

Update in Haematopoietic Stem Cell Transplantation

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The authors review the most important aspects of stem cell transplantation, starting with its objectives, general guidelines and specific issues in rare diseases, and series of complications arising from this complicated therapeutic procedure.

Introduction

In the 40 years since the first bone marrow transplant for the treatment of a patient suffering from a congenital immune deficiency, this therapeutic modality has become an option to be considered in the treatment of several haematologic, immunologic, metabolic and neoplastic disorders. This has been possible thanks to the progress in our knowledge of the major histocompatibility complex, the supportive therapy for patients with severe pancytopenia and the prevention and treatment of infections and other complications associated to transplantation [1].

Today, Haematopoietic Stem Cell Transplantation (HSCT), in its different modalities, is the treatment of choice in several malignant and non-malignant haematological diseases and one of the best options in many others [1].

By the 1980s, bone marrow transplantation had become a clear therapeutic option for many patients with haematological diseases. The progress made in our knowledge of the major histocompatibility complex, their progressive application to patients with neoplastic diseases in remission and with a better performance status, and the progress made in supportive measures (transfusions, prophylaxis and treatment of infections and other complications, growth factors), generalised the use of this therapeutic modality in patients with HLA-identical siblings or relatives. Only 25–30% of patients, however, had a donor of these characteristics and the falling birth rate in developed countries signalled that this percentage would not be improving in the future [1].

Objectives

The original objective of HSCT was to replace neoplastic, absent or malfunctioning haematopoietic cells with normal cells from the bone marrow of a compatible donor. The patients underwent an intensive treatment, called conditioning regimen, based on high doses of chemotherapy and, occasionally, radiotherapy. The goals of this conditioning regimen were:

1. To eradicate the abnormal population of cells causing the disease.

2. To immunosuppress the patient to avoid the rejection of the donor's haematopoietic stem cell (HSC).
3. To make space in the bone marrow to facilitate the engraftment of donor's HSC.

Nowadays we know that the conditioning treatment should not necessarily be intensive as a potent immunosuppression prevents graft rejection, facilitates the engraftment of the new HSC and permits the gradual replacement of the patient's haematopoiesis by that of the donor. This modality of transplantation is known as reduced intensity conditioning (RIC) HSCT [1,2,3].

Indications for HSCT

A. Allogeneic HSCT

As allogeneic HSCT involves the replacement of all body cells derived from the Haematopoietic Stem Cell, its use can be considered whenever the disease originates in one of these cells and can be cured if they are replaced by healthy ones.

This is basically the case in:

- a. Haematological cancers: acute myeloblastic and lymphoblastic leukaemia, chronic myeloid leukaemia and other myeloproliferative syndromes. Hodgkin's disease and non-Hodgkin lymphomas, chronic lymphocytic leukaemia and other chronic lymphoproliferative diseases, multiple myeloma and myelodysplastic syndromes.
- b. Bone marrow failure syndromes: severe aplastic anaemia and paroxysmal nocturnal haemoglobinuria.
- c. Immune deficiencies: different types.
- d. Congenital haemopathies: thalassaemia, Wiskott-Aldrich syndrome and Fanconi's anaemia, among others.
- e. Other congenital diseases affecting cells derived from the HSC: Gaucher's disease, osteopetrosis, mucopolysaccharidosis, mucopolipidosis and different lysosomal disorders [1].

B. Autologous HSCT

It is the treatment of choice when medullar toxicity is the main constraint for an intensive therapy. As autologous

HSCT always involves the risk of administering residual neoplastic cells present in the bone marrow or peripheral blood inoculum, their principal indications are diseases not affecting the bone marrow (Hodgkin's disease, non-Hodgkin lymphomas and solid tumours). However, autologous HSCT is also used to intensify treatment in patients with acute myeloblastic or lymphoblastic leukaemia, multiple myeloma, chronic lymphocytic leukaemia or other chronic lymphoproliferative diseases when there is no compatible donor or in which allogeneic HSCT involves unacceptable toxicity.

Autologous HSCT is also used for the treatment of primary amyloidosis, POEMS syndrome and autoimmune diseases refractory to conventional therapies (multiple sclerosis, systemic sclerosis, systemic erythematous lupus and rheumatoid arthritis, among others).

To establish the indication of allogeneic or autologous HSCT, besides the underlying disease and the availability or not of a histocompatible donor, other fundamental aspects have to be assessed, including the patient's clinical status and the stage of the disease [1,4].

HSCT in Ph-Negative Acute Lymphoblastic Leukemia (ALL)

The role of allogeneic HSCT in young patients with Ph-ALL is controversial. An older retrospective comparison in patients age 15–45 from the International Bone Marrow Transplant Registry did not show any difference in leukemia-free survival between chemotherapy alone versus matched sibling HSCT in complete remission (CR)-1 [5]; the lower relapse rate in transplanted patients was offset by a higher treatment-related mortality. The LALA-94 study also did not find any difference in survival between standard-risk patients assigned to HSCT compared to chemotherapy alone [6]. In contrast, more recently the MRC/ECOG study, using a similar design but larger numbers, found a 63% 5-year overall survival (OS) with HSCT versus 52% with chemotherapy ($p = 0.02$), in standard-risk adults up to age 35 [7]. The 10-year cumulative relapse rate was 24% in transplanted patients versus 49% in the chemotherapy-treated group.

For those considered at high risk, unrelated HSCT is another option, and recent data suggest the OS with closely matched unrelated donors is comparable to that of matched sibling transplants [8,9].

For adult patients who relapse, the prognosis is dismal, with failure rates approaching 100% using conventional therapy. HSCT is the only approach to date which has been capable of salvaging such patients. However, studies have shown that salvage rates are low; MRC/ECOG data showed a 5-year OS of 23% in patients undergoing matched sibling HSCT following relapse, and only 16% with unrelated HSCT [10]. Therefore, the identification of patients at higher risk of relapse in first CR is of major importance (9).

HSCT in Ph-Positive ALL

HSCT has been widely used for young patients in CR-1, and most studies demonstrate a survival advantage compared to chemotherapy alone [11,12,13]. A number of other questions remain, particularly the role of allogeneic HSCT in the era of TKIs. It appears that the use of tyrosine kinase inhibitor (TKIs), by increasing CR rates and duration, permits a higher proportion of patients to proceed to HSCT [14]. However, HSCT is still hampered by transplant-related mortality, in the range of 20–30% [15,9].

HSCT in Acute Myeloid Leukemia (AML)

While achievement of CR is critical for long-term survival [16], the crucial decision in younger AML patients is selection of the post-remission therapy that provides the best chance of cure. The choice between consolidation chemotherapy and allogeneic hematopoietic stem cell transplant should be based on the risk of relapse, with autologous HSCT as an alternative to consolidation chemotherapy [17].

A recent systematic review and meta-analysis of prospective biologic assignment studies in 3638 patients younger than 60 with AML in CR1 by cytogenetic risk demonstrated a relapse and survival advantage for alloHSCT over other approaches (chemotherapy or autologous HSCT) in patients with intermediate-risk and unfavorable-risk, but not favorable-risk, karyotypes [18]. The estimated 5-year survival rates were 52% versus 45% and 31% versus 20% for patients with intermediate-risk and unfavorable-risk karyotypes, respectively. This study confirmed the findings of an earlier meta-analysis [19,17].

In patients without a matched sibling donor (MSD) who require transplant in CR1, HLA-matched unrelated donor (MUD) HSCT is another option. Introduction of high-resolution allele-level HLA-typing allows better selection of unrelated donors (URD), and recent Center for International Blood and Marrow Transplant Research (CIBMTR) data showed that 47% of AML patients transplanted in CR1 in 2008 received URD allografts [20]. Recent studies have shown similar outcomes for MRD and MUD transplants in high-risk AML patients in first remission [17,21,22].

Another retrospective study of over 1000 patients 50–70 years old in CR1 demonstrated the benefit of alloHSCT (61% Reduced-intensity conditioning (RIC), 39% myeloablative) compared to chemotherapy in terms of both relapse free survival (RFS) and overall survival (OS) [23]. Data supporting the role of alloHSCT in AML patients older than 70 years are limited, as few are referred for transplant evaluation due to concern about transplant-related toxicity. Thus, patients should not be excluded from consideration of alloHSCT solely based on age, and alloHSCT may be an attractive option for older AML patients with few comorbidities and good performance status (PS) [17].

Table I. Advantages and disadvantages HSC sources [1]

HAEMATOPOIETIC STEM CELLS FROM PERIPHERAL BLOOD	
Advantages	<ol style="list-style-type: none"> 1. Less aggressive method for the donor 2. Obtains more HSC 3. Faster haematopoietic recovery 4. Faster immunological recovery
Disadvantages	<ol style="list-style-type: none"> 1. Need to administer G-CSF to the donor 2. It could require a central line 3. Post-donation thrombocytopenia 4. High incidence of chronic GVHD
HAEMATOPOIETIC STEM CELLS FROM UMBILICAL CORD BLOOD	
Advantages	<ol style="list-style-type: none"> 1. Easy to obtain and harmless for the donor 2. Faster availability 3. Prior knowledge of cellularity 4. Progenitors with greater clonogenic activity 5. Less immunological reactivity (less GVHD)
Disadvantages	<ol style="list-style-type: none"> 1. Limited number of HSC 2. Impossibility of a second donation 3. Possible transmission of genetic diseases

HSCT in non-Hodgkin lymphoma

Today, most patients with Hodgkin lymphoma (HL) achieve complete remission (CR) with first-line polychemotherapy with or without additional radiotherapy. More than 90% of patients with early favorable disease and over 80% of patients with early unfavorable or advanced disease obtain long-term tumor control with up-to-date regimens [24,25,26]. Thus 15% to 20% of patients cannot be cured, owing to either progressive disease during first-line therapy or later relapse after initial CR. Autologous stem cell transplantation has been evaluated as consolidation treatment after first-line therapy in high-risk patients and as salvage treatment in patients with progressive or relapsed HL [27].

HSCT in non-Hodgkin lymphoma

High-dose chemotherapy with autologous stem cell transplantation has an established role for treatment of patients with non-Hodgkin lymphoma. This treatment is effective not only as a salvage treatment but also as a consolidative treatment [28,29,30,31]. However, a significant portion of patients underwent a relapse or a progression after autologous transplantation. Prognosis of these patients was generally poor and treatment option is limited [32]. To overcome this limitation, allogeneic stem cell transplantation has been performed. Allogeneic transplantation can possibly offer graft-versus-lymphoma effect [33]. Some patients could achieve complete remission after allogeneic transplantation and survive for a long time despite prior progression after autologous transplantation [34,35,36]. However, the role of allogeneic transplantation in these patients has not been clarified yet. Moreover, transplant related mortality (TRM) of allogeneic transplantation was substantial [34,36]. Therefore, development of a specific marker which can predict TRM can help improve treatment results of allogeneic transplantation in these patients. However, no useful clinical marker has yet been identified [28].

HSCT in multiple myeloma (MM)

The administration of lethal doses of chemoradiation fol-

lowed by marrow grafting was first applied to cancer therapy in the 1950s. The approach offered a means by which to intensify chemotherapy and thus increase tumoricidal activity, although at the cost of significant treatment-associated toxicities such as prolonged myelosuppression. After the seminal observation made by McElwain and colleagues [37], several groups pioneered high-dose therapy and autologous stem cell transplantation (ASCT) in patients with relapsed MM, demonstrating the activity of high-dose therapy in patients who had become resistant to conventional therapy. Although early studies of ASCT in MM often utilized preparative regimens consisting of chemotherapy and total body irradiation, strategies using chemotherapy alone proved to be as effective and were associated with less toxicity [38,39].

Bone marrow transplantation in patients with Diamond-Blackfan anemia

Allo-HSCT is the only available curative treatment for Diamond-Blackfan anemia (DBA). The first "successful" allo-HSCT treatment of DBA was reported in 1976 [40]. The patient died, but hematopoietic engraftment from donor bone marrow confirmed DBA as a transplantable disease. Since the initial case, more than 70 transplants, the majority of which involved from HLA-matched sibling donors, have been reported in the literature [41,42]. The outcomes of patients who undergo alternative donor stem cell transplantation are significantly inferior to those of HLA-matched sibling donors [42,43].

In one case the transplant was done primarily for DBA and it raises the interesting possibility of allo-HSCT's being beneficial in the treatment of associated Duchenne muscular dystrophy (DMD), which is an otherwise incurable disease with 100% mortality. However, further clinical follow-up with serial muscle biopsies and molecular studies is needed to document the extent and duration of mixed chimerism in skeletal muscle in this patient. The purpose of this case report is to describe this interesting observation of a possible benefit in DMD and not to suggest HSCT as a modality of treatment until further studies show an unequivocal benefit, given the inherent risks associated with HSCT [43].

HSCT in Castleman's disease (CD)

Castleman's disease (CD) encompasses a group of rare lymphoproliferative disorders. CD was originally described as a solitary lesion without systemic manifestations [44]. However, a subset of patients with systemic symptoms, polylymphadenopathy and multi-organ involvement were later recognized as multicentric CD (MCD). Our understanding of CD has greatly expanded since the identification of its association with human immunodeficiency virus and human herpes virus 8 infections [45]. MCD was found to be associated with the development of malignancies, especially Kaposi's sarcoma and lymphoma. A wide variety of therapeutic approaches have been attempted.

However, there is no definitive gold standard treatment for MCD [46] (MCD) [47].

Source of the HSC

For many years, HSCT were performed with HSC obtained by multiple aspirations of medullar blood from the posterior, and occasionally anterior, iliac crests [48]. Years later, it was seen that, in certain conditions, large quantities of HSC could temporarily move from the bone marrow to peripheral blood, from which they can be harvested through cytoapheresis methods. This mobilisation occurs both during recovery from the marrow aplasia that follows intensive chemotherapy and after the administration of haematopoietic growth factors, the most frequently used of which is the granulocyte colony stimulating factor (G-CSF) [49].

The third source of haematopoietic progenitors is umbilical cord blood (UCB). Immediately after childbirth, after cutting the umbilical cord, around 100 ml of blood very rich in HSC can be harvested from the umbilical cord and the placenta. With the widespread use of HSC from peripheral and cord blood, the term bone marrow transplantation ceased to make sense, and the current usage is HSCT [1].

Relapse of the underlying host leukemia is the most frequent cause of treatment failure after allogeneic stem cell transplantation (SCT). However, secondary neoplastic complications, including post-transplant lymphoproliferative disorders, therapy-related *de novo* malignancies and, less commonly, donor cell leukemia (DCL) [50], can also occur in SCT patients. Cord blood (CB) is now recognized as a feasible alternative source for SCT. More than 10,000 CB transplants (CBT) have been performed worldwide, and only ten cases of DCL following CBT have been reported [51].

HSCT from unrelated donors

Different publications have confirmed that the outcomes of HSCT from unrelated donors are comparable to those obtained with HSCT from an HLA-identical sibling with regards to survival, transplant-related mortality and disease free survival [28–30]. This is thanks to the progress made in managing the complications presented by these patients and to the widespread search for donors with 10 out of 10 identities (loci A, B, C, DRB1 and DQB1) analysed by high resolution techniques. The only negative effect of this donor search policy is the logical reduction in the likelihood of finding one with such a degree of compatibility. The likelihood of finding a compatible donor with 8/8 or 10/10 identities in the first six months of the search is 40–50%, increasing by a further 10–15% if donors with a single incompatibility are accepted [52].

Given the lower alloreactivity of UCB progenitors, units can be accepted with some degree of incompatibility. Therefore, in spite of the progress made in HLA typing, the degree of unit-recipient identity continues to be evaluated only with loci A and B through low resolution and locus DRB1 through high resolution techniques. This is because

the studies which have analysed whether more precise unit typing would improve the outcome have been unable to show a benefit [53]. All these characteristics of UCB mean that it is possible to find a unit with an acceptable degree of compatibility (6/6, 5/6 or 4/6) for most patients. The small volume of the UCB units, however, means that in spite of their high concentration in HSC, the total quantity is insufficient for recipients with a high body volume. The location of valid units is therefore relatively simple in children and low-weight adolescents and more difficult in adults.

In view of the good outcomes obtained in children and adults [54,55] with umbilical cord blood HSCT, it is now mandatory to start all searches for unrelated donors at the same time among voluntary donor registries and cord blood banks, choosing one or the other, indistinctly, according to the degree of compatibility, cellularity and urgency of the procedure [1].

Complications of HSCT

The complications of HSCT are the consequence of the repeated aggressions suffered by the patient's organs and tissues due to the direct toxicity of the conditioning treatment, the massive release of cytokines, repeated infections, immune phenomena occurring during allogeneic HSCT and the toxicity of the immunosuppressors used to prevent and treat GVHD.

1. Early toxicity of the conditioning regimen [1]

Immediate side effects: The tissues most affected by conditioning are those with cells with a smaller duplication time (bone marrow, intestinal mucosa, hair follicles). Patients therefore present nausea, vomiting and diarrhoea of variable intensity. Oral and oesophageal mucositis is also common, often overinfected by viruses from the herpes group and fungi. Some patients suffer from parotiditis and pancreatitis. During the 12–21 days required for haematopoietic reconstitution, there is extreme pancytopenia with a subsequent risk of haemorrhage and infections. The haemorrhages, feared some years ago are now rare thanks to platelet support but, despite prophylactic measures, bacterial and fungal infections are still common. Alopecia, although it is reversible, can give rise to psychological problems [2].

Haemorrhagic cystitis is caused by one of the metabolites of cyclophosphamide, acrolein; it is highly toxic for the vesical mucosa and can cause from moderate erosions to large lesions with incoercible haemorrhages. Besides the above, immediately after transplantation (first 30–60 days) a series of complications with imprecise diagnostic criteria and overlapping clinical features can be observed as a result of the injury of the vascular endothelium. Depending on its location, this endothelial damage leads to the dysfunction of one or several organs. The best defined clinical symptoms are: a) capillary leak syndrome; b) engraftment syndrome; c) diffuse alveolar haemorrhage; d) thrombotic microangiopathy; e) idiopathic pneumonia syndrome; and, f) sinusoidal obstruction syndrome (also known as

hepatic veno-occlusive disease) [2].

Bronchiolitis obliterans (BO) after allogeneic stem cell transplantation (allo-SCT) is a late-onset, lifethreatening respiratory complication that significantly reduces a patient's quality of life [56].

Both infectious and non-infectious pulmonary complications occur in 40–60% of allo-SCT recipients, which significantly affect prognosis as well as cause 10–40% of transplant-related death and decrease in the quality of life (QOL) [57]. Late-onset non-infectious pulmonary complications (LONIPC) occurring beyond 90 days after allo-SCT include bronchiolitis obliterans (BO), bronchiolitis obliterans organizing pneumonia (BOOP) and interstitial pneumonia [58,59]. BO after allo-SCT was first described by Roca *et al.* [60] in a patient with chronic graft-versus-host disease (GVHD). The incidence of BO varies widely from 1.7 to 26% in different reports, in part, due to lack of a standard definition [56,61,62].

The International Bone Marrow Transplantation Registry (IBMTR) reported the incidence and risk factors for BO in 6275 adults leukaemia patients who underwent BMT or PBSCT from HLA-identical sibling donors [62]. In the report, the 2-year cumulative incidence of BO was 1.7% and the median time to onset of BO was 431 days.

In summary, we described the incidence and risk factors for BO in allo-SCT recipients. The incidence of BO was significantly higher in patients who underwent R-PBSCT than in those who underwent transplantation from other stem cell sources. R-PBSCT recipients who have already developed chronic GVHD have a high risk for developing BO and need extensive care and repeated PFTs [56].

Thrombotic events are recognized as the common and potentially fatal complications in HSCT recipients, such as hepatic veno-occlusive disease (VOD), transplantation-related thrombotic microangiopathy (TATMA), catheter-associated thrombosis, and deep vein thrombosis (DVT). It is generally assumed that endothelium damage and coagulation disturbance induced by pretransplant conditioning regimens or some other factors may contribute to the development of thrombotic events [63,64,65]. Many hemostatic abnormalities have been reported in various thrombotic events following allogeneic HSCT, including fibrinolytic and coagulation parameters [66]. In particular, elevated levels of plasma plasminogen activator inhibitor (PAI-1) antigen have been observed in patients with VOD or TA-TMA [67,68] and serve as one crucial noninvasive tool for the diagnosis of VOD [11]. The changes of other hemostatic parameters, including plasma protein C (PC), tissue-plasminogen activator (t-PA), antithrombin III (ATIII), and D-dimer (D-Di), have also been described in TRCs [68, 69,70].

2. Infectious complications

Infections are one of the most important complications of HSCT, although their associated morbidity and mortality has fallen considerably in recent years thanks to better

knowledge of the risk factors, post-HSCT immune recovery and the development of more effective antimicrobial drugs. HSCT is followed by an immune deficiency of variable intensity affecting both cellular and humoral immunity. Besides immunosuppression, there are other factors increasing the risk of infection, particularly: prolonged and profound neutropenia, alteration of anatomical barriers (mucositis, central lines) and the existence of latent infections, especially herpes viruses and *Toxoplasma gondii* [1,71].

Hematopoietic stemcell transplantation (HSCT) recipients frequently develop opportunistic infections, including paranasal sinusitis. Paranasal sinusitis in posttransplant recipients can be complicated by life-threatening infections. Patients receiving allogeneic HSCT seemed to develop paranasal sinusitis more frequently than did those receiving autologous HSCT. And use of total body irradiation (TBI) and presence of aGVHD and cGVHD did not correlate with development of post-HSCT paranasal sinusitis [72].

Increasing use of more aggressive treatment procedures in patients with hematological diseases leads to an increase in the frequency of invasive fungal infections, which remains to be the major cause of transplant related mortality in hematopoietic stem cell recipients [73,74]. Presence of active invasive fungal infection (IFI) does not seem to be an absolute contraindication for HSCT, particularly in high risk patients in whom delaying the treatment could be fatal [75]. Success rates might be lower than expected in this group of patients even with the most recently developed broad spectrum antifungal agents, which leads transplant physicians to search for adjunct alternative treatment methods [76]. Since duration of neutropenia has a major impact on transplantation, boosting the host defense system by granulocyte transfusions (GTX) might improve the outcome of neutropenia-associated infections. Data that confirm the value of GTX are limited, and results of the studies are heterogeneous and inconclusive [77,78,79,80].

Patients with multiple myeloma have many factors contributing to immunosuppression, including defects in cell-mediated immunity, neutropenia and hypogammaglobulinaemia. As a consequence, severe or recurrent viral, bacterial and fungal infections are frequently observed. Attempts to decrease infectious complications with pooled intravenous human immunoglobulin (IVIG) have been associated with a decreased risk of septicaemia and pneumonia in patients with plateau-phase multiple myeloma [81]. Higher-intensity treatment regimens, such as myeloablative conditioning with autologous haemopoietic stem cell transplantation (ASCT), compound the underlying risk for infection; therefore, peri-transplant administration of IVIG to patients with multiple myeloma is part of standard supportive care in many haematology units and has been included in prospective trials [82,83] in an attempt to decrease infectious complications. However, there are currently limited data to support a clinical benefit for the routine administration of IVIG in the context of ASCT in patients with multiple myeloma [84].

3. Complications of immunological origins

Graft rejection – engraft failure

Graft rejection occurs because of the recipient's residual immunity, which recognises the donor HSC as foreign. Its incidence is low (1-2%) and it is found nearly exclusively in HSCT performed to treat severe aplastic anaemia, HSCT from unrelated donors or UCB or those receiving HSC depleted of T-lymphocytes [85].

Graft versus host disease (GVHD)

This is the most feared complication of allogeneic HSCT. The cytokines (interleukins, interferons, tumour necrosis factor, among others) massively released as a result of the direct toxicity of the conditioning treatment on the tissues and the clonal proliferation and differentiation of the donor's T-lymphocytes when they recognise the recipient's histocompatibility antigens as foreign, are responsible for the aggression of the different target organs [86].

There are two forms of GVHD, acute and chronic. Acute GVHD occurs in 40-60% of the patients and is the cause of death in over 20%. Its basic target organs are the skin, the liver and the intestine. Chronic GVHD is presented by 20-50% of long-term survivors. Its clinical symptoms and anatomical/ pathological alterations are similar to those of different autoimmune diseases such as scleroderma, systemic erythematous lupus, primary biliary cirrhosis, diarrhoea, myasthenia or Sjogren's syndrome. The most commonly affected organs are the skin, mouth, liver, eyes, oesophagus and respiratory tract. Up to 50% of patients with extensive chronic GVHD die from this complication [86,87].

Several studies investigated the recovery of adaptive immunity after allogeneic stem cell transplantation focussing on the reconstitution of different lymphocyte subsets. Such data are available for patients who underwent either allogeneic bone marrow transplantation (BMT) or allogeneic PBSCT resulting in a detailed knowledge of several factors that have an impact on lymphocyte repopulation following transplantation. Some of the most important factors beside the stem cell source are the conditioning regimen, the immunosuppression after transplantation, the reactivation of cytomegalovirus (CMV) and the occurrence of graft-versus-host disease (GvHD) [88].

Due to a longer survival after allogeneic stem cell transplantation (allo SCT) as well as by enlarged treatment options, e.g., reduced-intensity conditioning regimens, treatment of evolving relapses after allo SCT is more and more challenging. Thereby, extramedullary (EM) relapses play an important role as they occur more frequently after allo SCT compared with non-transplant leukemia treatments. They can be accompanied by a bone marrow relapse but also occur separately [89]. The median time to EM relapse is usually longer compared with bone marrow relapse [89]. Allotransplanted patients suffering from graft-versus-host disease (GvHD) show a

Table II. Complications of HSCT [1]

EARLY TOXICITY OF CONDITIONING TREATMENT
Gastrointestinal disorders (nausea, vomiting and diarrhoea)
Bone marrow aplasia
Alopecia
Haemorrhagic cystitis
EARLY COMPLICATIONS OF MULTIFACTORIAL ORIGIN
Sinusoidal obstruction syndrome: veno-occlusive disease
Capillary leak syndrome
Engraftment syndrome
Diffuse alveolar haemorrhage
Thrombotic microangiopathy
Idiopathic pneumonia syndrome
INFECTIONS AND HAEMORRHAGES
COMPLICATIONS OF AN IMMUNOLOGICAL ORIGIN
Graft rejection. Engraftment failure
Graft versus host disease
Autoimmune disorders
LATE COMPLICATIONS
Endocrine deficiencies
Sterility
Cataracts
Pulmonary, dental, bone, hepatic alterations
Haemosiderosis
Second malignancies

significant reduction of bone marrow relapses compared with patients without GvHD, which is attributed to the coexistent graft-versus-leukemia (GvL) effect [90]. However, the rate of EM relapses seems to be independent on the rate of GVHD [91,92]. A possible explanation might be the concept of the so-called “sanctuary” sites for chemotherapy. These sites also might represent immunologically privileged organs, where there is only a slight GvL reaction if any at all [93,94]. This hypothesis is supported by the fact that there is apparently no influence on the EM relapse after systemic infusion of donor lymphocytes (DL) and subsequent occurrence of GvHD [95,96,97].

4. Late complications of HSCT [98]

The most common are endocrine disorders and cataracts. The former include: subclinical or symptomatic hypothyroidism requiring treatment (7–15%); growth percentiles lower than those observed in the general population (up to 80% of paediatric cases), worse in children receiving radiotherapy before they are 10 years old; gonadal dysfunction and sterility (variable intensity according to the patient's age and conditioning treatment received). The likelihood of a patient receiving total body irradiation developing cataracts is as high as 80% ten years after the HSCT. Other less common late complications are shown in Table II.

Voluntary donor registries

Because of the polymorphism of the HLA system, it was practically impossible to find a histocompatible unrelated voluntary donor. Several theoretical studies showed that, given the greater frequency of certain haplotypes in the population, if information could be obtained about the HLA typing of thousands of donors, a compatible

one could be found for some patients. The likelihood of finding such a donor followed a sigmoid curve with little variability at its extremes and rapid growth in the centre, showing that the likelihood of finding a compatible donor increased considerably from a certain number of registered donors on [99]. In order to have enough donors to make this hypothesis come true, the first donor registry was created in 1978 by the mother of Anthony Nolan, an English patient with Wiskott-Aldrich syndrome who required HSCT [100].

In the following years, all developed countries created donors' registries and there are now 58 registries in 43 different countries [101]. The function of all these registries is double. In the first place, they aim to promote bone marrow (and, in the last ten years, peripheral blood and umbilical cord blood) donation in their area of influence and administer a database with the basic information about registered donors. Secondly, they are designed to search for compatible unrelated donors among all the registries worldwide for patients in their own country who need them and among all the country's donors for foreign patients [1].

In 1991, the International Josep Carreras Foundation created a registry in Spain called REDMO (Registro de Donantes de M6dula Osea). Soon (1992) it achieved the internationally acknowledged by the WMDA (World Marrow Donor Association) and in 1994, an agreement with the Ministry of Health to become the official Spanish registry, responsible for the aforementioned registration and search functions [102]. In Europe, the creation by France Greffe de Moelle of a data sharing computer network (EMDIS) made a major contribution to the development and success of such registries. All the registries in France, Italy, Germany, Spain, Belgium, Holland, Czech Republic, Sweden, Switzerland and Wales, recently joined by those in the U.S. and Australia, are now interconnected by this registry network [1,103].

Update of transplantation technique

In spite of the enormous advances in medical technology, the procedure for collecting bone marrow cells (BMCs) has not changed in the past 40 years [104]. Therefore, healthy donors have been exposed to anesthetic procedures, blood loss, and multiple needle punctures, resulting in damage to the pelvis [105]. The novel method is called the "perfusion method" (PM), while the conventional method is called the "aspiration method" (AM). In the PM, there was minimal contamination of T cells and red blood cells (RBCs) with the peripheral blood (PB) in monkeys. In addition, the PM allowed us to enrich the hemopoietic stem cells (HSCs) [105,106].

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