

A general practitioner's guide to hematopoietic stem-cell transplantation

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ABSTRACT

Hematopoietic stem-cell transplantation (HSCT) is a medical procedure that consists of infusing stem cells after a short course of chemotherapy or radiotherapy, or both. It can be used in the treatment of various cancers, as well as some benign conditions. In the present review, we discuss the various types of HSCT and their main indications. The principles of the transplant procedure itself and the basics of recipient selection are reviewed. Special attention is given to both the immediate and the long-term complications of HSCT and their management strategies. Hematopoietic stem-cell transplantation is a potentially life-saving procedure and often the only curative option for a variety of diseases; however, it is not without significant toxicities.

Key Words Allogeneic transplantation, autologous transplantation, hematologic malignancies, complications of transplantation, graft-versus-host disease

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INTRODUCTION

Hematopoietic stem-cell transplantation (HSCT) was first performed in 1957 by E. Donnell Thomas as a new form of cancer treatment¹. Although initial attempts were largely unsuccessful, the procedure has dramatically evolved through the decades since². Today, more than 50,000 HSCT procedures are performed annually worldwide³ for a variety of malignant and benign diseases. In this article, we explore the various types of HSCT, we review the indications for HSCT in adults, and we discuss common complications and their management.

DISCUSSION

What Is the Rationale Behind HSCT?

In a HSCT procedure, a recipient's unhealthy native bone marrow cells and immune system are replaced with infused healthy stem cells and immune cells (the graft) after administration of a short course of chemotherapy or radiotherapy, or both. The procedure can eradicate residual cancer through exploitation of the graft-versus-tumour effect. A HSCT procedure cannot occur without a donor and a suitable, fit recipient. The primary goal of most transplants is to cure an underlying malignancy or hematologic disorder.

What Types of HSCT Exist?

In general, a HSCT can be classified by the source of the graft and by the relationship of the donor and recipient.

Stem cells can be obtained from peripheral blood, bone marrow, or umbilical cord units. Hematopoietic stem-cell transplantation can be either autologous (meaning that the stem cells are collected from the recipient) or allogeneic (meaning that the cells come from another individual or one or more umbilical cord blood units).

Before the introduction of granulocyte colony-stimulating factor, stem cells were harvested directly from donor bone marrow in the operating room⁴. At present, peripheral blood is the most commonly used source of stem cells for both autologous and allogeneic grafts. Apheresis is used to collect mobilized stem cells from the peripheral blood after administration of granulocyte colony-stimulating factor alone or in combination with drugs that promote the proliferation and migration of such cells out of the marrow compartment⁵. Compared with a stem-cell graft obtained from bone marrow, a graft using stem cells from peripheral blood offers the advantages of faster recovery of white blood cells and the immune system in the recipient and lower rates of graft failure. However, those benefits are counterbalanced by a higher

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incidence of graft-versus-host disease (GVHD), and thus some centres will preferentially select a bone marrow graft over a peripheral blood graft^{6,7}. Allogeneic grafts require that a healthy related or unrelated donor with acceptable human leucocyte antigen compatibility be identified. For recipients lacking such a donor, banked umbilical cord blood units or a partially matched family member (a “haploidentical” donor) can be used^{8,9}.

In autologous HSCT, stem cells are harvested from the recipient and cryopreserved to be later re-infused into the same individual after high-dose chemotherapy with or without radiotherapy. This form of HSCT allows the recipient to recover from the bone marrow aplasia that inevitably follows high-dose therapy and should be seen as a form of rescue therapy to mitigate toxicity. The antitumour effect is entirely derived from the chemotherapy and radiotherapy (if used) as opposed to the HSCT itself.

In allogeneic HSCT, stem cells are collected from a different person or from umbilical cord blood units. This form of HSCT can function in two ways. In addition to allowing for recovery from high-dose therapy as already described, the immune cells in the graft might also recognize malignant cells as foreign and mount a graft-versus-tumour response, an effect not seen in autologous HSCT¹⁰.

Who Can Benefit from HSCT?

Most HSCTs are performed for hematologic malignancies. Multiple myeloma and lymphoma are the leading indications for autologous HSCT. Acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndromes, and myeloproliferative neoplasms are the leading indications for allogeneic HSCT¹¹. A HSCT procedure might also be used to treat select solid tumours such as germ cell tumours¹², neuroblastoma¹³, Ewing sarcoma¹⁴, and medulloblastoma¹⁵.

The choice of autologous or allogeneic transplantation for a given disease is based on the modality that has shown better efficacy in clinical studies. Allogeneic transplantation is advantageous in diseases in which the graft-versus-tumour effect has been demonstrated.

Hematopoietic stem-cell transplantation can also be used to treat a variety of nonmalignant conditions such as severe aplastic anemia, inherited bone marrow failure syndromes, sickle cell disease, transfusion-dependent thalassemia, inherited immune deficiency syndromes, and certain metabolic disorders^{16–21}. Experimentally, HSCT has been used in severe refractory autoimmune diseases^{22,23}.

Guidelines setting out the indications and timing for HSCT referral are available online²⁴.

Not all recipients with a potential indication for HSCT are medically fit to undergo the procedure. The chemotherapy and radiotherapy used before the HSCT (called the “conditioning regimen”) can have major toxicities. Generally speaking, patients must have a chemotherapy-sensitive cancer and acceptable cardiac, respiratory, renal, and hepatic function. They must be free of uncontrolled active infections and be psychiatrically fit to comply with a period of intense medical therapy and follow-up. The upper age limit for HSCT eligibility is controversial; however, it is widely accepted that the biologic age of the recipient is more important than the chronologic age. The risk of complications after HSCT is commonly assessed using the

Hematopoietic Cell Transplantation–Specific Comorbidity Index²⁵. A comprehensive geriatric assessment can also be of value in older individuals²⁶.

How Is HSCT Performed?

Once a recipient with a suitable indication for HSCT is deemed medically fit and has an available stem-cell donor, the procedure is ready to go forward. The recipient is usually admitted to hospital for a period of 3–5 weeks, although some centres are now performing both autologous and allogeneic HSCT in the outpatient setting^{27,28}.

The first step involves administration of the conditioning regimen, which consists of either or both of chemotherapy and radiotherapy. The goal of the conditioning regimen is to ablate the recipient’s own bone marrow and to induce sufficient immunosuppression to allow for the infused stem cells to engraft and to provide nonspecific immune therapy for ongoing disease control. Conditioning regimens can be myeloablative (full-dose) or non-myeloablative (reduced intensity), depending on recipient age and fitness.

Once the conditioning regimen is complete, the bone marrow or peripheral blood stem-cell graft is infused intravenously through a central catheter, and prophylaxis against a variety of infectious and noninfectious complications is instituted. Depending on the type of transplantation procedure, that prophylaxis might address bacterial infections, candidiasis, *Pneumocystis jirovecii*, herpes viruses, hepatic sinusoidal obstruction syndrome, and GVHD (the subsection “What Are the Complications of HSCT?” contains a more detailed discussion of potential complications)^{29–31}.

Blood counts are monitored daily for engraftment, defined as the first of 3 consecutive days with a neutrophil count greater than $0.5 \times 10^9/L$. Time to engraftment is variable (with a usual range of 10–21 days) and depends on the source of the stem-cell graft, the cell dose administered, and whether granulocyte colony-stimulating factor has been prescribed. After engraftment, assuming no complications and good clinical status, the recipient is discharged and followed as an outpatient.

What Are the Complications of HSCT?

Complications of HSCT can be divided into 3 categories based on timing: those occurring during the pre-engraftment period (from the start of the conditioning regimen to neutrophil recovery), the early post-engraftment period (from neutrophil recovery to post-transplantation day 100), and the late post-engraftment period (day 100 and beyond).

Complications in the pre-engraftment period are typically a result of the toxicities of the conditioning regimen. The recipient can experience pancytopenia, gastrointestinal toxicities, infections, and organ dysfunction. The infections commonly seen during this period are often related to neutropenia and consist of gram-positive and gram-negative bacteria, herpes simplex virus, candidiasis, and invasive aspergillosis³¹. Blood products, anti-infectives, and general supportive care (including hydration and parenteral or enteral nutrition) are required to varying degrees. Organ failure requiring admission to the intensive care unit and even death can occur. The risks vary depending on the type of transplantation procedure,

the conditioning regimen, the underlying disease, and the recipient's comorbidities. A syndrome of endothelial injury affecting the liver ("hepatic sinusoidal obstruction syndrome," previously called veno-occlusive disease) can be seen, usually after myeloablative allogeneic HSCT. It is usually treated with defibrotide, a drug with a complex mechanism of action thought to aid in endothelial protection³². Hepatic sinusoidal obstruction syndrome is part of a group of HSCT complications called "early complications of endothelial origin," which also include capillary leak syndrome, engraftment syndrome, diffuse alveolar hemorrhage, and HSCT-associated thrombotic microangiopathy. Those complications usually occur between days 0 and 100 and are thought to result from injury at the capillary level³³.

In the early post-engraftment period, acute GVHD can appear. Graft-versus-host disease is exclusively seen in allogeneic transplantation. It results when transplanted immune cells recognize the recipient as foreign and mount an immune reaction, causing disease. Acute GVHD usually affects the skin, gastrointestinal system, and liver. The most common manifestations are rash, watery diarrhea, persistent nausea or vomiting, anorexia, cholestatic jaundice, and liver function test abnormalities. Systemic corticosteroids are the mainstay of therapy. There is no well-established treatment for steroid-refractory cases, although a variety of agents have been used. Severe acute GVHD is associated with poorer survival³⁴.

During the early post-engraftment period, patients remain at risk of infectious complications. Despite recovery from neutropenia, cellular and humoral immunity remain impaired, and there is a risk of opportunistic infections such as *P. jirovecii* and cytomegalovirus and increased susceptibility to common respiratory viruses such as influenza, respiratory syncytial virus, and adenovirus. As a general rule, the presence of GVHD and its treatment entail a greater degree of immunosuppression. Thus, recipients with active GVHD are at higher risk of invasive fungal infections and viral reactivation.

In the later post-engraftment period, chronic GVHD can occur. Its manifestations are protean, and it can affect one or many organs. Skin is most commonly affected, and recipients might have poikiloderma, lichen planus-like lesions, and changes similar to those seen with systemic sclerosis. Symptoms similar to genital lichen planus are common and not usually spontaneously reported by recipients. Deeper involvement can be seen in the form of myositis and fasciitis, which can lead to fibrosis and decreased mobility. The salivary and lacrimal glands can be affected, resulting in dry mucous membranes (sicca syndrome). Lung involvement can result in chronic obstructive or restrictive lung diseases (or both). As with acute GVHD, the gastrointestinal tract and liver can be affected³³. Patients with active chronic GVHD experience more frequent opportunistic infections and reduced quality of life³⁵. Multimodality treatment is often used, but management is usually based on immunosuppression. Topical and systemic corticosteroids are the first-line choices and are often combined with calcineurin inhibitors such as tacrolimus. Extracorporeal photopheresis, ibrutinib, and ruxolitinib act as

immunomodulators and are often effective in treating recipients with chronic GVHD for whom corticosteroids fail or cannot be tapered^{36–38}.

After HSCT, patients require re-administration of their primary immunizations, starting 6–12 months after the HSCT. Guidelines on the topic are available^{31,39}.

Throughout the entirety of the post-transplantation period, relapse of the underlying disease remains a major cause of mortality¹¹. Even recipients who enjoy a relatively uneventful clinical course after their HSCT are at increased long-term risk for cardiovascular disease⁴⁰; metabolic disorders including diabetes, dyslipidemia, hypothyroidism and osteoporosis^{41–43}; secondary malignancies⁴⁴; gonadal and reproductive dysfunction⁴⁵; and neuropsychiatric disorders⁴⁶ (Table 1). Increased vigilance and screening are thus required. Post-HSCT survivors, especially those with chronic GVHD, score lower in quality-of-life measures⁴⁸. Life expectancy for 5-year survivors can be as little as 70% of that in the general population⁴⁷.

SUMMARY

A potentially life-saving treatment for a variety of malignant and benign diseases, HSCT requires not only careful selection of candidate recipients, stem-cell donors, and conditioning regimens, but also close monitoring for complications. Survivors are at risk for both short- and long-term complications and can benefit from routine medical screening and care.

Key Points

- HSCT is a potentially life-saving procedure and often the only curative option for a variety of diseases.
- The two main types of HSCT are autologous (stem cells are harvested from the recipient) and allogeneic (stem cells are harvested from a different individual or from cord blood units).
- HSCT is associated with both immediate and long-term complications requiring increased vigilance and monitoring.
- HSCT complications can result in decreased quality of life and shortened life expectancy.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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TABLE 1 Late complications from hematopoietic stem-cell transplantation

| Neuropsychologic | |
|---|----------------------------------|
| Depression, anxiety | Posttraumatic stress disorder |
| Neurocognitive deficits | |
| Pulmonary | |
| Bronchiolitis obliterans syndrome | Cryptogenic organizing pneumonia |
| Pulmonary hypertension | |
| Renal | |
| Thrombotic microangiopathy | Nephrotic syndrome |
| Idiopathic chronic kidney disease | Persistent acute kidney injury |
| BK virus nephropathy | |
| Iron overload | |
| Bone | |
| Osteopenia | Osteoporosis |
| Avascular necrosis | |
| Endocrine | |
| Thyroid dysfunction | Gonadal dysfunction |
| Diabetes | Dyslipidemia |
| Metabolic syndrome | Adrenal insufficiency |
| Secondary cancers | |
| Mouth | Skin |
| Breast | Thyroid |
| Other sites | |
| Cardiovascular | |
| Cardiomyopathy | Congestive heart failure |
| Valvular disease | Arrhythmia |
| Pericarditis | Coronary artery disease |
| Hepatic | |
| Hepatitis B and C | Cirrhosis |
| Nodular regenerative or focal nodular hyperplasia | |
| Gonadal dysfunction or infertility | |
| Infectious | |
| <i>Pneumocystis jirovecii</i> | Encapsulated bacteria |
| Fungi | Varicella zoster virus |
| Cytomegalovirus | Respiratory syncytial virus |
| Influenza virus | Parainfluenza virus |

^a Adapted from Inamoto and Lee, 2017⁴⁷.

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