Cardiovascular Toxicity of Biologic Agents for Cancer Therapy

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This review will focus on newer FDA-approved targeted therapies associated with type II chemotherapy-related cardiac dysfunction, or generally reversible cardiotoxicity, and will provide the latest information on the incidence and clinical spectrum of cardiotoxicity associated with each therapy, modifiable risk factors where known, and the mechanisms of cardiotoxicity.

Introduction

Cardiovascular safety has been one of the most challenging aspects of drug development. The uncertainty of the reversibility and long-term safety of anticancer agents has complicated decision making with regard to treatment regimens. Even targeted therapies that were once considered less toxic have now been shown to affect the cardiovascular system in ways that require further investigation. The emerging field of cardio-oncology recognizes these toxicities, and has developed strategies to prevent or minimize cardiovascular toxicity and prevent long-term effects.

The National Cancer Institute broadly defines cardiotoxicity as “toxicity that affects the heart,” while the Cardiac Review and Evaluation Committee specifically defines drug-related cardiotoxicity as one or more of the following:

- Cardiomyopathy, either global or more severe in the septum, and resulting in a reduction in left ventricular ejection fraction (LVEF).
- Symptoms associated with congestive heart failure (CHF).
- Signs associated with CHF (such as tachycardia).
- A reduction in LVEF from baseline that is in the range of ≥ 5% to < 55% with accompanying signs or symptoms of CHF, or a reduction in LVEF in the range of ≥ 10% to < 55%, without accompanying signs or symptoms.

Cardiotoxicity can develop in an acute, subacute, or chronic manner.[1] There are two types of chemotherapy-related cardiac dysfunction (CRCD): type I and type II. Type I CRCD is more likely to cause irreversible myocyte destruction, leading to clinical CHF, and is associated with the traditional anticancer therapies, such as anthracyclines, alkylating agents, and antimicrotubule agents. While the cardiotoxicities of these agents have been well demonstrated, investigators are now looking into host susceptibility to anthracycline-related cardiomyopathy based on genotype to help risk-stratify patients.[2] A new type of cardiac dysfunction, type II CRCD, has also been identified. Type II CRCD was first reported with trastuzumab, although more recently it has been associated with newer targeted therapies, including vascular endothelial growth factor (VEGF) inhibitors and kinase inhibitors. Type II CRCD may lead to a temporary loss of cardiac contractility (for example, cardiac stunning). Type II CRCD has a broad range of incidence and severity, and is more likely to be reversible.[3,4]

This review will focus on newer US Food and Drug Administration (FDA)-approved targeted therapies associated with type II CRCD, or generally reversible cardiotoxicity, and will provide the latest information on the incidence and clinical spectrum of cardiotoxicity associated with each therapy, modifiable risk factors where known, and the mechanisms of cardiotoxicity.[5] Specific therapies for the treatment of type II CRCD are currently controversial and under review; however, these will be discussed briefly as well.

Cardiotoxicities of Targeted Agents

HER2-targeted agents

Trastuzumab. Trastuzumab is one of the most studied targeted therapies associated with cardiac toxicity. It is a humanized monoclonal antibody that binds to the extracellular domain of human epidermal growth factor receptor 2 (HER2, or ErbB2) and inhibits proliferation of malignant cells.
Trastuzumab is administered in 20% to 30% of patients with HER2-positive breast carcinoma.[6] Four large multicenter randomized controlled trials have shown a reduction in the recurrence of malignancy and death in patients with HER2-positive early breast cancer who were treated with trastuzumab and an anthracycline, cyclophosphamide, or paclitaxel.[7] However, trastuzumab use is limited by its association with type II CRCD.

The degree of cardiac damage induced by trastuzumab is highly variable. Cardiotoxicities range from asymptomatic LV dysfunction to severe symptomatic CHF.[7] Other cardiac complications reported in a prospective study by Piotrowski et al included asymptomatic right and left bundle branch blocks and new T-wave inversions on electrocardiogram (ECG), although no evidence of ischemia was seen on nuclear stress testing or echocardiography.[7] In a 2002 retrospective chart review by Seidman et al, the incidence of cardiotoxicity was highest in patients who received both trastuzumab and anthracyclines (27%), compared with trastuzumab and paclitaxel (13%) or trastuzumab alone (3.0%–7.0%).[8] A meta-analysis of adjuvant trastuzumab therapy in patients with ErbB2/HER2-positive breast cancer reported a 2.5-fold higher likelihood of cardiotoxicity with trastuzumab therapy compared with no adjuvant trastuzumab therapy.[9] Symptoms usually resolve within 6 weeks after discontinuation of trastuzumab.[10]

There appears to be increased cardiac morbidity in patients with coexisting cardiovascular disease and cardiac risk factors. Patients who have received previous cardiotoxic treatments, including anthracyclines and mediastinal irradiation, or who have impaired LV systolic function after previous therapy, are at increased risk.[11] Patients who are treated with trastuzumab after an anthracycline are also at higher risk for CHF, suggesting that trastuzumab may exacerbate anthracycline-related cardiac damage.[12-14] Concurrent administration of trastuzumab with chemotherapy (as opposed to sequential administration) may also be associated with increased cardiotoxicity.[15]

The likely pathomechanism of trastuzumab-related cardiac damage involves HER2 signal blockade with ErbB2 inhibition. ErbB2 facilitates cellular response to stress, growth promotion, and anti-apoptotic pathways within cardiomyocytes; therefore, inhibition of ErbB2 impairs these processes. Trastuzumab may also impair calcium homeostasis within cardiomyocytes and reduce the repair of oxidative damage within the myocardium caused by anthracyclines or other antineoplastic agents.[11]

While angiotensin-converting enzyme (ACE) inhibitors and beta-blockers are conventional therapies for CHF, they may also be specifically effective for the treatment of cardiotoxicity caused by trastuzumab. Animal studies have shown that ACE inhibitor therapy may reduce interstitial fibrosis and oxidative stress, improve intracellular calcium handling, and alter gene expression; this last effect helps with cardiomyocyte metabolism and mitochondrial function in patients who develop anthracycline-induced cardiotoxicity.[16-19] ACE inhibition may provide similar mechanisms of support in patients who develop trastuzumab-induced cardiotoxicity. There has been speculation that angiotensin receptor blockers may also be beneficial in preventing trastuzumab cardiotoxicity. Angiotensin is a downregulator of the ErbB system, which, as noted above, plays a pivotal role in cardiac protection. Thus, there is ongoing investigation into whether angiotensin receptor blockers may prevent trastuzumab-related cardiac injury by allowing for appropriate ErbB cascade signals that protect against cardiac injury within cardiomyocytes.[20]

Certain beta-blockers may also be useful in activating ErbB-related cardioprotective mechanisms. Carvedilol, alprenolol and nebivolol have been shown to initiate the ErbB-mediated prosurvival mitogen-activated protein kinase (MAPK)/ERK1/2 pathway, which may attenuate trastuzumab-induced cardiotoxicity in a manner similar to that of ACE inhibitors, mentioned above.[21,22] Dual therapy with beta-blockers and ACE inhibitors has been associated with LVEF recovery within 12 months, although large randomized clinical trials are needed to determine the benefit of these medications compared with placebo, as well as the utility of pharmacologic prophylaxis with beta-blockers and/or ACE inhibitors.[23,24]

**Pertuzumab.** While trastuzumab is used as monotherapy for the treatment of HER2-positive breast cancer, there have been recent studies suggesting that dual antibody therapy may provide a more comprehensive HER pathway blockade in patients with locally recurrent or metastatic HER2-positive adenocarcinoma. Pertuzumab is a humanized monoclonal antibody that inhibits the HER heterodimer that binds to the HER2 dimerization domain, thereby preventing the interaction of HER2 with other HER family members. Dual antibody therapy has shown promising activity in phase II studies of patients with HER2-positive breast cancer.

In a 2012 study by Baselga et al, patients with HER2-positive metastatic breast cancer were randomized to dual antibody therapy plus docetaxel vs trastuzumab and placebo plus docetaxel. The addition of pertuzumab did not appear to affect the cardiac toxicity of the backbone regimen of...
trastuzumab plus docetaxel. LV systolic dysfunction was actually higher in the control group than in the pertuzumab group (8.3% vs 4.4%), as was the rate of grade 3 or higher LV systolic dysfunction (2.8% in the control group vs 1.2% in the pertuzumab group). Furthermore, of the patients who had baseline assessments of their LVEF, only 3.8% of those who received pertuzumab experienced a decline of > 10% from baseline that resulted in an LV ejection fraction of < 50%, compared with 6.6% in the control group.[25] Phase III studies that are now underway will yield further information regarding the cardiac safety of dual antibody therapy.

**Lapatinib.** Lapatinib is a tyrosine kinase inhibitor that targets both the epidermal growth factor receptor (EGFR, or ErbB1) and HER2 and that can be used in the treatment of HER2-positive metastatic breast carcinoma.[26] The cardiac toxicity of lapatinib was studied in a large retrospective chart review of 3,689 patients by Perez et al in 2008; the review showed a 1.6% incidence of cardiac events. In this study, cardiac events included symptomatic CHF or an asymptomatic decrease in LVEF of > 20% relative to the patient’s baseline or to below the institution’s lower limit of normal.[27] Only 0.2% of the patients who experienced a cardiac event developed symptomatic CHF. Cardiac events were mostly reversible, with patients demonstrating partial or full recovery of cardiac function in a mean of 7.3 weeks.[27] The reversible nature of lapatinib-induced cardiotoxicity suggests a cellular mechanism of dysfunction, which is to say a type II cardiotoxicity. Lapatinib-induced cardiotoxicity may result from an inability of myofibril contractile elements to coordinate their activity. The reduced incidence of cardiac events associated with lapatinib compared with trastuzumab may be due to lapatinib-induced AMP-activated protein kinase (AMPK) activity, which increases ATP production and thus protects cardiomyocytes against apoptosis induced by tumor necrosis factor α (TNFα) and other cytokines that can induce cardiomyopathy.[4]

**VEGF-targeted agents**

Treatment with angiogenesis inhibitors, including bevacizumab, sunitinib, and sorafenib, plays a key role in anticancer therapy. VEGF is known to induce angiogenesis, cause endothelial cells to proliferate, and protect endothelial survival.[26] VEGF is produced by tumor cells and therefore has become a target of modern antineoplastic therapy.

**Bevacizumab.** Bevacizumab is a humanized recombinant monoclonal antibody that binds to VEGF and inhibits downstream signaling. It is used in the treatment of several advanced solid carcinomas, including breast, lung, colorectal, and renal carcinomas.[28] VEGF plays a significant role in vascular homeostasis, the disruption of which, secondary to bevacizumab, may lead to hypertension (HTN). HTN develops in 22% to 36% of patients, of whom 5.0% may develop severe HTN.[29,30] Hypertensive crises associated with encephalopathy and subarachnoid hemorrhages have also been reported.[29] The risk of HTN is dose-dependent, with patients treated with higher doses having a 7.5× increased chance of HTN developing.[31]

Other adverse cardiac events associated with bevacizumab therapy include CHF and arterial thromboembolic events. CHF has been reported in 2.0% to 4.0% of patients, with a higher incidence in patients who have been pretreated with an anthracycline or who have received prior radiation to the mediastinum.[29] In a 2008 study by Miller et al, patients with breast cancer receiving adjuvant therapy were randomized to receive bevacizumab either concurrently or sequentially with an anthracycline. A total of 9 out of 226 patients developed CHF with an LVEF of < 40%, although only 2.0% (n = 2) experienced symptoms.[32] Patients receiving bevacizumab are also at increased risk for stroke, myocardial infarction, coronary disease, and cardiac death.[33] Several mechanisms have been proposed as the cause of bevacizumab-induced cardiotoxicity. HTN may be a result of VEGF antagonism that causes inhibition of endothelial nitric oxide synthase. Reduced endothelial nitric oxide leads to vasoconstriction and a decrease of sodium excretion.[34] Vascular rarefaction with a subsequent increase in peripheral vascular resistance is another possible mechanism.[35] The pathogenesis of CHF is likely related to HTN, a decrease in myocardial capillary density, cardiac fibrosis, and global contractile dysfunction.[29] Thromboembolic events may be due to a decrease in the regenerative capability of endothelial cells, which leads to defects in the interior vascular lining, exposure of subendothelial collagen, and activation of tissue factors.[11]

**Sunitinib and sorafenib.** Sunitinib and sorafenib are tyrosine kinase inhibitors of VEGF and have been associated with HTN, intracranial hemorrhage, and CHF. The incidence of HTN is estimated at 15% to 47% in patients treated with sunitinib and 17% to 42% in patients treated with sorafenib.[36-38] The degree of HTN has been described as a rise in systolic blood pressure of 20 to 30 mm Hg and a rise in diastolic blood pressure of 9 to 17 mm Hg.[30,36] Patients may also develop CHF after treatment with sunitinib or sorafenib; sunitinib carries a particularly high risk of CHF (8.0%
to 12.5%), with a decrease in LVEF of 1.5% to 2.0% after each cycle of treatment.[36,39] Risk factors associated with LV dysfunction include prior cardiac disease and pre-existing HTN.[36]

Much like bevacizumab, sunitinib and sorafenib have direct effects on the vasculature; they result in HTN caused by endothelial dysfunction, dysfunctional nitric oxide metabolism, and vascular rarefaction.[30] Sunitinib also destroys pericytes, which wrap around blood vessels and are essential for blood vessel formation and maintenance. Destruction of these pericytes leads to blood vessel hyperperfusion and hemorrhage, which has made pericytes a new target of antiangiogenic therapies. Recent studies in mouse models suggest that thalidomide protects pericyte survival and function, and may reduce sunitinib-induced cardiotoxicity without affecting its anticancer properties.[40] CHF may occur as a result of direct cardiomyocyte mitochondrial damage and cytochrome-C–induced apoptosis.[36] Sunitinib therapy may also compromise myocyte energy homeostasis and inhibit the compensatory up-regulation of AMPK, which is important in maintaining the favorable myocardial energetics that reduce cell death.[41,42] Sorafenib has also been shown to increase the susceptibility of cardiomyocytes to pathologic stress by impairing an alternate pathway—prosurvival ERK signaling via RAF inhibition.[43] Further evaluation is needed to elucidate the wide array of kinases and intracellular pathways affected by tyrosine kinase inhibitors.

ACE inhibitors and beta-blockers have been shown to improve myocardial energetics and therefore may attenuate the degree of cell death that results from sunitinib-induced apoptosis.[42] Also, metformin may enhance AMPK activity, and it has been shown in animal models to prevent stress-induced LV dysfunction.[44] There is ongoing investigation of the use of metformin in humans to prevent VEGF inhibitor–induced cardiotoxicity. Alpha-adrenergic receptor agonists, such as phenylephrine, have also been shown to reduce sorfenib-induced cell death via ERK activation. Although alpha agonists are not conventionally used in the management of cardiomyopathy, the data suggest that certain beta-blockers that enhance ERK activity may be used for the treatment of sorafenib-induced cardiotoxicity.[19,43]

Other tyrosine kinase inhibitors

**Imatinib.** This competitive tyrosine kinase inhibitor of the BCR-ABL enzyme is used most notably for the treatment of Philadelphia chromosome–positive chronic myeloid leukemia (CML). Treatment with imatinib may cause CHF in approximately 2.0% of patients. There have also been reports of peripheral edema, pleural effusions, and pericardial effusions in 4.0% to 5.0% of patients.[11] The physiologic mechanism of the drug’s cardiotoxicity is similar to that of sunitinib and involves mitochondrial damage and cell death.[45]

**Dasatinib.** Dasatinib is FDA-approved for the treatment of chronic-phase Philadelphia chromosome–positive CML, chronic-phase CML with resistance to or intolerance of prior therapy, and CML and Philadelphia chromosome–positive acute lymphoblastic leukemia (ALL) with resistance to or intolerance of prior therapy. Most patients in the clinical trials for dasatanib were treated with a dose of 70 mg twice daily. In four single-arm multicenter studies, the most common side effect reported was fluid retention, seen in approximately 50% of patients. Nine percent of those patients experienced grade 3 or 4 fluid retention. Cardiac events observed included QTc prolongation, myocardial infarction, and CHF with LV dysfunction. Dasatinib prolonged the QTc interval by an average of 3 to 6 ms, although 2.9% of patients had an increase in their baseline QTc interval of > 60 ms, and 0.7% of patients experienced a QTc interval of > 500 ms. No relationship between QTc interval and cumulative exposure was seen. CHF or ventricular dysfunction was seen in 4% of patients, with a median time of 19 days from the start of the study drug to clinical detection of ventricular dysfunction. Half of patients who developed CHF or LV dysfunction had histories of cardiovascular disease. Of the cardiovascular events reported, fluid retention appeared to be one of the primary reasons that patients required dose reduction or interruption of therapy.[46]

**Nilotinib.** Nilotinib is an orally bioavailable inhibitor of the tyrosine kinase activity of ABL1 and the BCR-ABL1 fusion protein. It has improved target specificity and potency compared with imatinib, and is used for the treatment of patients with chronic- or accelerated-phase CML who are resistant to or intolerant of other therapies. QTc prolongation has been seen in early phase II and phase III studies with nilotinib. In a phase II trial, eight patients (2.5%) had a > 60 ms change from baseline in QTc interval, and four patients (1.2%) had a post-baseline QTc interval of > 500 ms.[47] In 2012, Larson et al published an international, open-label, randomized study comparing the efficacy and safety of nilotinib vs imatinib in patients with newly diagnosed Philadelphia chromosome–positive CML in chronic phase. Seven patients receiving nilotinib were diagnosed with peripheral arterial occlusive disease (PAOD) during the study, while no PAOD events were seen in the imatinib arm. Six of the affected patients had pre-existing risk factors and no patient discontinued the study as a result of
the PAOD. Ischemic heart disease was also more frequent with nilotinib than with imatinib (7.2% vs 1.1%, respectively). Approximately 50% of the ischemic heart disease events occurred between 2 and 3 years on the study. Three patients receiving nilotinib discontinued the study drug as a result of ischemic heart disease. No patients receiving nilotinib had a QTc interval of > 500 ms or an LVEF of < 45% during treatment.[48]

**Ponatinib.** Ponatinib is a kinase inhibitor used in the treatment of CML in chronic, accelerated, or blast phases or in adults with chronic-, accelerated-, or blast-phase CML for whom no other tyrosine kinase therapy is indicated. It is also used for T315I-positive, Philadelphia chromosome-positive ALL, or in patients with Philadelphia chromosome–positive ALL for whom no other tyrosine kinase inhibitor therapy is indicated. HTN is one of the most common vascular side effects of ponatinib, although there are several major cardiovascular toxicities that have significantly limited the use of this agent. In a phase II trial of ponatinib for Philadelphia chromosome–positive leukemias, both arterial and venous thrombotic events were observed. Cardiovascular, cerebrovascular, and peripheral vascular events were reported in 7.1%, 3.6%, and 4.9% of patients, respectively, although only a percentage of these adverse events were thought to be drug-related. Two patients discontinued ponatinib because of a vascular event. Approximately 55% of patients had a history of ischemic disease at enrollment, and 95% had one or more modifiable risk factors (HTN, diabetes mellitus, hyperlipidemia, or obesity) with or without a history of ischemic disease, nonischemic cardiac disease, or venous thromboembolism.[49] In October 2013, the FDA suspended the marketing and sales of ponatinib because of the risk of life-threatening blood clots and severe narrowing of blood vessels. Arterial and venous thrombosis and occlusions, as well as CHF, are listed in the boxed warning on the manufacturer’s website. Arterial and venous vascular events have occurred in at least 27% of ponatinib-treated patients; these events have included fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. CHF has been reported in 8% of patients receiving ponatinib. Although the FDA has suspended the use of ponatinib, it may be continued for appropriate patients for whom no other treatment is available, under an emergency Investigational New Drug application.

**Monoclonal antibodies**

**Alemtuzumab.** This anti-CD52 humanized immunoglobulin G1 (IgG1) monoclonal antibody is used in the treatment of hematologic malignancies. It is associated with infusion-related reactions, including hypotension, bronchospasm, and rash, which usually occur during the first week of therapy.[29] Acute coronary syndrome and LV dysfunction have also been reported with alemtuzumab therapy, although such events are rare.[50] LV dysfunction is more common in patients who have received prior cardiotoxic anticancer agents.[29]

**Rituximab.** Rituximab, a monoclonal antibody against the CD20 antigen, is used to treat patients with non-Hodgkin lymphoma and chronic lymphocytic leukemia (CLL). Most of the reactions associated with this agent are infusion-related; such reactions include orthostatic hypotension, angioedema, and bronchospasm. However, 5.0% to 6.0% of patients may develop HTN.[29,50] Less than 1.0% of patients will experience arrhythmias, angina pectoris, or sudden death related to myocardial infarction, ventricular fibrillation, or cardiogenic shock.[33]

**Cetuximab.** Cetuximab is a monoclonal antibody that binds to the human epidermal growth factor receptor and has been used in the treatment of metastatic colorectal carcinoma. There are no significant cardiac events associated with this therapy, although potentially fatal infusion reactions consisting of hypotension, bronchospasm, and urticaria may be seen in up to 3% of patients.[29]

**Histone deacetylase inhibitors**

**Vorinostat and romidepsin.** Vorinostat, also known as suberoylanilide hydroxamic acid (SAHA), and romidepsin are two histone deacetylase (HDAC) inhibitors used in the treatment of cutaneous and peripheral T-cell lymphomas (CTCL). In a phase II study of SAHA used in the treatment of refractory CTCL, hypotension and pulmonary embolism were reported in approximately 5.0% of patients.[51] Romidepsin, also known as depsipeptide, was thought to cause QTc prolongation. However, recently reported data suggest that its impact on the QT interval is minimal. Rather, romidepsin has been associated with nonspecific ST and T-wave changes in up to 75% of patients. Transient ST-segment flattening and depression appear to be the most reproducible ECG effects of the HDAC inhibitors, including romidepsin. While ST depression is most commonly associated with cardiac ischemia, subjects with ST depressions who had received romidepsin did not develop an elevation in troponins or mechanical dysfunction. The pathophysiology that gives rise to these ECG
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findings is unclear.[52]

Proteasome Inhibitors

**Bortezomib.** Bortezomib is the first therapeutic proteasome inhibitor to be approved for the treatment of multiple myeloma, Waldenström macroglobulinemia, and mantle cell lymphoma.[53,54] The proteasome is a multi-unit enzyme complex in the cell nucleus and cytoplasm that is responsible for the degradation of unnecessary or damaged intracellular proteins by proteolysis. Proteasome inhibition can target tumor cells, leading to cell death.[53] Bortezomib reversibly binds to the chymotrypsin-like catalytic site of the 20S proteasome core particle, which results in cell growth arrest and apoptosis.[55] Very few cases of bortezomib-induced cardiac toxicity have been reported in the literature, with most cases confounded by administration of an anthracycline prior to bortezomib.[54]

In a large randomized phase III study that included 669 multiple myeloma patients treated with bortezomib or high-dose dexamethasone, the incidence of cardiac events was 15% in those treated with bortezomib vs 13% in those treated with high-dose dexamethasone. No cardiac event occurred at an incidence of > 10% in either group. Two percent of patients in each group developed CHF during the study.[56] Ischemic heart disease has also been reported with bortezomib treatment, although the mechanism is unclear. One theory suggests that the inhibition of proteasome activity increases endothelial progenitor cell apoptosis, while decreasing endothelial progenitor cell proliferation and endothelial nitric oxide synthase, thus leading to coronary spasm.[57]

Immunomodulatory drugs

**Thalidomide and lenalidomide.** Thalidomide and lenalidomide are immunomodulatory drugs (IMiDs) inhibiting interleukin (IL)-6 that are commonly used to treat multiple myeloma. There have been rare reports of serious cardiac damage with these agents, although both have been associated with cardiac arrhythmias, specifically sinus bradycardia.[55,60] Most affected patients are asymptomatic; however, a pacemaker may be indicated in patients who are symptomatic or have coexisting conduction disorders.[60] Other less common adverse events associated with thalidomide include pulmonary and peripheral edema, as well as deep venous thrombosis.[11]

**Pomalidomide.** Pomalidomide is an orally bioavailable derivative of thalidomide used in the treatment of relapsed or refractory multiple myeloma. It appears to inhibit TNFα production, and enhance the activity of T cells and natural killer cells, as well as enhance antibody-dependent cellular cytotoxicity. In recent studies comparing the use of pomalidomide plus low-dose dexamethasone vs high-dose dexamethasone alone, patients who received pomalidomide were at increased risk for venous thrombosis. With thromboprophylaxis, venous thrombosis developed in 2% of patients in the pomalidomide plus low-dose dexamethasone group vs 1% of patients in the high-dose dexamethasone group. The median time to onset was reported as 4 months in the pomalidomide plus low-dose dexamethasone group and 2.3 months in the high-dose dexamethasone group. One patient in each group died of an acute venous thrombosis. Patients receiving pomalidomide are therefore encouraged to adhere to prophylactic antithrombotic measures.[61]

Cardiac Evaluation and Treatment

Data have been mounting over the last few years suggesting that a baseline cardiovascular examination coupled with close cardiovascular follow-up and management can help prevent adverse events resulting from anticancer therapy. These measures allow for immediate initiation of therapy in those patients who experience cardiovascular complications, and for exclusion of high-risk individuals whose risks of cardiovascular complications outweigh the benefits of therapy. Cardiac evaluation is highly recommended before, during, and after chemotherapy in select settings to detect subclinical cardiac damage. There are a series of diagnostic tools, including biomarkers and cardiac imaging, that can be used to assess a patient’s cardiac function. Increases in the levels of the biomarkers troponin I and myeloperoxidase offer additive data about the development of cardiotoxicity in breast cancer patients undergoing treatment with doxorubicin and trastuzumab.[62]

While there are no specific guidelines for the diagnosis and management of chemotherapy-induced cardiotoxicity, the American College of Cardiology and the American Heart Association have established therapies for cardiovascular disease that should be used to treat cancer patients with CHF.

The FDA has recommended specific monitoring parameters for cardiomyopathy to be used in conjunction with trastuzumab therapy. These require an assessment of EF prior to initiation of
therapy and at regular intervals; intervals may vary from monthly to every 3 months over the course of 12 months of treatment. While screening and surveillance echocardiograms have not been formally recommended for most of the newer targeted agents, clinical judgment should be used to determine which patients would benefit from cardiac imaging. If the EF is below the normal value of 55% or more than 10% below a previous finding on transthoracic echocardiography, then frequent monitoring via echocardiograms is recommended at appropriate intervals dependent on the severity and progression of cardiac disease. A 4-week interval between echocardiograms has been recommended if the EF is < 55% prior to the onset of therapy or if there has been an asymptomatic change in the EF of > 10%.[63] Patients who are at high risk for cardiac toxicity and those who develop cardiac toxicity should be managed by specialized cardio-oncology clinics or with close collaboration between oncologists and cardiologists.

Treatment for adults with CHF varies depending on the severity of the disease and the clinical setting (outpatient vs inpatient), but often includes loop diuretics, ACE inhibitors, or angiotensin receptor blockers and beta-blocker therapy. Specific use of ACE inhibitors and beta-blockers in the treatment of trastuzumab-, sunitinib-, and sorafenib-induced cardiotoxicity has been discussed earlier in this review. In patients with acute CHF from suspected acute myocardial ischemia, urgent catheterization and revascularization may be indicated. Advanced CHF therapies, including left ventricular assist devices and heart transplantation, may also be considered for select patients with chemotherapy-induced CHF. Further detailed management of CHF is beyond the scope of this review article.

**Conclusion and Future Directions**

As length of survival increases in patients with cancer, the cardiotoxicities associated with anticancer therapies have become a critical issue. While there have been tremendous strides in anticancer treatments that reduce unwanted side effects by providing targeted antitumor activity, adverse cardiovascular events associated with these newer therapies may limit their use if not detected in a timely manner and appropriately treated. A multidisciplinary team that involves both oncologists and cardiologists has formed to further investigate these toxicities and to develop methods to reduce modifiable risk factors, as well as prevent, detect, and treat potential cardiotoxicity. Early detection requires awareness of chemotherapy-related cardiac dysfunction, as well as appropriate pretreatment cardiac evaluation and follow-up, since many of the patients who develop adverse cardiovascular events have pre-existing cardiac risk factors or known cardiovascular disease for which they should be receiving appropriate treatment. Physicians should also be aware of other noncancer medications that may prolong the QTc interval, and which must be administered cautiously to patients receiving QTc-prolonging anticancer therapies. Future research should focus on defining cardiac risk for the newer therapies and implementing strategies to minimize this risk.

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