematological diseases. Broadly, there are three different categories of transplantation, autologous, allogeneic and syngeneic, which can be applied to most disease scenarios. Haematopoietic stem cells can be derived from the bone marrow, peripheral blood and umbilical cord blood. HSCT treatment can be divided into separate phases that start with the harvest of the stem cells and passing through the conditioning, aplasia and engraftment until the recovery of the haematopoietic functions. HSCT is indicated in many diseases, and these indications depend on numerous factors such as the disease type, stage and response to previous treatment. Among non-malignant diseases, aplastic anaemia, sickle cell disease and, more recently, autoimmune diseases can also be effectively treated with HSCT. One third of the transplants in children are performed for rare indications such as severe combined immunodeficiencies. Allogeneic HSCT can also cure a number of non-malignant diseases in children, such as Wiskott-Aldrich syndrome and chronic granulomatous disease (CGD). This chapter will include transplant in primary immunodeficiency in children as well as inherited bone marrow failure and inborn errors of metabolism.

Keywords

HSCT • Indications • Autoimmune diseases • Haemoglobinopathies Paediatric • Immunodeficiencies

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2.1 What Nurses Need to Know

2.1.1 Introduction

Haematopoietic stem cell transplantation (HSCT) is a therapeutic option for several haematological diseases including acute and chronic leukaemia, lymphoma and multiple myeloma, some of inherited disorders such as severe combined immunodeficiency and thalassemia and other inborn errors of metabolism (Maziarz 2015).

HSCT involves the use of autologous haematopoietic stem cells (HSC) obtained from the patient's own bone marrow (BM) or peripheral blood (PBSC) or allogeneic HSC where the donor cells come from a family-related or an unrelated donor, from the bone marrow, peripheral blood or cord blood.

The collected HSC are infused into a recipient (Gratwohl et al. 2010). Before the infusion, the recipient is treated with a conditioning regimen (see Chap. 6), involving the use of different types and dosages of chemo and/or radiotherapy and/or immunosuppressant drugs (such as antithymocyte globulin) (Copelan 2006).

2.1.2 Aims of HSCT

- In the autologous setting, patients with chemosensitive malignant diseases are offered high-dose chemotherapy in order to destroy or further reduce the malignant disease, ablating the marrow with this aggressive therapy. In this case, the stem cell infusion is intended to treat the prolonged chemotherapy-induced hypoplasia and not the disease itself (Maziarz 2015; Michel and Berry 2016).
- In the allogeneic setting (see below Sect. 2.2):
  - In malignant haematological disease, donor HSCs replace the immune system and help to eradicate malignancy (Maziarz 2015; Michel and Berry 2016).
  - In non-malignant diseases, where the cause is dysfunction of the haematopoietic stem cell (HSC), the HSCT procedure replaces the inefficient patient immune system with the donor one (Michel and Berry 2016; Hatzimichael and Tuthill 2010).

2.1.3 Outcomes

Outcomes vary according to:

- The stage of the disease
- The age of the patients
- The lapse of time from diagnosis to transplant
- The histocompatibility between donor and recipient
- The donor/recipient sex combination (the overall survival decreases for male recipients having a female donor) (Sureda et al. 2015a)
- Advances in immunogenetics and immunobiology
- Conditioning regimens
- Disease characterization and risk stratification
- Immunosuppression
- Antimicrobials
- Other types of supportive care

All these factors contribute to improvements in disease control and overall survival (Maziarz 2015).

Patient selection influences outcomes. Patients with better overall functional performance status, limited comorbidities and underlying organ damage have more favourable outcomes (Maziarz 2015).

2.1.4 Nursing Considerations

Patients require specific care to overcome the physical and emotional problems resulting from this treatment. Usually after myeloablative conditioning, HSCT recipients typically experience a period of profound pancytopenia lasting days to weeks depending on the donor source. The rapidity of neutrophil recovery varies with the type of graft: approximate recovery time is 2 weeks with G-CSF-mobilized peripheral blood stem cells, 3 weeks with marrow stem cells and can be as long as 4 weeks with umbilical cord blood stem cells.

However, re-establishment of immune system takes at least several months due to prolonged lymphocyte recovery process, and some patients continue to show immune deficits for several years after HSCT (Mackall et al. 2009). During this period, the patient has a high risk of developing complications; thus, HSCT units require multidisciplinary teams of physicians, nurses, pharmacists, social workers, nurse practitioners, physician assistants, nutrition experts and occupational and physical therapists, in addition to a specialized facility and technical resources (Maziarz 2015).

Nurses who work in HSCT units have a key role in treatment management and require specific training to:

- Understand, prevent and manage the early and late effects of HSCT.
- Care for multiply treated patients.
- Inform and educate patients and their caregivers.
- Administer drugs and blood products safely.
- Manage the central venous catheter (cvc).
- Give emotional support.

These topics will be covered in later chapters.

2.2 Different Types of HSCT

HSCs may be obtained from autologous (BM or PBSC) or allogeneic (HLA-matched related (MRD), HLA-matched unrelated (MUD) or HLA-mismatched related or unrelated donors and UCB) sources (Table 2.1).

Table 2.1 Summary of HSCT types and HSC sources

Type of transplantation	Cell source	Donor
Autologous	Bone marrow Peripheral blood	Recipient
Allogeneic	Bone marrow Peripheral blood Umbilical cord blood	Related Unrelated
Syngenic	Bone marrow Peripheral blood	Monochorionic twin

Adapted from Tura (2003)

2.2.1 Autologous Haematopoietic Stem Cell Transplantation

Autologous HSCT is defined as "a high dose chemotherapy followed by the reinfusion of the patient's own HSC" (cit. NCI Dictionary). After mobilization (see Chap. 5), the patient's HSCs are collected and cryopreserved. Auto-HSCT facilitates the prompt reconstitution of a significantly depleted or ablated marrow following very aggressive chemotherapy and sometimes radiotherapy intended to eradicate haematologic and non-haematologic malignancies (Michel and Berry 2016).

There is no risk of rejection or graft versus host disease (GvHD) and no GvT (graft versus tumour) effect (see Chaps. 11 and 12). Graft failure can occur rarely, and some trials demonstrate how relapse remains an issue for the majority of patients with multiple myeloma (Michel and Berry 2016; Mackall et al. 2009).

2.2.2 Allogeneic Stem Cell Transplantation

In allogeneic transplantation, the recipient receives HSCs from a *related* or *unrelated* donor who can be fully or partially human leukocyte antigen (HLA)-matched (Fig. 2.1); related donors are family members; unrelated donors are identified through a donor registry or from a cord blood bank. In allogeneic HSCT, the major histocompatibility complex (MHC) HLA class I and II molecules located on chromosome 6 play an important role (Maziarz 2015). (Please refer to Chap. 3 for HLA typing and donor selection.)

In allogeneic HSCT, the aim of conditioning is to:

- Kill tumour cells (in malignant diseases).
- Eradicate existing bone marrow tissue (in order to provide space for engraftment of transplanted donor stem cells).
- Suppress the patient's immune response and minimize the risk of graft rejection of the donor HSC (Maziarz 2015).

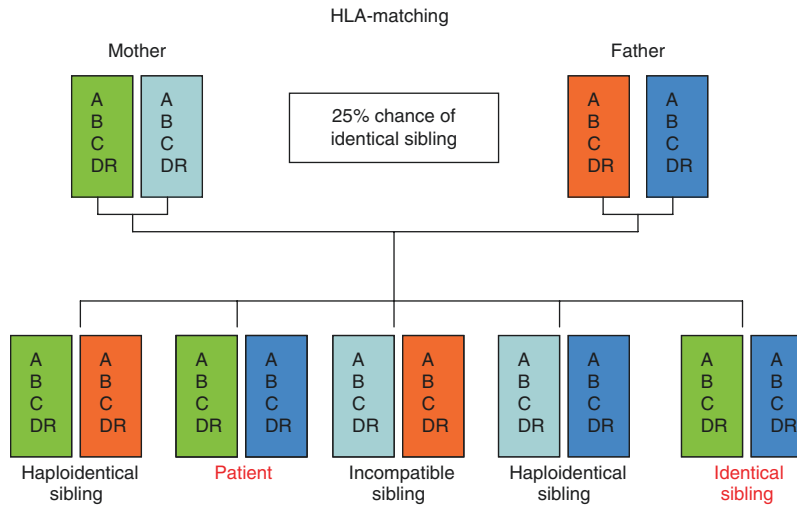


Fig. 2.1 Scheme of HLA compatibility (Adapted from: Soiffer 2008)

Allogeneic HSCT has been subject to several improvements during recent years.

Reduced intensity conditioning regimen, alternative donor transplants and new stem cell sources have increased the accessibility and availability, especially for older patients who have poor tolerance of the high toxicity of the treatment. These improvements have resulted in reduced transplant-related mortality, although relapse remains an issue (Michel and Berry 2016).

2.2.2.1 Allogeneic Transplantation from HLA-Matched Related Donor (MRD)

The ideal donor is an HLA-identical sibling. Patients have a 25% chance of each sibling being fully HLA-matched, because siblings inherit 50% haplotype from each parent (Fig. 2.1).

If donor is an identical twin, they are referred to as syngeneic (see Sect. 2.3).

2.2.2.2 Allogeneic from Unrelated Donor (MUD, MMUD)

If recipient has no sibling or the blood tests confirm that there is no HLA compatibility with the sibling, then a search of "Bone Marrow Donors Worldwide" registry database (BMDW) is activated (Apperley et al. 2012).

If the donor histocompatibility is fully matched with the recipient, the donor is called a matched unrelated donor (MUD); if there is a partial incompatibility, the donor is called a mismatched unrelated donor (MMUD).

The time between the activation of the unrelated donor research and the beginning of transplantation procedure is fundamental. The more time spent in the search phase, the greater is the risk that the patient's disease will worsen or die (Hatzimichael and Tuthill 2010).

2.2.2.3 Cord Blood Transplantation

Unrelated donor umbilical cord blood unit transplantation (UCBT) provides an alternative donor option in patients who lack a conventional MRD and MUD. Advantages of UCBT include the capacity to tolerate greater degrees of HLA mismatch than is possible using MUD (Bashey and Solomon 2014).

UCBT have the advantage that the cryopreserved units at the cord blood banks are readily available, with results comparable to those from an unrelated donor or only partially compatible units (also HLA 5/8 loci). UCBT shows a lower incidence of GvHD, without losing the GvL effect (Copelan 2006) (see Chap. 12). However, delayed haematopoietic recovery and slow immune reconstitution and acquisition cost remain important challenges (Bashey and Solomon 2014).

2.2.2.4 Haploidentical Transplantation

In case of unavailability of a conventional HLA identical sibling, MUD or CB unit, it is possible to transplant with an available haploidentical donor. The donor may be a parent, child, brother, sister or other relative that matches for one haplotype (HLA-mismatched related donors with compatibility >6/8 loci).

The most important criterion for a haploidentical transplant is the urgency of the transplant in order to avoid early relapse or progression of the disease (Aversa 2015).

The advantages of the haploidentical transplantation are:

- The donor can be changed in case of a poor stem cell mobilizer or if optimal graft composition was not achieved.
- Easy family donor availability (if patients are not fostered or orphans without other relatives).
- The benefit of natural killer (NK) cell alloreactivity.
- Easy access to donor-derived cellular therapies after transplantation (Aversa 2015).

There are two haploidentical procedures:

- Haploidentical transplantation with haematopoietic stem cells T-replete with cyclophosphamide in immediate post-transplant phase that involves the induction of transplantation tolerance; it appears to have overcome many of the obstacles historically associated with haploidentical donor transplantation, such as too high rates of graft rejection and post-transplant infections (Bashey and Solomon 2014), and promotes a graft versus leukaemia (GVL) therapeutic benefit with improved survival (Maziarz 2015).
- Haploidentical transplantation with depletion of T-lymphocytes exists in aggressive and severe immune depleting conditioning regimen followed by infusion of mega-doses of highly purified peripheral stem cells (Bashey and Solomon 2014).

2.2.2.5 Syngeneic Transplantation

Syngeneic is a type of transplantation where the donor is the recipient's monochorial twin and who is genetically identical to the patient. There is no immunological conflict such as GvHD (graft versus host disease) (see Chap. 11) but at the same time no beneficial GVL (graft versus Leukaemia) effect (Mackall et al. 2009).

(see Chaps. 9 and 11 for HSCT complications)

2.3 The Stem Cell Sources

HSC can be isolated from the bone marrow (BM), peripheral blood after mobilization (PBSC) and umbilical cord blood (UCB) (Maziarz 2015).

"Bone marrow cells are capable of repopulating all hematopoietic and lymphocytic populations while maintaining capacity for self-regeneration, assuring long -term immunologic and hematopoietic viability" (Maziarz 2015).

Until the early 1990s, the bone marrow (BM) represented the only source of stem cells. However, this practice has almost been replaced by peripheral blood stem cells (PBSC). More recently, cord blood (CB) has been shown to be a good alternative source of haematopoietic stem cells. All three types of HSCs regardless of source are capable of regeneration after a high-dose chemoradiotherapy treatment (Richard 2000).

2.3.1 Peripheral Blood Stem Cells

PBSCs have been increasingly used in both auto- and allo-HSCT. Mobilization of haematopoietic stem cells to the peripheral blood can be achieved by the administration of growth factors such as G-CSF (allo-HSCT) and/or myelosuppressive chemotherapy (auto-HSCT) (Apperley et al. 2012).

An advantage HSCT performed with PBSC is a relatively rapid recovery of haematopoiesis compared to BM and increases the disease-free survival and overall survival in high-risk haematological malignancies. The disadvantage is an

increased risk of chronic GvHD in the allogenic HSCT because of an increased number of T cells circulating (Maziarz 2015).

2.3.2 Bone Marrow

BM is traditionally harvested from the posterior iliac crests under general or epidural anaesthesia in a surgical room where trained haematologists or surgeons collect stem cells and blood directly from the bone marrow cavity in the bilateral posterior iliac crest region using aspiration needles.

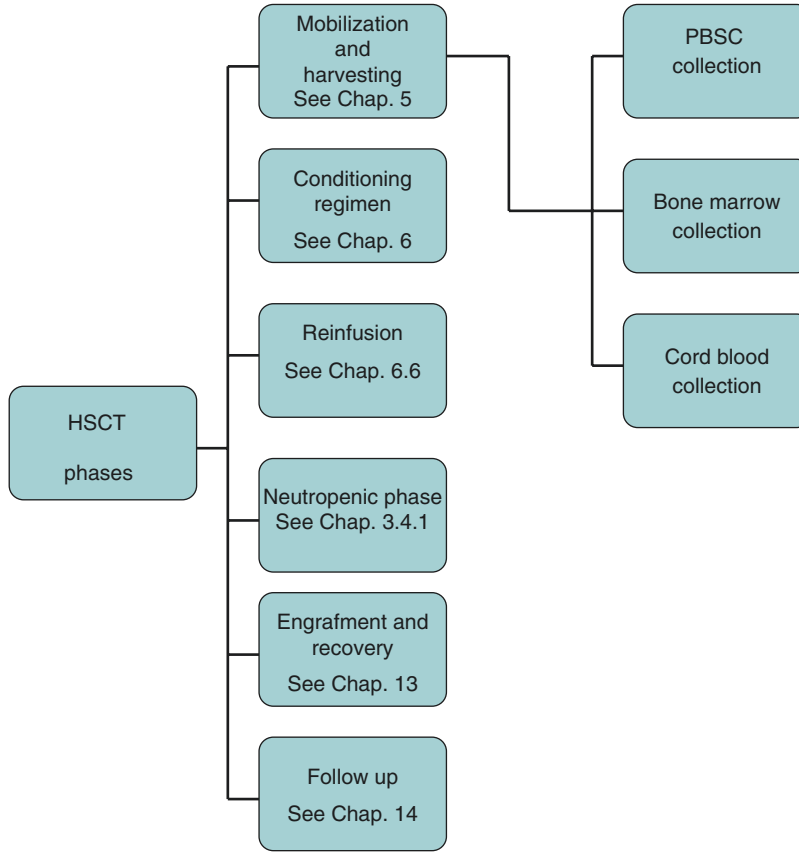
HSCT performed with BM leads to less GvHD compared to PBSC source, but has the disadvantage of a slower neutrophil and platelet engraftment (Maziarz 2015).

2.3.3 Umbilical Cord Blood

Cord blood cells are collected and cryopreserved from the umbilical cord immediately after birth, but generally before the placenta has been delivered in order to avoid clots (Demiriz et al. 2012). UCB cells have been used both in related and unrelated HLA-matched and HLA-mismatched allogeneic transplants in children and in adults (Demiriz et al. 2012; Apperley et al. 2012). The advantage is a low criteria for a match (4/6 match is acceptable) increasing the chance of identifying a suitable cord unit or cord units in a matter of days. Less GvHD is often observed. A key disadvantage is often slower engraftment compared to BM and PBSC and increased infection complications due to slow rate of haematopoietic recovery (Maziarz 2015).

(see Chaps. 3 and 5).

2.3.4 HSCT Phases



2.3.4.1 Neutropenic Phase

After the chemotherapy, the blood count decreases for about 7–14 days in autologous HSCT and until 20–30 days in allogeneic HSCT. The neutropenia occurs when the absolute neutrophil count is <500 cells/mm^3 (Maziarz 2015).

During this period, several complications may occur:

- Increased risk of infections due to a not effective immune system. Infection following HSCT is associated with significant morbidity and mortality, so prevention is critical to improve outcomes. The risk of infection is based on multiple variables including the type of transplantation (autologous or allogeneic), source of haematopoietic cells (related or unrelated donor, peripheral blood, bone marrow, or cord blood), underlying disease, disease status (remission or relapse), intensity of the preparative regimen (ablative or non-myeloablative), prior infections, endogenous microflora and environmental exposure to microorganisms. In addition, risk may vary based on infection control measures used by transplantation centres. Practices in infection control such as type of isolation, dietary restrictions and antimicrobial prophylaxis vary widely among transplantation centres. Nurses are pivotal in implementing practices to prevent and manage infections and associated effects following HSCT (Sureda et al. 2015a).
- Bleedings because of thrombocytopenia (platelets have a slow recovery after transplantation).
- Tiredness caused by the decreasing of haemoglobin levels.
- Pain because of mucositis.
- Reduced nutrition. Oral intake is usually severely reduced because of, on one side, the oral mucositis that many patients develop and, on the other side, the prolonged post conditioning nausea. When oral intake is reduced and the body mass index decrease, total enteral/parenteral nutrition may be provided especially for children.

2.4 Indications for Transplant in Malignant Disease

The patient assessment for a transplant procedure is complex and includes several factors such as the patient's overall health and performance status, comorbidities, disease risk/status (e.g. remission state and responsiveness to treatment) and graft and donor source. For example, autologous transplantation is not useful for diseases in which normal HSCs cannot be collected as in CML or myelodysplasia (Rowley 2013).

The indications for transplant are based on best available evidence from clinical trials or, where clinical trials are not available, registry, multicentre or single centre observational studies (Majhail et al. 2015). The HSCT specialist determines if transplant should be considered as an option for disease consolidation, but the final decision will be made in conjunction with the patient (Maziarz 2015).

There have been major changes in indications, such as the rise and fall of autologous HSCT for breast cancer or of allogeneic HSCT for chronic myeloid leukaemia (CML), and in technology, as illustrated by the change from the bone marrow to peripheral blood, the rapid increase in use of unrelated donors and the introduction of reduced intensity conditioning. It is clear how some guidance is warranted, for transplant teams, hospital administrators, health-care providers and also patients (Apperley et al. 2012).

The HSCT indications are not the same in children and in adults (Table 2.1).

The Table 2.2 is a scheme of the main indications for autologous and allogeneic transplantation. It includes the standard of care.

2.4.1 Indications for Allogeneic HSCT

Adult patients with acute myeloid leukaemia (AML) should always be considered for allo- or auto-HSCT, while allo-HSCT cannot be recommended as first-line treatment for chronic myeloid leukaemia (CML) because of the efficacy of the first-line therapy with imatinib for

Table 2.2 Indication for transplant: Recommendation categories (see text for definition): Standard of care (S); Standard of care, clinical evidence available (C); Standard of care, Rare indication (R)

	Adult		Paediatric	
Disease	Auto	Allo	Auto	Allo
Acute myeloid leukaemia				
CR1, intermediate risk/not in remission		C		C
CR1, high risk/CR2+		S		S
Acute promyelocytic leukaemia, relapse	R	R	R	R
Acute lymphoblastic leukaemia				
CR1, high risk/CR2		S		S
CR3+/not in remission		C		C
Chronic myeloid leukaemia		C		C
Myelodysplastic syndromes				
Low risk		C		C
High risk/juvenile myelomonocytic leukaemia/ therapy related		C		S
T-cell non-Hodgkin lymphoma				
CR1, high risk/CR2		S		S
CR3+/not in remission		C		C
Lymphoblastic B-cell non-Hodgkin lymphoma (non-Burkitt)				
CR1, high risk/CR2		S		S
CR3+/not in remission		C		C
Burkitt's lymphoma				
First remission/first or greater relapse, sensitive	C	C	C	C
First or greater relapse, resistant		C		C
Hodgkin lymphoma				
Primary refractory, sensitive/first relapse, sensitive/ second or greater relapse	C	C	C	C
Primary refractory, resistant/first relapse, resistant		C		C
Multiple myeloma	S	C		
Anaplastic large cell lymphoma				
Primary refractory, sensitive/first relapse, sensitive/ second or greater relapse	C	C	C	C
Primary refractory, resistant/first relapse, resistant		C		C
Solid tumours				
Germ cell tumour/Wilm's tumour, relapse/ osteosarcoma, high risk/medulloblastoma, high risk/ other malignant brain tumours	C		C	
Ewing's sarcoma, high risk or relapse	S		S	
Non-malignant diseases				
Severe aplastic anaemia, new diagnosis, relapse/ refractory		S		S
Sickle cell disease		C		C
Thalassemia		S		S

Table 2.2 (continued)

Disease	Adult		Paediatric	
	Auto	Allo	Auto	Allo
Fanconi's anaemia/dyskeratosis congenita/Blackfan-diamond anaemia/congenital amegakaryocytic thrombocytopenia/severe combined immunodeficiency/T-cell immunodeficiency, SCID variants/Wiskott-Aldrich syndrome/haemophagocytic disorders/lymphoproliferative disorders/severe congenital neutropenia/chronic granulomatous disease/other phagocytic cell disorders/IPEX syndrome/other autoimmune and immune dysregulation disorders/mucopolysaccharoidoses (MPS-I and MPS-VI)/other metabolic diseases/ osteopetrosis/globoid cell leukodystrophy (Krabbe)/ metachromatic leukodystrophy/cerebral X-linked adrenoleukodystrophy		R		R
Juvenile rheumatoid arthritis/systemic sclerosis	R		R	

Adapted from: Majhail et al. (2015)

chronic patients, even if HSCT remains the only curative treatment. Allo-HSCT at the moment is the only curative option for patients with myeloproliferative disorders such as primary myelofibrosis and is considered the treatment of choice for adult patients with myelodysplastic syndromes (MDS). Allo-HSCT from an HLA-identical sibling or MUD is a treatment option for young patients previously treated with fludarabine-containing regimens and poor-risk disease. Patients with acquired severe aplastic anaemia (SAA) are considered for a first-line HLA-identical sibling HSCT (if available) or in case a haploidentical donor or a mismatch 9/10 donor. Allo-HSCT is the only treatment for Fanconi anaemia. More than 20% of allo-HSCT are performed in patients under 20 years, and at least one third are performed for rare indications. Clinical trials are limited because of small numbers, and chronic GvHD is still major limitation for the procedure. Well-matched donors must be considered as the primary cell source (Sureda et al. 2015a; Majhail et al. 2015; Rowley 2013).

2.4.2 Indications for Autologous HSCT

Auto-HSCT remains the standard of care for patients with Hodgkin lymphoma in first chemosensitive relapse or refractory to the first-line therapy and in chemosensitive relapse of DLBCL (diffuse large B-cell lymphoma), while in relapsed patients, allo-HSCT should be considered. Auto-HSCT is clearly indicated for patients with multiple myeloma (MM) who respond to first-line treatment, but age and general health should be considered; in MM all-HSCT has a curative potential, but the risk of mortality needs to be considered; autologous is also a standard of care for follicular lymphoma in first or subsequent relapse, while the auto-HSCT consolidation is considered a standard part of first-line treatment of younger(<60–65 yrs) patients with mantle cell lymphoma and for peripheral T-cell lymphomas and represent a reasonable treatment option. Patients with amyloidosis and without severe heart failure benefit from high dose-

therapy and auto-HSCT, while allo-HSCT should be considered in relapsed younger patients after at least one new drug such as lenalidomide or bortezomib (Sureda et al. 2015a).

HSCT in solid tumours needs further prospective trials (Sureda et al. 2015a).

For further information on HSCT in non-malignant paediatric indication, see below.

2.5 Indications for Transplant in Non-malignant Diseases in Children

More than 20% of allogeneic haematopoietic stem cell transplants (HSCT) are performed in patients below 20 years. However, at least one third of HSCTs in children are performed for rare indications (Sureda et al. 2015b). Allogeneic HSCT can cure several non-malignant disorders in children.

2.5.1 Transplant in Primary Immunodeficiencies

Primary immunodeficiencies are genetic disorders characterized by defective or impaired innate or adaptive immunity. Of these, severe combined immunodeficiencies (SCIDs) are the most severe, leading to death in infancy or early childhood unless treated appropriately (Sureda et al 2015b).

2.5.2 Severe Combined Immunodeficiencies

Severe combined immunodeficiencies (SCIDs) are a genetically heterogeneous group of rare inherited defects characterized by severe abnormalities of immune system development and function (Gaspar et al. 2013; Gennery 2015). Most of the genetic defects responsible for SCID are inherited in an autosomal recessive fashion and therefor are more common in infants born to consanguineous parents (Rivers and Gaspar 2015). The incidence of SCID varies according to ethnicity (Booth et al. 2016). The different forms of SCID can have different patterns of lymphocyte development. Nearly all SCIDs have absent T cells but are then further divided by the presence or absence of B and NK cells (Fig. 2.2; Rivers and Gaspar 2015; Booth et al. 2016). Patients with SCID usually present in early infancy with recurrent, severe or opportunistic infections. Multiple pathogens may coexist, and opportunistic infection, for example, with *Pneumocystis jiroveci*, is common (Gennery 2015). This can also be accompanied by failure to thrive with persistent diarrhoea and persistent oral thrush. Infants that present with lymphopenia should be further evaluated (Rivers and Gaspar 2015).

The severity of the clinical and immunologic situation requires prompt intervention, and for most patients, the only curative treatment is allogeneic HSCT (Gaspar et al. 2013; Gennery 2015). Gene therapy and enzyme replacement therapy are available for some specific genetic subtypes (Gennery 2015). The objective of HSCT in patients with SCID is to provide normal haematopoiesis, facilitating correction of the immune defect. Therefore, it is critical to minimize potential long-term effects of treatment but to establish effective long-term immune function (Gennery 2015). Once the diagnosis of SCID is made, there is an urgency of finding a suitable donor (Gaspar et al. 2013) and proceeding to transplant. Factors

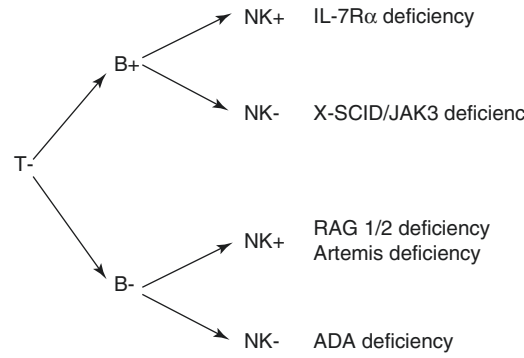


Fig. 2.2 Some of the more common immunophenotypes in SCID (Reproduced from Rivers and Gaspar 2015)

that influence the prognosis include the age, the type of SCID and the clinical state at the time of diagnosis, in particular the presence of infection and the degree of HLA matching with the donor (Sureda et al. 2015b).

2.5.3 Non-SCID Primary Immunodeficiencies

The three of the more common non-SCID primary immunodeficiency (PID) disorders are as follows: 1. Chronic granulomatous disease (CGD) patients with CGD have a reduced ability of phagocytes (particularly neutrophils) to kill bacterial and fungal pathogens. 2. Wiskott-Aldrich syndrome (WAS) is an X-linked immunodeficiency caused by mutations in the WAS gene, presenting with thrombocytopenia, eczema and immunodeficiency. 3. Haemophagocytic lymphohistiocytosis (HLH) is a life-threatening disease of severe hyper inflammation caused by uncontrolled proliferation of activated lymphocytes and macrophages (Booth et al. 2016).

Conditioning There is a debate about the best approach of treatment. Different centres are using a wide variety of conditioning regimes (Booth et al. 2016). In the presence of an HLA-identical family donor, HSCT can be performed in certain types of SCID (particularly those with an absence of NK cells) without any conditioning regimen. These patients can have donor T-cell (and occasionally B-cell) reconstitution, thereby potentially sparing short- and long-term toxicities (Dvorak et al. 2014; Gennery 2015; Sureda et al. 2015b). Dvorak et al. (2014) compared the outcome of transplants in SCID patients' undergoing unrelated donors or unrelated cord blood transplants with matched sibling transplants both with no conditioning. They concluded that patients lacking a matched sibling donor can proceed to an unrelated transplant without the use of conditioning chemotherapy in the same manner as with a matched sibling donor but with careful GvHD prophylaxis.

In contrast to SCID disorders, HSCT in non-SCID PID always requires conditioning therapy. Over the last 15 years, the use of reduced intensity conditioning approaches has been explored in order to reduce acute and late effects (Booth et al. 2016). The EBMT and ESID (European Society for Immunodeficiencies) have published in 2011 guidelines for stem cell transplantation for primary immunodeficiencies (EBMT and ESID 2011).

Outcome In recent years, the outcome of HSCT has improved considerably with overall survival rates now approaching 90% in optimal circumstances (Gennery 2015). This is most likely due to earlier diagnosis; improved supportive care, including the initiation of bacterial and fungal prophylaxis; and early referral for HSCT (Booth et al. 2016). For many patients with PID, partial donor chimaerism is sufficient to induce cure if the affected recipient cell lineage is replaced completely or partially by donor cells, although complete donor chimaerism is best in some diseases (Gennery 2015). Pai et al. (2014) reported the results of 240 infants who received a transplant for SCID, at 25 centres in the USA between January 2000 and December 2009. The overall survival rate at 5 years was 74%; most deaths were within the first year after transplant and were due to infections (39%) or pulmonary complications (37%). Mortality was increased for patients who had active infection at the time of transplantation.

2.5.4 Newborn Screening

Over the past decade, the concept of newborn screening for SCID has moved into reality in a number of countries around the world. Early diagnosis of these conditions will significantly improve the outcome for SCID patients, allowing a rapid move to curative therapy before symptoms and infections accrue (Gaspar et al. 2013; Booth et al. 2016). Detection of SCID at birth allows immediate protection with prophylactic Immunoglobulin substitution and antibiotics, thus keeping children free from infection until a definitive procedure can be undertaken (Gaspar et al. 2013). Screening is based on a qPCR assay for T-cell receptor excision circles (TRECs)

which can be performed on the dried blood spot tests—Guthrie already taken as part of universal newborn screening for other inherited conditions. TRECs are essentially a marker of thymic output and their levels are severely reduced in SCID and in a number of other conditions. If low TREC levels are detected, then assay is repeated before the patient is called for further immunological evaluation (Booth et al. 2016).

The optimal way to approach transplant in those infants identified through newborn screening programs has yet to be determined (Booth et al. 2016). It generated considerable debate among many members of the SCID transplant community (Gaspar et al. 2013). The use of chemotherapy in pre-symptomatic children with SCID is difficult for physicians and families to accept (Booth et al. 2016).

2.5.5 Inherited Bone Marrow Failure

The inherited bone marrow failure (BMF) syndromes are a rare group of syndromes that are characterized by impaired haematopoiesis and cancer predisposition. Most inherited BMF syndromes are also associated with a range of congenital anomalies (Mehta et al. 2010).

Fanconi anaemia (FA) is the most common inherited BMF syndrome (Mehta et al. 2010). It is an autosomal recessive disorder that is characterized by a wide variety of congenital abnormalities, defective haematopoiesis and a high risk of developing acute myeloid leukaemia and certain solid tumours. The indication for HSCT in FA is the development of bone marrow failure (Tischkow and Hodgson 2003). Virtually all patients with FA will require treatment with allogeneic HSCT (Mehta et al. 2010).

Diamond-Blackfan anaemia (DBA) is characterized by red cell failure, the presence of congenital anomalies and cancer predisposition. The classic presentation of DBA usually includes anaemia with essentially normal neutrophil and platelet counts, in a child younger than 1 year (Vlachos and Muir 2010).

Dyskeratosis congenita (DC) is a multisystem disorder, with a disruption in telomere biology leading to very short telomeres underpinning its pathophysiology. Bone marrow failure is a key feature in DC and is the leading cause of mortality (Barbaro and Vedi 2016). DC is genetically heterogeneous with X-linked, autosomal dominant and autosomal recessive subtypes. The clinical features include cutaneous manifestations of abnormal skin pigmentation, nail dystrophy, mucosal leukoplakia and BMF, pulmonary fibrosis and predisposition to malignancy. Allogeneic HSCT remains the only curative approach for the BMF (Mehta et al. 2010).

Congenital amegakaryocytic thrombocytopenia (CAMT) is a rare autosomal recessive disorder characterized by isolated thrombocytopenia at birth due to ineffective megakaryocytopoiesis and progression to pancytopenia in later childhood. HSCT remains the only known curative treatment for CAMT (Mehta et al. 2010).

2.5.6 Inherited Diseases: Inborn Errors of Metabolism

Most of the metabolic diseases considered for HSCT are lysosomal storage diseases that rely on transfer of enzyme from donor-derived blood cells to the reticuloendothelial system and solid organs (Sureda et al. 2015b). This group of rare diseases includes mucopolysaccharidosis (MPS) as Hurler's syndrome and leukodystrophy as X-linked adrenoleukodystrophy (X-ALD) and infantile Krabbe disease. The success of SCT in metabolic diseases is determined particularly by the degree of tissue damage present by the time of transplantation and the rate of progression of the disease (Steward and Jarisch 2005). If damage to the central nervous system is present, it is irreversible and therefore a contraindication for transplant (Boelens et al. 2008).

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