Chapter 23
Cardiovascular Complications

Stephen B. Heitner and Stanley Chou

The antecedent assessment and attention to the cardiovascular system of patients undergoing hematopoietic stem cell transplant (HSCT), as well as an awareness of the treatment's potential long-term cardiac effects, are critical in the overall care of these complex and often very ill patients. The issues facing patients and their treating providers are primarily centered in three arenas: (1) cardiovascular comorbidities and the overall cardiovascular reserve, (2) chemotherapy and radiation associated cardiovascular toxicities, and (3) long-term effects of HSCT.

Patients with hematologic malignancies may have preexisting cardiovascular comorbidities that interfere with the successful delivery of high-dose chemotherapy and most effective cell-based treatments. Awareness of these comorbidities allows the treatment team to address these issues actively and improve the outcomes for patients from an oncology perspective. Early identification and treatment of cardiotoxicities, as well as the potential prediction of at-risk patients, will allow the treating hematologists to ensure that the most appropriate therapies are delivered at the most efficacious doses.

Lastly, the monitoring of patients for long-term effects of HSCT may prevent the success of cancer therapy from being overshadowed by cardiovascular morbidity and mortality.

S. B. Heitner (✉)
Knight Cardiovascular Institute, Oregon Health & Science University,
3181 SW Sam Jackson Park Road, UHN62, Portland OR 97239 USA
e-mail: heitner@ohsu.edu

S. Chou
Cedars-Sinai Heart Institute, Cedars-Sinai Medical Center, 8700 Beverly Blvd.,
Los Angeles, CA 90048 USA
e-mail: stanley.chou@gmail.com

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23.1 Baseline Cardiac Evaluation

1. History and physical examination
    a. Risk factors for post-transplant cardiac complications
        i. Advanced age (> 70 years old)
        ii. Prior anthracycline use
        iii. Cyclophosphamide-based conditioning regimens

Adequate blood pressure control in hypertensive patients is important as post-transplant immunosuppressive medications (cyclosporine, tacrolimus) can worsen hypertension (HTN).

2. Twelve-lead electrocardiogram (EKG)
    a. QT-interval prolongation is an independent risk factor for developing acute heart failure post-transplantation.
        i. Normal QTc is 390–450 ms for men and 390–460 ms for women.
    b. QT-interval dispersion (difference between the maximum and minimum QT intervals) has also been suggested as a risk factor for developing acute heart failure post-transplantation.
        i. Normal QT-interval dispersion is 40–50 ms.
    c. Conduction or rhythm abnormalities should be documented (hematopoietic cell transplant-comorbidity index (HCT-CI) risk assessment, see Chap. 4). Patients are at risk of supraventricular tachyarrhythmias (and less commonly ventricular arrhythmias) during the immediate post-transplant period.
3. Chest X-ray
    a. Presence of cardiomegaly (increased cardiothoracic ratio) suggests cardiomyopathy.
    b. Pulmonary edema and pleural effusions suggest congestive heart failure (CHF).
4. Assessment of left ventricular ejection fraction (LVEF)
    a. LVEF ≥45–50 % is arbitrarily chosen as an eligibility criterion for HSCT by most centers.
    b. Transthoracic echocardiography (TTE) and multigated radionuclide angiography (MUGA) are commonly available and validated diagnostic modalities.
        i. MUGA when compared to TTE
            ii. Higher specificity
            iii. Less interobserver variability
            iv. More expensive
            v. Radiation risk

ii. TTE
    i. Provides additional information such as valvular function, diastolic function, and global strain when compared to MUGA.
    ii. With the added benefit of objective measurement of global longitudinal strain (early indicator of myocardial dysfunction with the potential to predict future systolic dysfunction), TTE becomes a more attractive method to assess left ventricle (LV) function in experienced centers.

5. Noninvasive stress testing

   a. No conclusive data to suggest that stress testing improves the ability to predict risk of post-transplant cardiac complications. However, some centers routinely perform noninvasive stress testing as part of the pre-transplant evaluation.
   b. If pre-transplant evaluation reveals an indication to perform noninvasive stress testing independent of the HSCT, stress testing should be performed.
      i. Current indications for stress testing include, but are not limited to, patients with a history or physical examination findings that are suggestive of ischemic heart disease
      ii. Newly diagnosed cardiomyopathy
      iii. Valvular heart disease
      iv. Certain arrhythmias
      v. Significant risks for coronary artery disease in patients who are undergoing non-cardiac surgery.
   c. Further cardiac evaluation and management should be pursued if indicated based on the results of the stress test.

23.2 Systolic Heart Failure

1. Etiologic considerations in HSCT patients

   a. Cyclophosphamide cardiotoxicity
      i. Heart failure associated with cyclophosphamide therapy occurs in 7–28 % of patients.
      ii. Dose-related risk (> 150 mg/kg and 1.5 g/m2/day).
      iii. Occurs within 1–10 days after administration of the first dose.
   b. Other risk factors include prior anthracycline therapy and mediastinal irradiation.
   c. Hypoalbuminemia, fluid shifts, tachyarrhythmias, ischemia, and renal failure may exacerbate acute decompensated heart failure in patients with preexisting cardiomyopathies.

2. Symptoms
    a. Low output
        i. Fatigue
        ii. Weakness
        iii. Altered mental status
    b. Congestion
        i. Dyspnea
        ii. Orthopnea
        iii. Paroxysmal nocturnal dyspnea
        iv. Peripheral edema
3. Physical exam
    a. Elevated jugular venous pressure (JVP)
    b. Positive hepatojugular reflux with right upper quadrant (RUQ) abdominal pressure (4 cm increase in JVP; suggests pulmonary artery wedge pressure >15 mmHg)
    c. Presence of S3 on cardiac auscultation
    d. Rales and/or crackles
    e. Decreased breath sounds at bases due to pleural effusion
    f. Peripheral edema and ascites
4. Diagnostic studies
    a. Lab studies
        i. Increased SCr and BUN
        ii. Decreased Na
        iii. Abnormal LFTs
        iv. Elevated BNP or NT-proBNP
    b. Chest x-ray
        i. Pulmonary edema
        ii. Pleural effusions
        iii. Cardiomegaly as evidenced by increased cardiothoracic ratio
    c. Echocardiogram
        i. Decreased LVEF
        ii. Increased LV chamber size
        iii. Valvular abnormalities
        iv. Pericardial abnormalities
    d. Pulmonary artery catheterization
        i. Increased pulmonary capillary wedge pressure
        ii. Decreased cardiac output or cardiac index
        iii. Increased systemic vascular resistance

5. Management
   a. Treatment of acute pulmonary edema (LMNOP)
      i. Lasix® (furosemide) or other diuretics such as bumetanide (Bumex) or torsemide
      ii. Morphine
      iii. Nitrates
      iv. Oxygen
      v. Position (sit patient up)
   b. Treatment of advanced heart failure
      i. Consider pulmonary artery catheter-guided therapy
      ii. Intravenous vasodilators
      iii. Inotropes
      iv. Ultrafiltration
      v. Mechanical circulatory support in consultation with cardiology
   c. Treatment of chronic heart failure
      i. Treatment of CHF in HSCT patients is generally consistent with treatment of CHF in the general population as outlined in the American College of Cardiology/American Heart Association Guidelines.
         • Use of an angiotensin converting enzyme inhibitor (ACE inhibitor) or angiotensin receptor blocker (ARB), beta-blocker (carvedilol or metoprolol succinate), and aldosterone antagonists
      ii. Prophylactic use combination therapy with enalapril and carvedilol has been shown to reduce the risk of chemotherapy-induced cardiomyopathy.

23.3 Atrial Fibrillation

1. Common complication in HSCT patients.
2. Risk factors, independent of transplantation
   a. Advanced age (> 70 years)
   b. HTN
   c. Obesity
   d. Underlying cardiac disease
3. Possible precipitants
   a. Direct effects from the chemotherapy agents
      i. Melphalan
      ii. Etoposide
      iii. High-dose corticosteroids

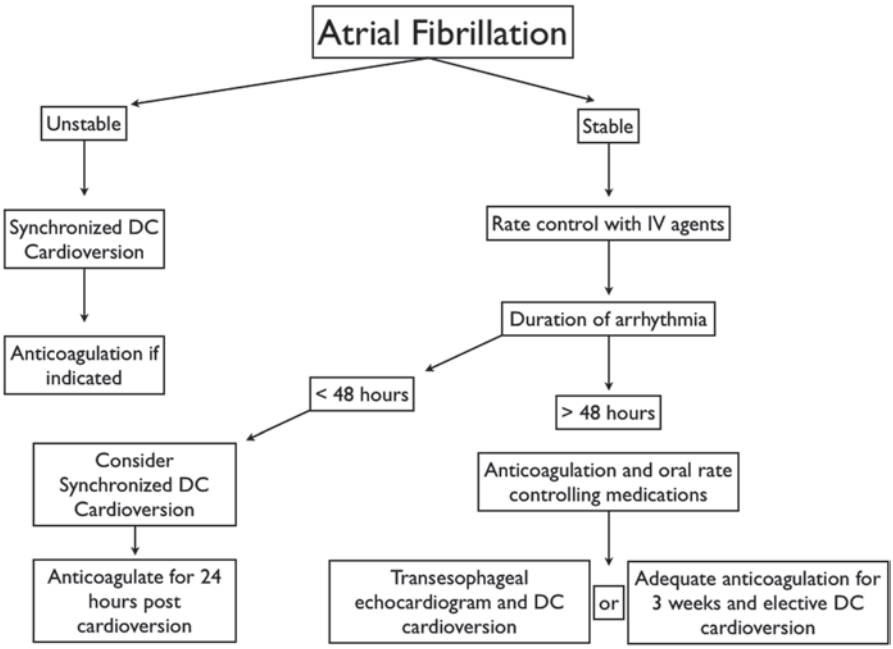

Fig. 23.1 Standard approaches to acute atrial fibrillation

b. Cardiac
   i. CHF
   ii. Pericarditis
   iii. Ischemia
c. Pulmonary
   i. Hypoxia
   ii. Pulmonary embolism
d. Metabolic
   i. High catecholamine state
   ii. Infections
   iii. Electrolyte disturbances

4. DMSO.
5. Symptoms may include palpitations or light-headedness. Many patients are also asymptomatic.
6. Diagnosis is made by capturing the rhythm on telemetry or EKG.
7. Management
   a. Standard approach to acute atrial fibrillation (see Fig. 23.1)
   b. Rate controlling agents (all can cause hypotension and bradycardia and should be administered in a monitored setting)

i. Metoprolol 5 mg intravenous (IV), every 5 min × 3, 25–200 mg/day po in divided doses
ii. Diltiazem 0.25 mg/kg IV, may repeat after 15 min, 120–360 mg/day po in divided doses (caution with decreased LVEF)
iii. Digoxin 1 g IV or po load in three divided doses every 4–8 h given as 50 % initially and then 25 % × 2, then 0.125–0.375 mg po daily (need to adjust for creatinine clearance)
iv. Amiodarone 150 mg IV over 10 min, and then 0.5–1 mg/min IV

23.4 Cardiac Ischemia

1. Etiologic considerations in HSCT recipients
   a. Etoposide has been associated with vasospastic angina and myocardial infarction (MI).
   b. Patients with underlying CAD are at risk for cardiac ischemia and MI due to physiologic stresses associated with transplantation.
2. Management of cardiac ischemia and acute coronary syndrome is often complicated by limitations in the use of antithrombotic and anticoagulant therapies due to thrombocytopenia from HSCT conditioning therapy or from the underlying hematologic disease.
3. If percutaneous coronary intervention is indicated, strongly consider the use of bare-metal stents or balloon angioplasty alone over drug-eluting stents depending on the clinical scenario due to shorter duration of required dual antiplatelet therapy (see Chap. 13).
4. Oncology and cardiology should work closely together in managing HSCT patients with active cardiac ischemia.

23.5 Hypertension

1. Chronic immunosuppression with calcineurin inhibitors (CNIs (cyclosporine, tacrolimus)) is the mainstay of therapy for prevention of graft-versus-host disease (GVHD).
2. CNI-associated HTN occurs in 15–50 % of patients and typically develops within a month of starting therapy.
3. The treatment of choice is calcium channel blockade which reduces peripheral vascular resistance (including the renal arteriolar constriction associated with CNIs) and lowers blood pressure by causing direct vasodilation in the peripheral arteries of the vascular smooth muscle.
   a. Nifedipine XL (Adalat CL) 30–60 mg po daily
   b. Amlodipine (Nirvase) 2.5–10 mg po daily

4. Posterior reversible encephalopathy syndrome (PRES) is a neurologic complication seen occasionally in patients with CNI-associated HTN.
    a. The clinical syndrome includes headache, mental status changes, and seizures with specific radiologic features.
    b. Management includes withdrawal of the drug and aggressive blood pressure control.

23.6 Pericarditis

1. Pericarditis and accompanying pericardial effusion with or without cardiac tamponade are associated with cyclophosphamide and cytarabine therapy.
2. Chronic GVHD can involve the pericardium with resultant pericardial effusion, cardiac tamponade, constrictive pericarditis, or effusive–constrictive pericarditis.
3. Cardiac tamponade
    a. Increased intrapericardial pressure results in cardiac chamber compression and decreased venous return, resulting in decreased cardiac output.
    b. Clinically presents as cardiogenic shock without pulmonary edema.
    c. Beck's triad
        i. Distant heart sounds
        ii. Increased JVP
        iii. Hypotension
    d. Pulsus paradoxus is present with a decrease in systolic pressure ≥10 mmHg with inspiration.
        i. Exaggeration of normal physiology with inspiration causing a decrease in intrapericardial and right atrial pressures, increasing right-sided venous return and right ventricular size.
        ii. Due to increased ventricular interdependence, increased right-sided filling is at the expense of decreased left ventricular filling, resulting in decreased left ventricular stroke volume and blood pressure.
    e. Diagnosis is made by clinical manifestations and presence of pulsus paradoxus.
    f. Echocardiographic findings include
        i. Pericardial effusion.
        ii. Dilated inferior vena cava (IVC).
        iii. Diastolic collapse of the right-sided cardiac chambers.
        iv. Respirophasic changes in transvalvular velocities are supportive.
    g. Treatment
        i. Intravascular volume

   ii. Inotropes
   iii. Pericardiocentesis

4. Constrictive pericarditis

   a. Stiff pericardium limits diastolic filling.
   b. Clinically presents as right-sided > left-sided heart failure.
   c. Physical exam

      i. Increased JVP with a prominent y descent
      ii. Pericardial knock
      iii. Kussmaul's sign (increased JVP with inspiration)

   d. Diagnosis

      i. Suggested by clinical manifestations and echocardiographic findings of a "septal bounce."
      ii. Thickened pericardium can also be seen on echocardiogram, computed tomography (CT), or magnetic resonance imaging (MRI).
      iii. Definitive diagnosis is established by cardiac catheterization.

   e. Primary treatment is with diuretics to manage volume status.
   f. Surgical pericardiectomy is reserved for cases that have failed conservative management, although outcomes are generally poor.
   g. Effusive–constrictive pericarditis is an uncommon pericardial syndrome with features of both pericardial effusion with cardiac tamponade and constrictive pericarditis.

23.7 Effects of Radiation Therapy

1. Radiation therapy can lead to the accelerated development of CAD.

   a. Both endovascular proliferation and accelerated atherosclerosis appear to be involved in the disease process.
   b. Ostial lesions are common, with the left anterior descending artery most frequently involved due to its location.
   c. Management of radiation-associated CAD is similar to conventional treatment for ischemic heart disease, although coronary artery bypass surgery may be more difficult because of prior irradiation to the surgical field.

2. Radiation therapy can cause fibrotic changes to the heart valves and valvular heart disease.

   a. Regurgitant lesions are more common than stenotic lesions.
   b. Left-sided valves are more commonly affected.

3. Mediastinal irradiation can cause acute pericarditis, subacute and chronic pericardial effusions, constrictive pericarditis, and, rarely, cardiac tamponade.

   a. The right side of the heart is more frequently involved.

4. Radiation therapy can cause myocardial fibrosis and small-vessel ischemic disease, leading to a spectrum of sequelae ranging from diastolic dysfunction to restrictive cardiomyopathy.
5. In restrictive cardiomyopathy, decreased myocardial compliance leads to increased end-diastolic pressures despite normal end-diastolic volumes. This causes increased systemic and pulmonary venous pressures.

    a. Clinically, restrictive cardiomyopathy presents as right-sided > left-sided heart failure with more peripheral edema and less dyspnea. Patients can be "refractory" to diuresis.
    b. Physical exam findings can include increased JVP, Kussmaul's sign, S3 and S4, hepatomegaly, ascites, and peripheral edema.
    c. Echocardiographic findings of biatrial enlargement and abnormal diastolic parameters are suggestive.
    d. Definitive diagnosis is established by hemodynamics on cardiac catheterization.
    e. Management is with gentle diuresis, heart rate control, and maintenance of sinus rhythm.
    f. Tachyarrhythmias lead to significant decreases in ventricular filling and are poorly tolerated.

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