CURRENT ONCOLOGY
A Canadian Cancer Research Journal

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

A. Bazinet MD* and G. Popradi MD*

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

Curr Oncol. 2019 June;26(3):187-191 www.current-oncology.com

INTRODUCTION

Hematopoietic stem-cell transplantation (HSCT) was first performed in 1957 by E. Donnell Thomas as a new form of cancer treatment[1]. Although initial attempts were largely unsuccessful, the procedure has dramatically evolved through the decades since[2]. Today, more than 50,000 HSCT procedures are performed annually worldwide[3] 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 room[4]. 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 compartment[5]. 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

This series is brought to you in partnership with the Canadian Association of General Practitioners in Oncology.

THE CANADIAN ASSOCIATION OF GENERAL PRACTITIONERS IN ONCOLOGY

Correspondence to: Gizelle Popradi, Royal Victoria Hospital, McGill University Health Centre, 1001 Decarie Boulevard, D2.7719, Montreal, Quebec H4A 3J1. E-mail: gizelle.popradi@mcgill.ca ■ **DOI:** https://doi.org/10.3747/co.26.5033

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 HSCT[10].

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 HSCT[11]. A HSCT procedure might also be used to treat select solid tumours such as germ cell tumours[12], neuroblastoma[13], Ewing sarcoma[14], and medulloblastoma[15].

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 online[24].

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 Index[25]. A comprehensive geriatric assessment can also be of value in older individuals[26].

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 0.5×10^9/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 aspergillosis[31]. 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 protection[32]. 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 level[33].

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 survival[34].

During the early post-engraftment period, patients remain at risk of infectious complications. Despite recovery from neutropenia, cellular and humoural 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 affected[33]. Patients with active chronic GVHD experience more frequent opportunistic infections and reduced quality of life[35]. 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 mortality[11]. Even recipients who enjoy a relatively uneventful clinical course after their HSCT are at increased long-term risk for cardiovascular disease[40]; metabolic disorders including diabetes, dyslipidemia, hypothyroidism and osteoporosis[41–43]; secondary malignancies[44]; gonadal and reproductive dysfunction[45]; and neuropsychiatric disorders[46] (Table I). Increased vigilance and screening are thus required. Post-HSCT survivors, especially those with chronic GVHD, score lower in quality-of-life measures[48]. Life expectancy for 5-year survivors can be as little as 70% of that in the general population[47].

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.

AUTHOR AFFILIATIONS

*Division of Hematology, McGill University Health Centre, Montreal, QC.

REFERENCES

1. Thomas ED, Lochte HL Jr, Lu WC, Ferrebee JW. Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. *N Engl J Med* 1957;257:491–6.
2. Appelbaum FR. Hematopoietic-cell transplantation at 50. *N Engl J Med* 2007;357:1472–5.
3. World Health Organization (WHO). Haematopoietic Stem Cell Transplantation HSCtx [Web page]. Geneva, Switzerland: WHO; 2018. [Available at: https://www.who.int/transplantation/hsctx/en; cited 6 January 2019]
4. Thomas ED, Buckner CD, Banaji M, *et al.* One hundred patients with acute leukemia treated by chemotherapy, total body

irradiation, and allogeneic marrow transplantation. *Blood* 1977;49:511–33.
5. Gertz MA. Current status of stem cell mobilization. *Br J Haematol* 2010;150:647–62.
6. Anasetti C, Logan BR, Lee SJ, *et al.* on behalf of the Blood and Marrow Transplant Clinical Trials Network. Peripheral-blood stem cells versus bone marrow from unrelated donors. *N Engl J Med* 2012;367:1487–96.
7. Stem Cell Trialists' Collaborative Group. Allogeneic peripheral blood stem-cell compared with bone marrow transplantation in the management of hematologic malignancies: an individual patient data meta-analysis of nine randomized trials. *J Clin Oncol* 2005;23:5074–87.
8. Wagner JE, Barker JN, DeFor TE, *et al.* Transplantation of unrelated donor umbilical cord blood in 102 patients with malignant and nonmalignant diseases: influence of CD34 cell dose and HLA disparity on treatment-related mortality and survival. *Blood* 2002;100:1611–18.
9. Kanakry CG, Fuchs EJ, Luznik L. Modern approaches to HLA-haploidentical blood or marrow transplantation. *Nat Rev Clin Oncol* 2016;13:132. [Erratum in: *Nat Rev Clin Oncol* 2016;13:132]
10. Ringden O, Karlsson H, Olsson R, Omazic B, Uhlin M. The allogeneic graft-versus-cancer effect. *Br J Haematol* 2009;147:614–33.
11. Center for International Blood and Marrow Transplant Research. Summary slides—HCT trends and survival data [Web resource]. Milwaukee, WI: The Medical College of Wisconsin; 2017. [Available at: https://www.cibmtr.org/ReferenceCenter/SlidesReports/SummarySlides/pages/index.aspx; cited 12 January 2019]
12. Adra N, Abonour R, Althouse SK, Albany C, Hanna NH, Einhorn LH. High-dose chemotherapy and autologous peripheral-blood stem-cell transplantation for relapsed metastatic germ cell tumors: the Indiana University experience. *J Clin Oncol* 2017;35:1096–102.
13. Pasqualini C, Dufour C, Goma G, Raquin MA, Lapierre V, Valteau-Couanet D. Tandem high-dose chemotherapy with thiotepa and busulfan–melphalan and autologous stem cell transplantation in very high-risk neuroblastoma patients. *Bone Marrow Transplant* 2016;51:227–31.
14. Laurence V, Pierga JY, Barthier S, *et al.* Long-term follow up of high-dose chemotherapy with autologous stem cell rescue in adults with Ewing tumor. *Am J Clin Oncol* 2005;28:301–9.
15. Gajjar A, Chintagumpala M, Ashley D, *et al.* Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial. *Lancet Oncol* 2006;7:813–20.
16. Peinemann F, Grouven U, Kroger N, Bartel C, Pittler MH, Lange S. First-line matched related donor hematopoietic stem cell transplantation compared to immunosuppressive therapy in acquired severe aplastic anemia. *PLoS One* 2011;6:e18572.
17. Dalle JH, Peffault de Latour R. Allogeneic hematopoietic stem cell transplantation for inherited bone marrow failure syndromes. *Int J Hematol* 2016;103:373–9.
18. Gluckman E, Cappelli B, Bernaudin F, *et al.* on behalf of the Eurocord, the Pediatric Working Party of the European Society for Blood and Marrow Transplantation, and the Center for International Blood and Marrow Transplant Research. Sickle cell disease: an international survey of results of HLA-identical sibling hematopoietic stem cell transplantation. *Blood* 2017;129:1548–56.
19. Baronciani D, Angelucci E, Potschger U, *et al.* Hemopoietic stem cell transplantation in thalassemia: a report from the European Society for Blood and Bone Marrow Transplantation Hemoglobinopathy Registry, 2000–2010. *Bone Marrow Transplant* 2016;51:536–41.
20. Wahlstrom JT, Dvorak CC, Cowan MJ. Hematopoietic stem cell transplantation for severe combined immunodeficiency. *Curr Pediatr Rep* 2015;3:1–10.

TABLE I 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	
Pneumocystis jirovecii	Encapsulated bacteria
Fungi	Varicella zoster virus
Cytomegalovirus	Respiratory syncytial virus
Influenza virus	Parainfluenza virus

[a] Adapted from Inamoto and Lee, 2017[47].

21. Krivit W, Sung JH, Shapiro EG, Lockman LA. Microglia: the effector cell for reconstitution of the central nervous system following bone marrow transplantation for lysosomal and peroxisomal storage diseases. *Cell Transplant* 1995;4:385–92.
22. Hugle T, Daikeler T. Stem cell transplantation for autoimmune diseases. *Haematologica* 2010;95:185–8.
23. Mancardi G, Sormani MP, Muraro PA, Boffa G, Saccardi R. Intense immunosuppression followed by autologous haematopoietic stem cell transplantation as a therapeutic strategy in aggressive forms of multiple sclerosis. *Mult Scler* 2018;24:245–55.
24. National Marrow Donor Program/Be The Match and the American Society for Blood and Marrow Transplantation. Transplant referral timing guidelines [Web page]. Minneapolis, MN: National Marrow Donor Program; 2019. [Available at: https://bethematchclinical.org/transplant-indications-and-outcomes/referral-timing-guidelines; cited 19 January 2019]
25. Sorror ML, Maris MB, Storb R, *et al.* Hematopoietic Cell Transplantation (HCT)–Specific Comorbidity Index: a new tool for risk assessment before allogeneic HCT. *Blood* 2005;106:2912–19.
26. Muffly LS, Kocherginsky M, Stock W, *et al.* Geriatric assessment to predict survival in older allogeneic hematopoietic cell transplantation recipients. *Haematologica* 2014;99:1373–9.
27. Gertz MA, Ansell SM, Dingli D, *et al.* Autologous stem cell transplant in 716 patients with multiple myeloma: low treatment-related mortality, feasibility of outpatient transplant, and effect of a multidisciplinary quality initiative. *Mayo Clin Proc* 2008;83:1131–8.
28. Guru Murthy GSG, Hari PN, Szabo A, *et al.* Outcomes of reduced-intensity conditioning allogeneic hematopoietic cell transplantation performed in the inpatient versus outpatient setting. *Biol Blood Marrow Transplant* 2019;25:827–33.
29. Nash RA, Pineiro LA, Storb R, *et al.* FK506 in combination with methotrexate for the prevention of graft-versus-host disease after marrow transplantation from matched unrelated donors. *Blood* 1996;88:3634–41.
30. Ruutu T, Eriksson B, Remes K, *et al.* on behalf of the Nordic Bone Marrow Transplantation Group. Ursodeoxycholic acid for the prevention of hepatic complications in allogeneic stem cell transplantation. *Blood* 2002;100:1977–83.
31. Tomblyn M, Chiller T, Einsele H, *et al.* on behalf of the Center for International Blood and Marrow Research, the National Marrow Donor program, the European Blood and Marrow Transplant Group, the American Society of Blood and Marrow Transplantation, the Canadian Blood and Marrow Transplant Group, the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, the Association of Medical Microbiology and Infectious Disease Canada, and the Centers for Disease Control and Prevention. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant* 2009;15:1143–238.
32. Dalle JH, Giralt SA. Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: risk factors and stratification, prophylaxis, and treatment. *Biol Blood Marrow Transplant* 2016;22:400–9.
33. Carreras E, Dufour C, Mohty M, Kröger N, eds. *The EBMT Handbook: Hematopoietic Stem Cell Transplantation and Cellular Therapies.* 7th ed. Cham, Switzerland: Springer Nature Switzerland; 2019.
34. Cutler C. Acute graft-vs-host disease. In: Wingard J, ed. *Hematopoietic Stem Cell Transplantation: A Handbook for Clinicians.* Bethesda, MD: American Association of Blood Banks; 2009: 331–43.
35. Jagasia MH, Greinix HT, Arora M, *et al.* National Institutes of Health Consensus Development project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant* 2015;21:389–401.
36. Flowers ME, Apperley JF, van Besien K, *et al.* A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease. *Blood* 2008;112:2667–74.
37. Miklos D, Cutler CS, Arora M, *et al.* Ibrutinib for chronic graft-versus-host disease after failure of prior therapy. *Blood* 2017;130:2243–50.
38. Zeiser R, Burchert A, Lengerke C, *et al.* Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey. *Leukemia* 2015;29:2062–8.
39. National Marrow Donor Program (NMDP)/Be The Match. 2018 Long-Term Survival Guidelines—Post-Transplant Care Recommendations [Web page]. Minneapolis, MN: NMDP; 2018. [Available at: https://bethematchclinical.org/post-transplant-care/post-transplant-guidelines; cited 10 March 2019]
40. Tichelli A, Bucher C, Rovo A, *et al.* Premature cardiovascular disease after allogeneic hematopoietic stem-cell transplantation. *Blood* 2007;110:3463–71.
41. Majhail NS, Flowers ME, Ness KK, *et al.* High prevalence of metabolic syndrome after allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant* 2009;43:49–54.
42. Tauchmanova L, Colao A, Lombardi G, Rotoli B, Selleri C. Bone loss and its management in long-term survivors from allogeneic stem cell transplantation. *J Clin Endocrinol Metab* 2007;92:4536–45.
43. Medinger M, Zeiter D, Heim D, *et al.* Hypothyroidism following allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia. *Leuk Res* 2017;58:43–7.
44. Baker KS, DeFor TE, Burns LJ, Ramsay NK, Neglia JP, Robison LL. New malignancies after blood or marrow stem-cell transplantation in children and adults: incidence and risk factors. *J Clin Oncol* 2003;21:1352–8.
45. Hammond C, Abrams JR, Syrjala KL. Fertility and risk factors for elevated infertility concern in 10-year hematopoietic cell transplant survivors and case-matched controls. *J Clin Oncol* 2007;25:3511–17.
46. Poppelreuter M, Weis J, Mumm A, Orth HB, Bartsch HH. Rehabilitation of therapy-related cognitive deficits in patients after hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2008;41:79–90.
47. Inamoto Y, Lee SJ. Late effects of blood and marrow transplantation. *Haematologica* 2017;102:614–25.
48. Pidala J, Kurland B, Chai X, *et al.* Patient-reported quality of life is associated with severity of chronic graft-versus-host disease as measured by NIH criteria: report on baseline data from the Chronic GVHD Consortium. *Blood* 2011;117:4651–7.