Chemotherapy-associated cardiomyopathy is a well known cardiotoxicity of contemporary cancer treatment and a cause of increasing concern for both cardiologists and oncologists. As cancer outcomes improve, cardiovascular disease has become a leading cause of morbidity and mortality among cancer survivors. Asymptomatic or symptomatic left ventricular systolic dysfunction in the setting of cardiotoxic chemotherapy is an important entity to recognize. Early diagnosis of cardiac injury through the use of novel blood-based biomarkers or noninvasive imaging modalities may allow for the initiation of cardioprotective medications or modification of chemotherapy regimen to minimize or prevent further damage. Several clinical trials are currently underway to determine the efficacy of cardioprotective medications for the prevention of chemotherapy-associated cardiomyopathy. Implementing a strategy that includes both early detection and prevention of cardiotoxicity will likely have a significant impact on the overall prognosis of cancer survivors. Continued coordination of care between cardiologists and oncologists remains critical to maximizing the oncologic benefit of cancer therapy while minimizing any early or late cardiovascular effects. (J Cardiac Fail 2014;20:841–852)

Key Words: Cardiotoxicity, chemotherapy, congestive heart failure.
ventricular (LV) dysfunction associated with cancer therapy. However, there remains no clear consensus on the appropriate use of these therapies in the cancer setting. We will review the current evidence relating to the early detection, treatment, and prevention of cancer therapy-associated cardiomyopathy.

Clinical Criteria for Chemotherapy-Associated Cardiomyopathy

The term “cardiotoxicity” refers broadly to any cardiovascular side effect related to cancer therapy (ie, heart failure, cardiomyopathy, arrhythmias, ischemia, valvular disease, pericardial disease, hypertension, or thrombosis). For the purposes of this review, however, cardiotoxicity will be used to refer to LV dysfunction that develops as a result of chemotherapy-induced myocardial injury. Anthracycline-induced cardiomyopathy was first described in the 1970s and was defined in early trials by the presence of clinical signs and symptoms of heart failure thought to be secondary to anthracycline exposure. The diagnosis can be confirmed by endomyocardial biopsy, which shows several characteristic findings including myofibrillar dropout, distortion and disruption of Z-lines, mitochondrial disruption, and intramyocyte vacuolization. Although it is considered to be the most sensitive and specific test for anthracycline-induced cardiomyopathy, use of endomyocardial biopsy is limited in clinical practice owing to its invasive nature.

More recently, inconsistencies in the literature on the definition and criteria for cardiotoxicity pose a major challenge to the field of cardio-oncology, especially in the context of newer targeted therapies (eg, trastuzumab) that are associated with adverse cardiac effects. In 2002 a Cardiac Review and Evaluation Committee (CREC) was formed to obtain independent and unbiased estimates of trastuzumab-associated cardiac dysfunction, and the following criteria for cardiotoxicity were proposed: (1) cardiomyopathy characterized by a decrease in cardiac LVEF (global or septal predominance), (2) symptoms of...
congestive heart failure (CHF), (3) associated signs of CHF (ie, S3 gallop, tachycardia, or both), or (4) a decline in LVEF of $\geq 5\%$ to $< 55\%$ with signs/symptoms of CHF, or decline of 10% to $< 55\%$ without symptoms. Despite this effort, significant heterogeneity exists in the criteria for cardiotoxicity in subsequent clinical trials (Table 2), leading to significant variability in the reported incidence of chemotherapy associated cardiac dysfunction.

**Imaging for Early Detection of Cardiotoxicity**

**Radionuclide Ventriculography and Echocardiography**

Measurement of LVEF is the most commonly used method to evaluate for cardiotoxicity, and a baseline LVEF is routinely obtained before the initiation of cardiotoxic chemotherapy. Repeated serial LVEF assessments are recommended in the setting of certain cardiotoxic agents, such as trastuzumab, and can also be performed as needed if signs or symptoms of CHF develop. Radionuclide ventriculography, or multiple-gated acquisition scan, has been validated as an accurate and reproducible method for LVEF estimation, but it exposes patients to $\sim 6$–$7$ mSv ionizing radiation per examination. Echocardiography is often preferred because it is a readily accessible and safe technology that does not involve the use of ionizing radiation. Although 2-dimensional (2D) echocardiography can be limited by significant variability and poor agreement with reference methods, it has significantly improved with the use of ultrasound contrast agents. In a study of 110 patients by Malm et al, LVEF by unenhanced echocardiography and cardiac MRI differed by $\geq 10\%$ in 23 patients (26%) versus 0 with contrast echocardiography. Three-dimensional (3D) echocardiography offers additional incremental benefit over 2D techniques for determination of LVEF. Moreover, among cancer patients undergoing serial monitoring of LVEF, noncontrast 3D echocardiography is feasible, accurate, and reproducible. Although some studies suggest that diastolic dysfunction may be an early sign of cardiotoxicity, the utility of diastolic function assessment during cancer treatment remains uncertain.

**Table 2. Chemotherapy-Associated Cardiomyopathy Data From Adjuvant Trastuzumab Clinical Trials**

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Imaging Modality for LVEF Determination</th>
<th>Frequency of Monitoring</th>
<th>Criteria for Withholding Trastuzumab</th>
<th>Cardiac Event Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-31</td>
<td>MUGA</td>
<td>Baseline, after AC, and at 6, 9, and 18 months</td>
<td>LVEF decrease of $\geq 16%$, or decrease of 10%–15% below the LLN (defined by each institution)</td>
<td>Discontinuation of trastuzumab in 14% of patients owing to asymptomatic decrease in LVEF; NYHA functional class III or IV heart failure or death from cardiac causes occurred in 1.3% in control vs 4% in trastuzumab arm after 7-year follow-up.</td>
</tr>
<tr>
<td>HERA</td>
<td>Echo or MUGA</td>
<td>Baseline and 3, 6, 12, 18, 24, 30, 36, and 60 months after randomization</td>
<td>Symptomatic heart failure with LVEF $&lt; 45%$, or LVEF decrease of $\geq 10%$ to $&lt; 50%$</td>
<td>During median follow-up of 3.6 years, NYHA functional class III or IV heart failure occurred in 0% of control vs 0.8% of trastuzumab group; significant decrease in LVEF occurred in 2.9% of control vs 9.8% of trastuzumab group.</td>
</tr>
<tr>
<td>N-983126</td>
<td>Echo or MUGA</td>
<td>Baseline, after AC, and at 6, 9, and 18 months</td>
<td>LVEF decrease of $\geq 16%$, or decrease of 10%–15% below the LLN (defined by each institution)</td>
<td>NYHA functional class III or IV heart failure or death from cardiac causes at 3 years: 0.3% in control vs 3.3% in concurrent trastuzumab-paclitaxel group.</td>
</tr>
<tr>
<td>FinHer</td>
<td>Echo or MUGA</td>
<td>Before chemotherapy, after FEC, and 12 and 36 months after chemotherapy</td>
<td>None</td>
<td>No patients receiving trastuzumab developed heart failure or a decline in LVEF $&gt; 10%$ to $&lt; 50%$.</td>
</tr>
<tr>
<td>BCIRG 006</td>
<td>Echo or MUGA</td>
<td>Seven time points throughout study period</td>
<td>LVEF decrease of $\geq 16%$, or decrease of 10%–15% below the LLN (defined by each institution), or decrease of $&lt; 10%$ to $\leq 6%$ below the LLN</td>
<td>NYHA functional class III or IV heart failure occurred in 0% of AC-T, 0.4% of TCH, and 2% AC-T + trastuzumab group; $&gt; 10%$ decrease in LVEF occurred in 11.2% AC-T, 9.4% of TCH, and 18.6% of AC-T + trastuzumab group.</td>
</tr>
</tbody>
</table>

NSABP, National Surgical Adjuvant Breast and Bowel Project; HERA, Herceptin Adjuvant; FinHer, Finland Herceptin; BCIRG, Breast Cancer International Research Group; MUGA, multiple-gated acquisition scan; AC, doxorubicin and cyclophosphamide; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; LVEF, left ventricular ejection fraction; LLN, lower limit of normal; NYHA, New York Heart Association; T, docetaxel; TCH, docetaxel, carboplatin, and trastuzumab.
may indicate the presence of irreversible myocardial damage. An earlier study by Ewer et al. showed that biopsy-proven abnormalities due to anthracycline cardiotoxicity correlated poorly with LVEF, suggesting that LVEF is an insensitive marker for cardiotoxicity. More sensitive and specific noninvasive markers of LV dysfunction would be useful for identifying patients at increased risk for treatment-associated LV dysfunction, thereby allowing oncologists and cardiologists to tailor the treatment regimen for optimal efficacy while minimizing cardiac toxicity.

**Myocardial Strain Imaging**

Tissue Doppler and speckle-tracking strain imaging have emerged as 2 quantitative techniques for estimating global and regional myocardial mechanical function and have the potential to detect early signs of LV dysfunction. The first description of strain was derived from tissue Doppler imaging (TDI) for assessment of regional myocardial function and was validated in an ischemia model. However, the technique is both user and angle dependent and is unable to differentiate translational motion or tethering effects from myocardial contractility. Speckle-tracking echocardiography is an angle-independent technique that uses an image-processing algorithm for analyzing motion of “speckles” or “fingerprints” within a 2D echo image, and it has replaced TDI strain as the preferred method for quantitative assessment of cardiac deformation (Fig. 1).

Several studies have evaluated the utility of strain imaging for the detection of chemotherapy-associated cardiotoxicity. Fallah-Rad et al. evaluated 42 patients with breast cancer overexpressing human epidermal growth factor receptor 2 (HER2) receiving trastuzumab in the adjuvant setting after anthracycline therapy. Within 3 months, peak global longitudinal and radial strain detected preclinical changes in LV systolic function before a decrease in LVEF observed several months later. A more recent prospective multicenter study by Sawaya et al. demonstrated that global longitudinal strain <19% was predictive of subsequent cardiotoxicity as defined by CREC criteria and was present in all patients who later developed symptoms of heart failure. Abnormalities in strain parameters can also be seen several years after a cardiotoxic exposure. This was reported in a study among 75 asymptomatic breast cancer survivors who received anthracycline with or without adjuvant trastuzumab, in which global longitudinal strain was significantly decreased in the chemotherapy group up to 6 years after therapy compared with control subjects.

Although these novel echocardiographic markers of subclinical LV dysfunction may allow for earlier detection of patients at increased risk for developing cardiotoxicity, the clinical significance of these changes remains unclear. Further studies are required to determine which patients would benefit most from this additional testing, when the testing should occur, and whether changes in these early echocardiographic markers are of sufficient clinical relevance to warrant an alteration in the oncologic treatment plan or intervention with cardioprotective medication.

**Cardiac Magnetic Resonance Imaging**

Cardiac MRI provides accurate measurements of LV dimensions and is considered to be the criterion standard with which other imaging modalities are compared for LVEF determination. Unlike echocardiography, cardiac MRI does not rely on geometric assumptions for calculating volumes and is not hindered by poor acoustic windows. As a result, it has been shown to have superior intra- and interobserver reproducibility and accuracy compared with echocardiography. The use of echocardiography and cardiac MRI for evaluation of LV structure and function was compared in 114 adult survivors of childhood cancer by Armstrong et al. Compared with cardiac MRI, 2D and 3D echocardiography were less sensitive (25% and 53%, respectively) for the detection of LVEF <50%. However, the use of a higher LVEF cutoff of <60% by echocardiography increased the sensitivity to 75% for detecting LVEF <50% by cardiac MRI. These results suggest that the prevalence of cardiotoxicity may be underestimated by 2D echocardiography compared with more sensitive volumetric measures of LVEF such as cardiac MRI.

Beyond cardiac function and remodeling, cardiac MRI can directly assess myocardial tissue characteristics that are potentially useful for the identification of cardiotoxicity during or after cancer therapy. Several studies have shown the presence of myocardial fibrosis with the detection of late gadolinium enhancement (LGE) during and soon after completion of cancer therapy, although the prevalence of LGE appears to be low (<10%) during long-term follow-up. New tissue characterization methods, such as T1 mapping, enable quantification of extracellular volumes, and preliminary studies have shown this to be elevated among patients with anthracycline-associated cardiotoxicity. Additional studies are needed to determine the role that cardiac MRI will play in the surveillance and diagnostic algorithm for cardiotoxicity. Evaluation of chemotherapy-associated cardiomyopathy and quantification of LV function are both approved indications for cardiac MRI based on the 2006 American College of Cardiology (ACC)/American Heart Association (AHA) appropriate use guidelines, but key disadvantages of cardiac MRI are high cost and limited availability of cardiac MRI scanners and trained personnel.

**Biomarkers for Prediction of Cardiotoxicity**

Cardiac biomarkers may serve a role as an alternate diagnostic tool for the detection of chemotherapy-associated cardiotoxicity. A biomarker strategy would allow for early intervention with cardioprotective medications or alteration in the cancer treatment regimen to minimize the risk
of cardiac dysfunction. Several biomarkers have been proposed, including troponin, natriuretic peptide, and C-reactive protein (CRP).

**Troponin**

Cardiac troponins T and I (TnT and TnI), long known for the important role they play in the diagnosis of acute coronary syndromes, are sensitive and specific markers for myocardial injury. Multiple studies have investigated the role of troponin as a promising biomarker for the diagnosis of chemotherapy-associated cardiomyopathy (Table 3). In one study of 204 patients receiving high-dose chemotherapy, TnI was elevated in 32% of patients and occurred >50% of the time soon after the end of drug administration. LVEF was also significantly reduced among patients with positive TnI. A follow-up study to investigate the time course of TnI elevation and its impact on clinical outcome showed that patients with negative TnI (<0.08 ng/mL), immediately and 1 month after chemotherapy, showed no reduction in LVEF and a very low incidence of cardiac events. In contrast, patients with positive TnI had a higher incidence of adverse cardiac events, consisting mostly of heart failure and asymptomatic LV

*Fig. 1. Two-dimensional myocardial strain measurement. Example of assessment of longitudinal myocardial strain in the apical 4-chamber view: (A) normal longitudinal strain in a healthy patient; (B) abnormal longitudinal strain in a Hodgkin lymphoma survivor previously treated with anthracycline chemotherapy and mediastinal radiotherapy. The colored lines represent measurements of regional myocardial deformation. The white dotted line represents the global average of all segments in each view.*
Elevated troponin may also identify those who are less likely to recover despite maximal heart failure therapy, whereas negative troponin may suggest that any incident LV dysfunction will be transient. This information could help clinicians to risk stratify patients and minimize unnecessary interruption of cancer treatment.

More sensitive troponin assays have recently been developed which allow for detection of troponin release at an earlier stage of myocyte stress. Several studies have demonstrated better diagnostic accuracy of these newer assays in the early diagnosis of acute coronary syndrome, but their role in the detection of cardiotoxicity is still unclear. Sawaya et al evaluated the utility of ultrasensitive TnI for predicting subsequent cardiotoxicity among 81 patients with HER2+ breast cancer and found that ultrasensitive TnI > 30 pg/mL combined with global longitudinal strain < 19% was associated with subsequent decline in LVEF and symptomatic CHF.

### Natriuretic Peptide

Natriuretic peptides have been studied extensively for their diagnostic and prognostic role in cardiovascular disease. Both A-type and B-type natriuretic peptides (ANP and BNP) are important for salt and water handling and are produced by the heart in response to high ventricular filling pressure, as is typically seen with heart failure. Several studies have looked at the value of both ANP and BNP levels for monitoring and/or prediction of chemotherapy-induced cardiotoxicity, but the results have been inconclusive. An early study by Suzuki et al suggested the possible role of BNP in the assessment of cardiac function after anthracycline administration for hematologic malignancies. However, other studies performed in patients of varying ages and different malignancies have failed to show an association between BNP and risk of cardiotoxicity. Daugard et al studied 107 patients receiving anthracycline for a variety of cancer diagnoses, including breast cancer, sarcoma, and lymphoma, and concluded that neither baseline levels nor a change in ANP or BNP were predictive of a change in LVEF. More recently, in a homogeneous group of 81 women with HER2+ breast cancer treated with anthracyclines followed by taxanes and trastuzumab, Sawaya et al found that elevated N-terminal pro-BNP was not predictive of subsequent LVEF decline or symptomatic heart failure.

### Table 3. Utility of Troponin as a Biomarker for Predicting Chemotherapy-Associated Cardiomyopathy

<table>
<thead>
<tr>
<th>Author</th>
<th>Criteria for Biomarker Positivity</th>
<th>Patient Population</th>
<th>n</th>
<th>Frequency of Monitoring</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broeyer et al</td>
<td>TnT ≥0.01 ng/mL</td>
<td>Recipients of doxorubicin chemotherapy</td>
<td>26</td>
<td>Before, at completion, and 24 h after chemotherapy administration</td>
<td>TnT below limit of detection in most cases</td>
</tr>
<tr>
<td>Cardinale et al</td>
<td>Tnl &gt; 0.4 ng/mL</td>
<td>Recipients of HDC</td>
<td>204</td>
<td>Before, immediately after, and 12, 24, 36, and 72 h after each cycle</td>
<td>LVEF &lt;50% observed in 19/65 (29%) TnI- and 0/139 TnI – patients (P &lt; .001) Higher cardiac event rate in patients with Tnl positivity</td>
</tr>
<tr>
<td>Cardinale et al</td>
<td>Tnl ≥0.08 ng/mL</td>
<td>Recipients of HDC</td>
<td>703</td>
<td>Before, immediately after, 12, 24, 36, and 72 h after each cycle (early TnI), and 1 month after (late TnI) last administration of HDC</td>
<td></td>
</tr>
<tr>
<td>Cardinale et al</td>
<td>Tnl ≥0.08 ng/mL</td>
<td>Early, advanced, and metastatic HER2+ breast cancer patients treated with receiving trastuzumab</td>
<td>251</td>
<td>Before and soon after each trastuzumab treatment</td>
<td>Trastuzumab-induced cardiotoxicity was more frequent in patients with elevated TnI (62% vs 5%; P &lt; .001); LVEF recovery occurred less frequently in patients with elevated TnI (35% vs 100%; P &lt; .001)</td>
</tr>
<tr>
<td>Fullah-Rad et al</td>
<td>TnT ≥0.01 ng/mL</td>
<td>HER2+ breast cancer patients receiving adjuvant trastuzumab</td>
<td>42</td>
<td>Before initiation of anthracycline, before initiation of trastuzumab, and 3, 6, 9, and 12 months after initiation of trastuzumab</td>
<td>TnT remained within normal limits for both the normal cohort and those who developed trastuzumab-mediated cardiomyopathy</td>
</tr>
<tr>
<td>Sawaya et al</td>
<td>hsTnl &gt; 0.015 μg/L</td>
<td>HER2+ breast cancer treated with anthracyclines and trastuzumab</td>
<td>43</td>
<td>Before chemotherapy and after 3 and 6 months of treatment</td>
<td>Elevated hsTnl at 3 mo is an independent predictor of later cardiotoxicity (P &lt; .02)</td>
</tr>
<tr>
<td>Sawaya et al</td>
<td>hsTnl &gt; 30 pg/mL</td>
<td>HER2+ breast cancer patients treated with adjuvant anthracyclines, taxanes, and trastuzumab</td>
<td>81</td>
<td>Before chemotherapy and after 3, 6, 9, 12, and 15 months</td>
<td>Elevated hsTnl at the completion of anthracycline therapy is predictive of subsequent cardiotoxicity</td>
</tr>
</tbody>
</table>

TnT, troponin T; Tnl, troponin I; HDC, high-dose chemotherapy; LVEF, left ventricular ejection fraction; hsTnl, high-sensitivity troponin I.
recent single-center clinical trial demonstrated that high-sensitivity CRP had a high sensitivity (92.9%) and negative predictive value (94.1%) for predicting trastuzumab-induced cardiotoxicity. \(^7^0\) Another study by Ky et al investigated the association of multiple conventional and novel biomarkers with cardiotoxicity, including growth differentiation factor 15, myeloperoxidase (MPO), placental growth factor, soluble Fms-like tyrosine kinase receptor 1, and galectin-3. \(^7^1\) Among 78 breast cancer patients treated with doxorubicin and trastuzumab, changes in TnI and MPO but not CRP were associated with subsequent cardiac dysfunction. Additional studies are needed to validate the utility of candidate biomarkers before application in clinical practice.

**Management of Cardiotoxicity**

In 2005, ACC/AHA introduced a new classification system of heart failure that emphasized the preventable nature of heart failure, and this was accompanied by recommendations to treat cardiovascular risk factors to prevent or delay the onset of heart failure. \(^7^2\) Based on this new classification system, patients with chemotherapy-associated cardiomyopathy and asymptomatic LV dysfunction are classified with stage B heart failure. According to the 2013 ACC/AHA Guideline for the Management of Heart Failure, patients with stage B heart failure should be treated with ACE-Is (Class I, Level of Evidence A) and beta blockers (Class I, Level of Evidence C). \(^7^3\) The use of therapies such as implantable cardioverter-defibrillators or cardiac resynchronization therapy for more advanced stages of heart failure should take into consideration the patient’s overall prognosis and quality of life. A proposed diagnostic and treatment algorithm for patients exposed to cardiotoxic therapy is shown in Figure 2.

Evidence supporting the use of contemporary heart failure therapies is largely based on studies in patients with ischemic or nonischemic dilated cardiomyopathies, and limited data exist regarding the treatment of patients with chemotherapy-associated cardiomyopathy. \(^7^4\)–\(^7^6\) Cardinale et al evaluated the response of anthracycline-induced cardiomyopathy to modern heart failure therapy and included 201 patients with a LVEF ≤45% \(^7^7\). Enalapril and, when possible, carvedilol were initiated at the time of detection of LVEF impairment and up-titrated to the maximal tolerated dose, and LVEF was followed serially with the use of echocardiography. A total of 85 patients (42%) normalized their LVEF, 26 patients (13%) showed an increase in LVEF of >10% but remaining <50%, and 90 patients (45%) showed <10% increase in LVEF. A short time to initiation of heart failure therapy was an important predictor of LVEF recovery. This was one of the first prospective studies to show the efficacy of ACE-Is and beta-blockers for the treatment of anthracycline-mediated cardiomyopathy, suggesting that early treatment may be important to increase the likelihood of LVEF recovery. Several questions remain unanswered, including which specific medication to use, how much, and for what duration. Additional studies are needed to address these gaps in knowledge and better inform the optimal heart failure management of chemotherapy-associated cardiomyopathy.

**Strategies for Prevention of Cardiotoxicity**

Current management strategies have relied on early detection of myocardial injury through serial monitoring of LVEF or cardiac biomarker testing during treatment, followed by temporary or permanent discontinuation of further cardiotoxic exposures. A major goal of cardio-oncology is to prevent the development of cardiotoxicity, either by modification of the cardiotoxic exposure or by initiation of cardioprotective medications. Here we review some of the preventive strategies that have been proposed.

**Chemotherapy Modification**

Anthracycline cardiotoxicity is related to cumulative dose, \(^7^8\) and cumulative doxorubicin doses should be limited to 450–500 mg/m\(^2\) in adults. However, given that the sensitivity to cardiotoxic effects of anthracycline can vary by patient, routine surveillance of cardiac function is critical for the prevention of cardiotoxicity, even at lower anthracycline dose ranges. Prolonged infusion schedules have been shown to lower the incidence of cardiotoxicity compared with bolus therapy. \(^7^9\) In a Cochrane database review of 6 randomized controlled trials in which different anthracycline dosage schedules were used in cancer patients, the rate of heart failure was significantly lower with a long infusion (≥6 h) compared with shorter (relative risk [RR] 0.27, 95% confidence interval [CI] 0.09–0.81). \(^8^0\) This strategy has not been shown to adversely affect the cancer response rate or overall survival.

Liposomal preparations of anthracyclines, first used in the early 1990s for the treatment of AIDS-associated Kaposi sarcoma, are associated with a lower incidence of cardiotoxicity compared with standard anthracycline preparations. \(^8^1\) Liposomal preparations of anthracyclines were found to be effective in a variety of malignancies, including breast cancer, ovarian cancer, and multiple myeloma, while associated with less cardiac toxicity. \(^4^,^5^,^8^2,^8^3\) Less severe cardiac changes were seen on endomyocardial biopsy among patients receiving pegylated liposomal doxorubicin compared with patients receiving non-liposomal doxorubicin. \(^8^5\) Liposomal anthracycline preparations are currently in use for the treatment of ovarian cancer and multiple myeloma.

**Dexrazoxane**

Dexrazoxane is an EDTA-like chelator that binds to iron and reduces the formation of superhydroxide radicals that can cause oxidative damage of cardiac tissue. The efficacy of dexrazoxane was recently addressed in a Cochrane database review that included 10 randomized clinical trials of 1,619 patients. \(^8^6\) The majority of patients included in the
studies were adults with advanced breast cancer treated with either doxorubicin or epirubicin, and treatment with dexrazoxane significantly reduced the incidence of heart failure (RR 0.29, 95% CI 0.20–0.41; \( P < .00001 \)). Although there have been some concerns that dexrazoxane may compromise tumor response to chemotherapy, this meta-analysis showed no significant difference in tumor response rate, progression-free survival, overall survival, adverse effects, or secondary malignant disease with dexrazoxane treatment.

The American Society of Clinical Oncology (ASCO) published guidelines in 2008 for the use of dexrazoxane in patients with breast cancer and other malignancies and recommended the following:

1. Dexrazoxane should be considered for patients with metastatic breast cancer or other malignancies who have received >300 mg/m² doxorubicin in the metastatic setting and who may benefit from continued doxorubicin therapy.
2. Dexrazoxane can be considered for patients with non-breast malignancies who have received \( \geq 300 \) mg/m² of doxorubicin-based therapy. Caution should be exercised in settings where doxorubicin-based therapy has been shown to improve survival.
3. The use of dexrazoxane in the adjuvant setting is not recommended outside of a clinical trial.
4. There is insufficient evidence to support routine use of dexrazoxane among patients with cardiac risk factors or underlying structural heart disease. Despite the current ASCO guidelines, dexrazoxane is not routinely used in clinical practice owing to continued concern regarding its interference with conventional cancer treatment. Several clinical trials are currently underway to evaluate the efficacy of dexrazoxane in other cancer patient populations.

### Prophylaxis With Cardioprotective Medications

One of the first clinical trials to investigate the role of cardioprotective medical therapy in preventing cardiotoxicity was performed by Kalay et al. In that small study, 50 patients with planned anthracycline treatment (doxorubicin or epirubicin) were randomized to 12.5 mg carvedilol once daily versus placebo. LV systolic and diastolic function was evaluated with the use of echocardiography before and after exposure to anthracycline treatment. At 6-month follow-up, patients in the control group had a significantly lower LVEF and larger LV systolic and diastolic dimensions compared with the carvedilol group. A retrospective study by Seicean et al also showed that beta-blocker use was associated with a lower incidence of heart failure among patients with breast cancer receiving anthracycline and trastuzumab therapy. One of the proposed mechanisms for the protective effect of carvedilol is its ability to reduce free oxygen radicals, which have been implicated in the pathogenesis of anthracycline-mediated toxicity. More recently, a study by Zhang et al showed that topoisomerase-II-beta plays an important role in the pathogenesis of doxorubicin-induced cardiotoxicity through the mediation of structural and functional changes in mitochondria of cardiomyocytes as well as generation of reactive oxygen species.

The role of angiotensin antagonists for the prevention of cardiotoxicity was investigated in a randomized trial by
Cardinale et al. Among patients with elevated TnI (>0.07 ng/mL) after high-dose chemotherapy, early treatment with 20 mg enalapril daily, started 1 month after chemotherapy and continued for 1 year, prevented the development of cardiotoxicity (defined as an absolute decrease in LVEF of >10% to <50%). Although the mechanism by which enalapril prevents cardiotoxicity remains unclear, it is postulated that ACE-Is block cardiotoxicity-associated renin-angiotensin system activity, reduce LV remodeling, and decrease oxidative stress. This was the first study to implement a prophylactic cardioprotective strategy among patients at high risk of cardiotoxicity with the use of a biomarker-directed approach. The Prevention of Left Ventricular Dysfunction During Chemotherapy (OVERCOME) study recently evaluated the effects of combined enalapril and carvedilol in patients with hematologic malignancies treated with intensive chemotherapy and found that LVEF did not change in the enalapril and carvedilol group but significantly decreased in those treated with placebo (P = .04). These results show that the combination of enalapril and carvedilol may be effective in preventing LV dysfunction during intensive chemotherapy and could have important clinical implications.

Statins, well known for the protective effects in patients treated for coronary artery disease, also have been investigated for their potential to attenuate cardiotoxicity. Riad et al showed that mice pretreated with fluvastatin showed improved LV function compared with untreated mice after exposure to doxorubicin. Observational data from Seicane et al also showed that statin therapy appears to be associated with a reduced risk of heart failure and cardiac-related mortality among breast cancer patients treated with anthracycline. but prospective clinical trials are needed to further evaluate any association between statin therapy and risk of cardiotoxicity.

Several clinical trials are currently underway to further investigate the efficacy of prophylactic cardioprotective medications among patients treated with cardiotoxic chemotherapy. The Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research Trial (MANTICORE 101-Breast) is a randomized trial among HER2+ early breast cancer patients to determine if periopridol or bisoprolol therapy can prevent trastuzumab-associated LV remodeling as measured by LV volume indices with the use of cardiac MRI. A similar trial sponsored by the National Cancer Institute is studying the effect of lisinopril and carvedilol on trastuzumab-induced cardiotoxicity as measured by LVEF (clinicaltrials.gov no. NCT01009918).

**Exercise Training**

Aerobic exercise training has been proposed as a non-pharmacologic therapy that may attenuate the deleterious effects of heart failure. It has been shown to correct endothelial dysfunction by both improving nitric oxide (NO) formation and endothelium-dependent vasodilation of the skeletal muscle vasculature, improve cardiac and skeletal muscle energy metabolism and function, and improve diastolic filling and increase stroke volume. All of these adaptations lead to an improvement in systolic and diastolic function with augmentation of cardiac output and increase in maximal oxygen uptake (VO_{2max}), resulting in improved exercise tolerance and decreased fatigability in heart failure. Several animal studies have investigated the effects of aerobic exercise training before and during doxorubicin therapy and shown that exercise prevents doxorubicin-induced impairments in LV function. Exercise training represents a promising strategy for prevention and/or treatment of chemotherapy-associated cardiomyopathy, but additional studies are required to better understand the mechanism of this benefit and to inform future recommendations for exercise training among cancer patients.

**Conclusion**

Given the potential interaction between cancer therapy and the cardiovascular system, cardiologists and oncologists must collaborate to ensure the best long-term clinical outcome for cancer patients. Newer targeted therapies are changing the landscape of cancer care, and the impact of cardiotoxicity on overall morbidity and mortality will increase as cancer outcomes improve. Future diagnostic strategies will likely incorporate the use of novel imaging techniques (eg, speckle-tracking strain or cardiac MRI) and biomarker testing to identify patients with early or subclinical signs of cardiotoxicity. Translational studies are needed to better understand the mechanism in which cardiotoxic agents cause myocardial injury, and this may help to inform the design of future trials investigating the use of cardioprotective medications for the prevention of chemotherapy-associated cardiomyopathy. A continued interdisciplinary cardio-oncology approach is critical to maintain a balance between the oncologic benefit of cancer treatment and its associated cardiac toxicities.

**Disclosures**

None.

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