Chapter 23
Cardio-oncology

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Introduction

- As cancer survivorship continues to improve due to advancements in treatment and screening, a large number of cancer survivors are entering the population [1]. Many of these individuals are subject to cardiovascular (CV) complications, which are critical for the hospitalist to be aware of both at the time of, and years after, therapy [2].

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Screening and Prevention

- Obtain complete history and physical exam detail, including baseline clinical assessment based on established risk factors and anticipated cancer treatment [3].
- Cardiac risk factor optimization for all patients [4].
- Consider baseline assessment of left ventricular ejection fraction (LVEF) based on risk factors and anticipated cancer treatments [5].
- If there is baseline left ventricular dysfunction, engage cardiology and oncology providers regarding selection of chemotherapy options with lower risk of cardiotoxicity or additional cardioprotective drugs (e.g., beta blocker or angiotensin-converting enzyme inhibitors (ACE-i)) [4, 6].

Cardiac Toxicities of Cancer Therapies

Heart Failure

- Myocardial dysfunction can present early after exposure or after several years due to myocardial injury that occurred at the time of oncological therapy [7–9].
- Cardiotoxicity is defined as > 10% point decrease of LVEF to a value below the lower limit of normal (usually LVEF <50%) by echocardiography or nuclear cardiac imaging (MUGA). A > 15% relative percentage reduction from baseline of global longitudinal strain (GLS) can also suggest cardiotoxicity.

Clinical Pearl
Global longitudinal strain measured by echo may help detect more subtle myocardial dysfunction than monitoring for changes with LVEF.

- Chemotherapies associated with myocardial dysfunction, as well as incidence of LV dysfunction associated with each agent, are presented in Table 23.1 [3].
- Screening for detection of cardiotoxicity includes cardiac imaging through echocardiography, nuclear imaging, cardiac magnetic resonance imaging, or through biomarkers (i.e., brain natriuretic peptide, troponin) [7, 10–12].
- Timing and frequency of monitoring depend on specific treatment, cumulative dose of chemotherapy, duration of therapy, and patient's baseline CV risk [3].
- Of note, LV dysfunction with immunotherapies, such as the anti-*HER2* monoclonal antibody trastuzumab, is usually reversible with interruption of chemotherapy and treatment with heart failure therapies; rechallenge is often well tolerated. This is *in contrast* to the cardiotoxicity associated with anthracyclines, which often leads to an irreversible dilated cardiomyopathy.

Table 23.1 Chemotherapies associated with myocardial dysfunction

Agents associated with myocardial dysfunction (incidence % of LV dysfunction)
Anthracyclines – dose-dependent effect [e.g., doxorubicin (3–48%), idarubicin (5–18%), epirubicin (0.9–11.4%), mitoxantrone (2.6%)]
Alkylating agents [e.g., cyclophosphamide (7–28%), ifosfamide (0.5–17%)]
Antimetabolites [e.g., clofarabine (27%)]
Antimicrotubule agents [e.g., docetaxel (2.3–13%), paclitaxel (<1%)]
Monoclonal antibodies [e.g., *anti-HER2*: trastuzumab (1.7–20.1%), pertuzumab (0.7–1.2%); *anti-VEGF:* bevacizumab (1.6–4%)]
Small molecule tyrosine kinase inhibitors [e.g., sunitinib (2.7–19%), sorafenib (4–8%), dasatinib (2–4%), imatinib (0.2–2.7%)]
Proteosome inhibitors [e.g., carfilzomib (11–25%), bortezomib (2–5%)]
Immune checkpoint inhibitors – associated with myocarditis in 1.1%

- Immune checkpoint inhibitors (pembrolizumab, nivolumab, ipilimumab, tremelimumab, atezolizumab, avelumab, durvalumab) have an uncommon but severe association with myocarditis presenting within 3 months of starting therapy [13]. Patients presenting with this require cessation of the agent, high-dose steroids, and urgent cardiology/cardio-oncology consultation.

Clinical Pearl
Immune checkpoint inhibitor myocarditis is associated with a poor prognosis. Keep a high index of suspicion and treat early.

- If LV dysfunction or heart failure occurs during therapy, patients are likely to benefit from traditional heart failure management like ACE-i/ARB and beta-blocker therapy [6]. Recommend risk-benefit discussion with cardiology and oncology provider regarding interruption of cancer therapy or adjustment of chemotherapeutic strategy [5].
- In addition to managing overall cardiovascular risk, specific strategies to reduce chemotherapy-induced cardiotoxicity can vary by agent.
  - For anthracyclines and analogs, limiting cumulative dose, altering delivery system (e.g., liposomal doxorubicin) and continuous infusions, use of dexrazoxane with anthracyclines to reduce anthracycline toxicity in appropriate patients, cardioprotective medications (ACE-i/ARBs, beta-blockers, statins), and aerobic exercise can reduce the risk of cardiotoxicity.
  - For trastuzumab, cardioprotective medications (ACE-i/ARBs) are an important consideration [3].

Coronary Artery Disease/Therapy-Related Ischemia

- Myocardial ischemia can occur through a number of mechanisms from cancer therapies, including vasospasm, endothelial injury, acute arterial thrombosis, or through premature atherosclerosis [14–16].
- Therapies associated with myocardial ischemia are listed in Table 23.2 [14, 15, 17–20].
- Baseline screening for preexisting CVD is important as preexisting CVD increases the risk of developing treatment-related CVD [16].
- For patients who develop signs or symptoms of ischemia on cancer therapy, in particular pyrimidine analogs (e.g., 5-FU, capecitabine), consider withholding treatment and referral to cardiology for evaluation and discussion with oncology regarding the risk benefit of continued use given the high rates of symptom recurrence [3, 14, 21].
- Additionally, patients treated with radiation therapy can develop premature atherosclerotic disease. Consensus documents suggest regular screening beginning 5–10 years after receiving radiation therapy [22].
- Management with antiplatelets and anticoagulants is particularly challenging in this population, given the prevalence of treatment-related thrombocytopenia [23]. An individualized risk-benefit discussion is recommended.

Table 23.2 Therapies associated with myocardial ischemia

Therapy	**Mechanism of ischemia**
Fluoropyrimidines (e.g., 5-FU, capecetabine, gemcitabine)	Endothelial injury, vasospasm
Cisplatin	Procoagulant, direct endothelial toxicity
VEGF inhibitors (bevacizumab, sorafenib, sunitinib)	Endothelial injury, arterial thrombosis, vasospasm
Radiotherapy	Endothelial injury, plaque rupture, thrombosis

Clinical Pearl

- When possible, avoid premature/unnecessary cessation as this may affect cancer curability. In addition to optimizing preexisting cardiovascular disease/risk factors for patients receiving fluoropyrimidines, screening treadmill may not be sufficient, and coronary CT angiogram or left heart catheterization should be considered. Coronary spasm due to fluoropyrimidines is usually reversible but usually recurrent upon reexposure if not treated with nitrates-/calcium-channel blockers

Valvular Disease

- Radiation therapy can be associated with fibrosis and calcification of the aortic root or cardiac valves [16, 20, 24].
- Echocardiography is the imaging test of choice for assessing for valvular disease, though cardiac MRI or computed tomography (CT) may also be used [25, 26].
- If valve repair is required, surgery is often challenging due to fibrosis and impaired wound healing. Transcatheter options may be a suitable alternative [27].

Arrhythmia

- Patients treated with chemotherapy can experience a number of arrhythmias during their treatment course, including tachyarrhythmias or bradyarrhythmias and conduction disturbances [28].
- QT prolongation has been associated with arsenic trioxide and tyrosine kinase inhibitors, in particular vandetanib [29–31]. Management consists of correction of any electrolyte abnormalities (hypocalcemia, hypokalemia, hypomagnesemia) and avoidance or withdrawal of any QT-prolonging medication.

- Conduction disturbances, including complete heart block, have been noted with paclitaxel and thalidomide [32].
- Atrial fibrillation/flutter (AF/AFL) can occur due to comorbidities and malignancy, as well as ibrutinib [33]. Management of this rhythm generally requires anticoagulation, though this can be challenging in this population due to thrombocytopenia.

Arterial Hypertension

- Arterial hypertension can be associated with VEGF inhibitors [34]. Early and aggressive management is warranted with ACE-i/ARB, beta-blocker, or dihydropyridine calcium channel blocker to avoid CV complications, such as heart failure [35].
- If blood pressure remains uncontrolled, the VEGF inhibitor should be held or reduced until blood pressure is adequately controlled (<140/90 mmHg or lower in case of overt proteinuria), at which point the VEGF inhibitor can be restarted [31, 35].

Thromboembolic Disease

- Malignancy contributes to a pro-thrombotic state, placing cancer patients at risk for both arterial and venous thrombosis [36].
- Low molecular weight heparin is preferred currently due to lower rates of recurrent venous thrombosis in those patients who are able to be anticoagulated (CLOT, 2003) [37]. Direct oral anticoagulants are being studied within this population [38]. If recurrence of thrombosis occurs despite therapy, the provider can consider adjusting anticoagulation strategy or consider placement of an inferior vena cava filter [39].

Peripheral Vascular Disease and Stroke

- Severe atherosclerotic and non-atherosclerotic peripheral arterial disease can occur with nilotinib, ponatinib, or *BCR-ABL* tyrosine kinase inhibitors [40].
- Ischemic stroke has also been associated with head and neck radiotherapy [41, 42].
- Risk factor control is critical. In cases of severe PAD, the decision for revascularization should be individualized with multidisciplinary input from cardio-oncology, vascular surgery, and hematology/oncology [43].
- Patients irradiated for head and neck cancer are at higher risk for developed cerebrovascular disease following radiation therapy [44].

Pulmonary Hypertension

- Pulmonary hypertension can occur following dasatinib therapy, stem cell bone marrow transplantation, or alkylating agent therapy (due to veno-occlusive disease) [45, 46].
- Baseline echocardiogram should be considered prior to dasatinib therapy [47].
- Signs of elevated pulmonary artery pressure may require cardiology or a pulmonary hypertension team assessment, as etiology of pulmonary hypertension may affect therapy

Key Learning Points

- The CV effects of cancer and cancer-related therapies are a challenging reality of the treatment of these conditions.
- There should be a particular emphasis on screening and optimization of cardiac risk factors prior to receiving potentially cardiotoxic treatments.
- It is important to recognize that the CV effects can occur early or years after oncological treatment.

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