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HOW TO

How to Perform Hematopoietic Stem Cell Transplantation

Navneet S. Majhail, MD, MS

Hematopoietic cell transplantation (HCT) is offered for the treatment of high-risk hematologic malignancies and other life-threatening diseases. It involves administration of high doses of chemotherapy with or without radiation (also known as conditioning regimen) followed by infusion of hematopoietic progenitor cells from the patient (autologous HCT) or from a related or unrelated donor (allogeneic HCT). The number of patients who receive HCT continues to increase due to improvements in transplantation technology and supportive care, introduction of newer indications, and greater utilization of alternative donors. Approximately 25,000 patients in the United States and 60,000 patients worldwide receive HCT annually (1). At present, there are an estimated 250,000 HCT survivors in the United States (2).

In autologous HCT recipients, the procedure relies on the effectiveness of high-dose chemotherapy for disease control (3). The patient's hematopoietic progenitor cells are mobilized with growth factors (granulocyte colony-stimulating factor, plerixafor) with or without chemotherapy, collected by apheresis, and are infused back immediately after administration of conditioning regimen. Autologous HCT recipients do not experience an alloreactive graft-versus-tumor effect and do not need immunosuppression. On the other hand, allogeneic HCT recipients get the benefit of the graft-versus-tumor effect exerted through donor T cells in addition to the conditioning regimen effect of high-dose chemotherapy with or without total body irradiation (TBI). Because there is some level of immune incompatibility between the recipient and the donor, they receive immunosuppression for a period of time to prevent graft rejection and graft-versus-host disease (GVHD), an immune complication of HCT (3). Donor selection is an important aspect of optimizing success of allogeneic transplantation, and human leukocyte antigen (HLA)-identical sibling donors are preferred because they are associated with lower risks of graft failure and GVHD. However, only 20% to 30% of patients have HLA-identical sibling donors, and in these patients alternative options may include matched or mismatched unrelated donors, haploidentical donors (parents, siblings, or children), or banked umbilical cord blood (4). Irrespective, a suitable donor can be identified for nearly all patients who need a transplant in the current era. In contrast with autologous HCT in which the conditioning regimen is always myeloablative, some older and frail allogeneic HCT recipients and patients with highly immune-reactive diseases may receive a less intense reduced-intensity or nonmyeloablative regimen that relies mostly on the graft-versus-tumor effect for disease control.

The transplant episode can be divided into a pretransplantation assessment phase, an early post-transplantation phase (start of conditioning regimen to ~3-6 months post-transplant), and a late post-transplantation phase (more than ~3-6 months post-transplant). The initial phase consists of an assessment of patient's candidacy for the procedure (work-up period) to determine disease status and organ function, along with psychosocial evaluation and education about the procedure. Patients may be referred for additional evaluations to determine and possibly mitigate their risk for complications. Several critical decisions are made during this phase depending on patients' underlying disease status,

From the Blood and Marrow Transplant Program, Cleveland Clinic, Cleveland, Ohio, USA.
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comorbidities, and assessment results, such as selecting a donor, type and intensity of conditioning regimen, regimen to prevent GVHD, and appropriate supportive care protocols. Some patients may not be deemed as suitable candidates if the risks of treatment-related mortality (TRM) and morbidity exceed any potential benefit in survival they may receive from this procedure. During this phase, autologous HCT recipients and donors for some allogeneic HCT recipients undergo apheresis for peripheral blood stem cell collection, which are then cryopreserved for infusion at the time of transplantation (typically 1-4 weeks later).

The early post-transplantation phase is characterized by administration of conditioning regimen and patients are closely monitored for chemotherapy or TBI-associated toxicity and serious complications such as graft failure, infections, organ failure, and acute GVHD. Subsequently, patients transition to a long-term follow-up phase in which the focus is rehabilitation and monitoring for chronic GVHD and late complications of transplantation. The latter includes late organ toxicity, secondary malignancies, late infections, psychosocial and quality-of-life impairments, and issues with growth and development in children (5). Although risks for relapse decrease over time, surveillance for disease recurrence continues in the long-term follow-up phase.

Table 1 highlights some cardiovascular issues that are relevant for various phases of HCT. Assessment and management of cardiovascular risk factors and disease is an important aspect of optimizing short- and long-term transplantation outcomes (6).

CASE

A 56-year-old man with high-risk myelodysplastic syndrome (MDS) was referred for allogeneic HCT. He had been treated with 4 cycles of azacytidine and had a suitable HLA-identical sibling donor. He had a 40 pack-year history of smoking and offered a prior history of hyperlipidemia, essential hypertension, atrial fibrillation, and coronary artery disease (CAD). He had undergone successful ablation for atrial fibrillation. He underwent percutaneous coronary intervention to the left circumflex artery 3 years ago, and since then denied any cardiac symptoms. A recent 2-dimensional echocardiogram showed a left ventricular ejection fraction of 50%.

The decision to proceed with transplantation involves an assessment and discussion of the mortality and morbidity risks related to the procedure versus the benefit conferred by disease control and prolongation of survival. Using the previous case as an example, the median survival for high-risk MDS is 1 to 2 years, and patients receiving allogeneic HCT can expect a 3-year overall survival of ∼50% compared with ∼25% for patients who do not have a suitable donor. There are validated instruments to assess the risks of TRM, and a commonly used tool (HCT-Specific Comorbidity Index) estimates the 1-year risk at ∼20% for this patient based just on his cardiac comorbidities (7). The pre-transplantation period provides an opportunity to optimize cardiovascular risk, recognize pre-existing cardiovascular disease, and anticipate and mitigate risks of common cardiovascular complications (**Figure 1**), while recognizing the typical urgency to proceed with transplantation in appropriate candidates. The previous patient can be counseled about smoking cessation and referred for additional testing to identify and reverse ischemia as well as medical management of CAD, cardiomyopathy, and hypertension. Although a myeloablative conditioning regimen would offer greater probability of MDS control, it would also be associated with prohibitive risks of TRM with his known cardiovascular comorbidities, and he would be better suited for transplantation using a reduced-intensity regimen. Similarly, some chemotherapeutic agents and high-dose TBI would be avoided to further reduce the risk of cardiovascular complications. Donor choice can be an important consideration; for example, haploidentical related donor HCT with post-transplantation high-dose cyclophosphamide as the primary GVHD prevention regimen has been associated with higher risks of cytokine release syndrome and cardiotoxicity. Hence, the "package" of donor type, graft source, conditioning regimen, and GVHD prophylaxis is relevant to assessing and mitigating cardiovascular risk in HCT recipients.

CASE CONTINUED

The patient was referred to cardio-oncology and underwent a technetium tetrofosmin-gated single-photon emission computed tomography myocardial perfusion imaging, which showed a moderate fixed perfusion defect in the left circumflex territory with no inducible ischemia. The medical management of his cardiac comorbidities was further optimized. He proceeded with allogeneic HCT using a reduced-intensity regimen of busulfan and fludarabine with a tacrolimus and mycophenolate mofetil-based regimen to prevent GVHD. He had issues with fluid retention, but overall had a rather uneventful course

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease
GVHD = graft-versus-host disease
HCT = hematopoietic cell transplantation
HLA = human leukocyte antigen
MDS = myelodysplastic syndrome
TBI = total body irradiation
TRM = treatment-related mortality

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TABLE 1 Phases of HCT and Related Cardiovascular Issues

HCT Phase	Characteristics of HCT Phase	Cardiovascular Considerations
Pre-transplantation (work-up period)	- Assessment of disease status - Assessment of comorbidities and organ function - Psychosocial assessment - Patient and caregiver education - Donor assessment (allogeneic HCT) - Stem cell mobilization and collection - Overall assessment of HCT candidacy	- Assessment of cardiovascular risk associated with prior treatments (eg, anthracyclines, radiation), including suitability for HCT - Assessment of cardiac function (ECG and 2D/3D transthoracic echocardiogram) - Disease-specific cardiac assessment (eg, TnT and NT-proBNP in amyloidosis) - Referral for additional assessment and mitigation of cardiac risk if indicated - Management of cardiovascular risk factors (eg, smoking, HTN, diabetes, dyslipidemia)
Early post-transplantation (start of conditioning regimen to ~3-6 mo after HCT)	- Administration of conditioning regimen chemotherapy and/or TBI - Infusion of hematopoietic progenitor (stem) cells - Period of myelosuppression prior to engraftment - Prevention and management of acute GVHD (allogeneic HCT) - Monitoring for early complications (eg, organ toxicity, infections, sinusoidal obstruction syndrome)	- Optimizing conditioning regimen based on risk of cardiotoxicity - Monitoring drug effect on arrhythmia risk (eg, QTc prolongation) - Fluid management in patients with cardiac dysfunction - Prevention and management of early cardiotoxicity - Management of cardiovascular risk factors (eg, smoking, HTN, diabetes, dyslipidemia)
Late post-transplantation (beyond ~3-6 mo after HCT)	- Surveillance for disease recurrence - Prevention and management of chronic GVHD (allogeneic HCT) - Surveillance and prevention of late complications (eg, organ toxicity, infections, secondary neoplasms)	- Assessment of exposures (eg, TBI, iron overload) and risk for cardiovascular late complications (eg, CAD, cardiomyopathy) - Surveillance for cardiovascular late complications - Management of cardiovascular risk factors (eg, smoking, HTN, diabetes, dyslipidemia) - Monitoring and mitigating cardiovascular risk associated with treatments for disease relapse

2D = 2-dimensional; 3D = 3-dimensional; CAD = coronary artery disease; ECG = electrocardiology; GVHD, graft-versus-host-disease; HCT = hematopoietic cell transplantation; HTN = hypertension; NT-proBNP = N-terminal pro-B-type natriuretic peptide; TBI = total body irradiation; TnT = troponin T.

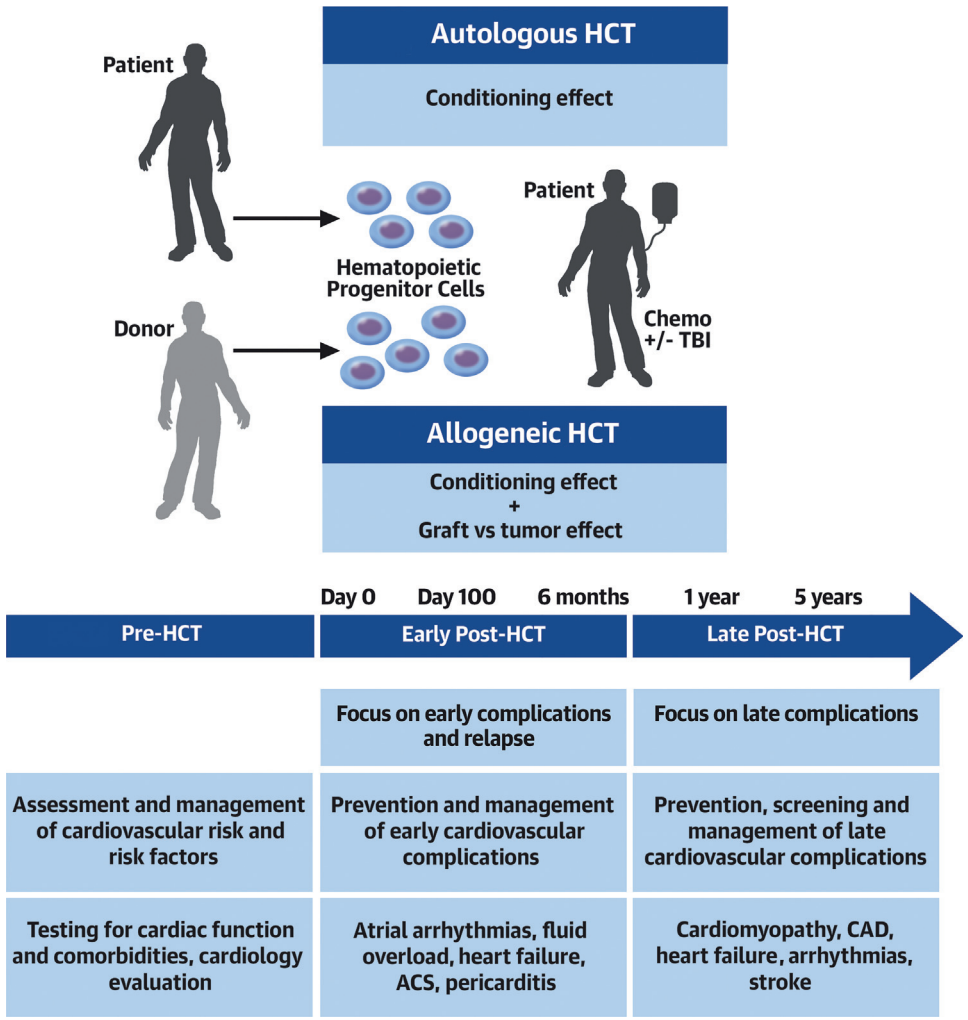
over the first 3 months post-transplantation. He subsequently developed mild chronic GVHD of the skin, which was successfully treated with systemic corticosteroids.

The overall incidence of early cardiotoxic events has been reported to range from 5% to 20% in HCT recipients, with common complications including atrial arrhythmias, fluid overload, and pulmonary edema, and rarer but more serious complications such as heart failure, acute coronary syndrome, myopericarditis, and sudden cardiac arrest (**Figure 1**) (8). The incidence of the later is 1% to 2%, with the caveat that there exists a selection bias toward healthier patients who ultimately receive HCT. Older age, pre-existing cardiovascular disease, prior cardiotoxic exposures (eg, anthracyclines), conditioning regimen (eg, high-dose cyclophosphamide, thiotepa, or TBI), and GVHD prophylaxis (eg, post-transplantation cyclophosphamide) are predisposing risk factors. Cardioprotective agents such as beta-blockers or angiotensin-converting enzyme inhibitors may reduce the risk of long-term heart failure, although well-controlled randomized studies addressing their utility are generally lacking.

As patients transition from the early to late phase post-transplantation, the focus changes from active monitoring with frequent clinician visits to surveillance and prevention of late cardiovascular effects (**Figure 1**). Patients who survive 2 or more years after HCT have 2 to 4 times higher risks of cardiovascular death, cardiomyopathy and heart failure, CAD, vascular disease, and rhythm disorders compared with their peers from the general population (8). When considering survivorship care in HCT recipients, it is important to tailor a surveillance and prevention strategy based on individual patient treatment exposures and risk factors, including exposures that may have occurred prior to transplantation (9). For instance, the association between prior chest radiation and pre-transplantation anthracycline exposure and heart failure has been well defined (8). Similarly, TBI exposure has been associated with higher risks of CAD in HCT survivors (8). Iron overload owing to red cell transfusions during the peritransplantation period may predispose to cardiomyopathy.

A cardiovascular risk prediction model that considers age, smoking, anthracycline dose, chest radiation exposure, hypertension, and diabetes has been proposed, in which the 10-year risk of heart failure and CAD in HCT survivors who are ≥1 year post-transplantation has been shown to range from 4% in low-risk versus 26% in high-risk patients (10). Guidelines provide recommendations for periodic assessments to mitigate the risks of cardiovascular complications, including aggressive management of hyperlipidemia, obesity, hypertension, and diabetes mellitus, along with counseling for smoking cessation, exercise, and health lifestyle (5). Some patients

FIGURE 1 HCT Procedure and Related Cardiovascular Considerations



ACS = acute coronary syndrome; CAD = coronary artery disease; HCT = hematopoietic cell transplantation; TBI = total body irradiation.

at high risk for cardiovascular complication may also be candidates for screening with periodic echocardiograms, although this strategy has not been validated in clinical trials.

As transplantation techniques get increasingly sophisticated and a greater number of sicker and older patients benefit from the procedure, it is imperative that HCT recipients receive care in collaboration with cardiology or cardio-oncology to manage cardiovascular issues. This multidisciplinary care may also include other clinicians to optimize management of these issues (eg, pharmacists to address drug interactions, physical therapists to improve exercise tolerance). There are significant gaps in our understanding of cardiovascular complications in this patient population, such as the role of blood and imaging biomarkers to stratify risk and identify cardiac events early, and the efficacy of interventions to reduce the risk of cardiotoxicity and prevent progression of subclinical cardiac injury. Hence, ongoing research is necessary to guide practice and optimize HCT outcomes.

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ADDRESS FOR CORRESPONDENCE: Dr Navneet Majhail, Cleveland Clinic, 9500 Euclid Avenue, CA60, Cleveland, Ohio 44195, USA. E-mail: nsmajhail@hotmail.com. Twitter: @BldCancerDoc.

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