Prevention and Management of Cardiotoxicity From Antineoplastic Therapy

Asher Chanan-Khan, MD, Sridhar Srinivasan, MD, and Myron S. Czuczman, MD

Various antineoplastic agents can cause cardiovascular toxicity. Of them, anthracyclines are the best recognized, though other chemotherapeutic and biologic agents are now known to have cardiac side effects. The clinical spectrum of cardiac dysfunction depends not only on the particular antineoplastic agent but also on the dose and schedule. Toxicities vary from direct myocardial injury resulting in myocardial infarction to conduction defects with arrhythmia, myocarditis and/or pericarditis, cardiomyopathy and congestive heart failure, hypertension, and nonspecific electrocardiographic (ECG) abnormalities. These events may occur acutely, during or immediately after the infusion; subacutely, within days to weeks of receiving the agent; or chronically, months and sometimes years after therapy. Various risk factors (Table 1) may predispose patients to cardiac side effects [1–11]. Recognizing these factors can help prevent cardiotoxicity by risk modification and/or careful monitoring during therapy.

The aim of this article is to review the important cardiovascular side effects associated with antineoplastic chemotherapy and biologic agents and provide evidence-based guidelines for their detection and management.

Cardiotoxicity Associated With Anthracyclines

Doxorubicin and other anthracyclines have been used in the treatment of a number of cancers for many years. Although extensive information is now available regarding the toxicity profile of this class of drugs, the exact etiology remains somewhat unclear. Current data suggest that doxorubicin induces a state of increased oxidative stress by decreasing endogenous antioxidants while increasing the generation of free radicals, which may be responsible for its myocardial toxicity [12–14].

Lefrak et al [15] reviewed the charts of 399 patients and found that cardiomyopathy and congestive heart failure after treatment with doxorubicin were dose-dependent. The incidence of congestive heart failure in this series was 4% at a cumulative dose of 500–550 mg/m², 18% at 551–600 mg/m², and 36% at ≥601 mg/m².

Several risk factors that predispose patients to an increased risk of anthracycline-associated cardiomyopathy have been identified. Of the nine factors listed in Table 1, cumulative dose, pre-existing heart disease, and patient age are the most important. The spectrum of doxorubicin-related cardiotoxicity ranges from rare serious events, such as myocarditis, pericarditis [16], myocardial infarction, or sudden cardiac death [17], to nonspecific ECG changes, such as a prolonged QT interval, flattening of the T waves, and loss of R-wave voltage [6, 18, 19]. The most serious side effects are delayed-onset cardiomyopathy and congestive heart failure, which have poor clinical outcomes [19]. It is important to note that cardiomyopathy from anthracyclines can develop as late as 20 years after cessation of therapy [20].

DIAGNOSIS

Typical symptoms and signs of congestive heart failure include gallop rhythm, jugular vein
Possible use of liposomal-encapsulated doxorubicin in patients with established underlying cardiac pathology [4, 24–27]. Polyethylene glycol (PEG)-coated liposomal doxorubicin (Doxil) permits higher cumulative doses with a lower incidence of congestive heart failure and equivalent efficacy to free doxorubicin. The overall incidence of cardiac adverse events in patients treated with liposomal-encapsulated doxorubicin ranged from 3% to 9% [28].

Unfortunately, despite these measures, the possibility of developing cardiomyopathy remains. There is great individual variability in anthracycline sensitivity among patients. As cumulative dose is the strongest predictor for development of cardiotoxicity, 550 mg/m² of doxorubicin is empirically established as the maximum cumulative dose to be given to patients. Epirubicin and idarubicin are analogs of doxorubicin with reportedly less cardiotoxicity; however, although both these agents appear to be similar in efficacy, no head-to-head comparisons have been made [23].

Dexrazoxane is an iron-chelating agent that is thought to decrease the cardiotoxic effect of doxorubicin by blocking the generation of free radicals. Although it is known to decrease the immediate cardiotoxicity of doxorubicin, its benefits against delayed cardiomyopathy remain unknown. Its effect on augmenting the myelosuppressive properties of doxorubicin and the hypothetical possibility of yielding protective benefit to the neoplastic cells have resulted in underutilization of this agent [29, 30].

We recommend that patients with established cardiac risk factors such as underlying heart disease and advanced age (>65 years) or those who require continued therapy with an anthracycline (doxorubicin) beyond 300 mg/m² may be concurrently treated with dexrazoxane for prevention of cardiotoxicity. The recommended dosage ratio of dexrazoxane:doxorubicin is 10:1; doxorubicin should be given within 30 minutes of giving dexrazoxane. At our institution, we have more often relied on the use of the liposomal formulation of doxorubicin for patients who are determined clinically to fall into a high-risk category and for patients who require long-term therapy on doxorubicin.

There is no ideal monitoring test for patients at high risk for cardiotoxicity from anthracyclines. Current standard of practice involves baseline evaluation of left ventricular ejection fraction (LVEF) and thereafter monitoring patients for

---

**Table 1**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative dose</td>
<td>1, 2</td>
</tr>
<tr>
<td>Dose per treatment</td>
<td>3</td>
</tr>
<tr>
<td>Rate of administration</td>
<td>4, 5</td>
</tr>
<tr>
<td>Pre-existing heart disease</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Mediastinal irradiation</td>
<td>6, 7</td>
</tr>
<tr>
<td>Age</td>
<td>3</td>
</tr>
<tr>
<td>Female sex</td>
<td>8, 9</td>
</tr>
<tr>
<td>Drug combinations: doxorubicin with</td>
<td>10, 11</td>
</tr>
<tr>
<td>trastuzumab</td>
<td></td>
</tr>
</tbody>
</table>

---

Cardiotoxicity

5. Possible use of liposomal-encapsulated doxorubicin in patients with established underlying cardiac pathology [4, 24–27]. Polyethylene glycol (PEG)-coated liposomal doxorubicin (Doxil) permits higher cumulative doses with a lower incidence of congestive heart failure and equivalent efficacy to free doxorubicin. The overall incidence of cardiac adverse events in patients treated with liposomal-encapsulated doxorubicin ranged from 3% to 9% [28].

Unfortunately, despite these measures, the possibility of developing cardiomyopathy remains. There is great individual variability in anthracycline sensitivity among patients. As cumulative dose is the strongest predictor for development of cardiotoxicity, 550 mg/m² of doxorubicin is empirically established as the maximum cumulative dose to be given to patients. Epirubicin and idarubicin are analogs of doxorubicin with reportedly less cardiotoxicity; however, although both these agents appear to be similar in efficacy, no head-to-head comparisons have been made [23].

Dexrazoxane is an iron-chelating agent that is thought to decrease the cardiotoxic effect of doxorubicin by blocking the generation of free radicals. Although it is known to decrease the immediate cardiotoxicity of doxorubicin, its benefits against delayed cardiomyopathy remain unknown. Its effect on augmenting the myelosuppressive properties of doxorubicin and the hypothetical possibility of yielding protective benefit to the neoplastic cells have resulted in underutilization of this agent [29, 30].

We recommend that patients with established cardiac risk factors such as underlying heart disease and advanced age (>65 years) or those who require continued therapy with an anthracycline (doxorubicin) beyond 300 mg/m² may be concurrently treated with dexrazoxane for prevention of cardiotoxicity. The recommended dosage ratio of dexrazoxane:doxorubicin is 10:1; doxorubicin should be given within 30 minutes of giving dexrazoxane. At our institution, we have more often relied on the use of the liposomal formulation of doxorubicin for patients who are determined clinically to fall into a high-risk category and for patients who require long-term therapy on doxorubicin.

There is no ideal monitoring test for patients at high risk for cardiotoxicity from anthracyclines. Current standard of practice involves baseline evaluation of left ventricular ejection fraction (LVEF) and thereafter monitoring patients for

---

**Table 1**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative dose</td>
<td>1, 2</td>
</tr>
<tr>
<td>Dose per treatment</td>
<td>3</td>
</tr>
<tr>
<td>Rate of administration</td>
<td>4, 5</td>
</tr>
<tr>
<td>Pre-existing heart disease</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Mediastinal irradiation</td>
<td>6, 7</td>
</tr>
<tr>
<td>Age</td>
<td>3</td>
</tr>
<tr>
<td>Female sex</td>
<td>8, 9</td>
</tr>
<tr>
<td>Drug combinations: doxorubicin with</td>
<td>10, 11</td>
</tr>
<tr>
<td>trastuzumab</td>
<td></td>
</tr>
</tbody>
</table>
signs and symptoms suggestive of left ventricular dysfunction. Schwartz et al [31] have proposed that anthracycline therapy not be given to patients with baseline LVEF of ≤30%; this seems like a reasonable recommendation. Those with an LVEF of 30%–50% can be treated with anthracyclines as long as LVEF is closely monitored. Patients whose baseline LVEF is ≥50% should have a repeat evaluation at 250–300 mg/m² and again at 450 mg/m² cumulative dose. A 10% decrease in LVEF or a drop from ≥50% to ≤50% or from 30%–50% to ≤30% should prompt cessation of further therapy with doxorubicin.

Once established, management of congestive heart failure is directed at symptom control. Most patients are refractory to conventional therapy for heart failure. Recently, a β₁ blocker (metoprolol) has been used with some success; digoxin can also be used for symptom control. Heart transplantation has been reported with successful results in patients with anthracycline-induced cardiomyopathy and could be considered when feasible [32–34].

Cardiotoxicity Associated With Other Chemotherapeutic Agents

**5-FLUOROURACIL (5-FU)**

5-FU (Table 2) is perhaps the second most common cause of chemotherapy-associated cardiotoxicity. Cardiac events related to 5-FU occur predominantly in the first 72 hours of the initial treatment cycle and may include chest pain, ECG changes, arrhythmia, pulmonary edema, myocardial infarction, and, rarely, cardiac arrest [35]. Up to 8% of patients may develop cardiac side effects from 5-FU. Infusional administration, concurrent radiotherapy, and pre-existing cardiac disease are thought to be significant predisposing factors [35–39]. Capecitabine (Xeloda), the oral prodrug of 5-FU, is also reported to have similar cardiac toxic effects [40].

**Prevention and management.** Careful clinical monitoring during 5-FU administration in patients with pre-existing cardiac disease is important. Administration of 5-FU should be stopped immediately in patients who develop a cardiac event. These patients should not be retreated with this agent, as the risk of a subsequent, potentially more serious cardiac event increases with repeat exposure [35]. Most patients respond to conservative antianginal therapy and supportive care.

The role of prophylactic calcium channel blockers and nitrates remains unclear [44–46]. We recommend close clinical monitoring of these patients in collaboration with a cardiology consultation. Patients who develop acute myocardial ischemia should be treated on the established guidelines for myocardial infarction in a coronary care unit. Further therapy with 5-FU is not recommended in these patients.

**CYCLOPHOSPHAMIDE**

Cyclophosphamide is an alkylating agent used in treating various solid and hematologic malignancies. At higher doses, it is commonly used as part of the preparative regimen for bone marrow transplantation. It is associated with acute cardiac toxicity that is independent of cumulative dose, although higher doses (>1.5 g/m²/day), as used in stem-cell transplantation [47, 48] or concurrent doxorubicin administration, are associated with an increased risk of cardiotoxicity [48, 49]. Prior irradiation to the chest or mediastinum is also a risk factor [49]. Acute cardiac events, such as myocarditis, pericarditis, or severe fatal congestive heart failure, have been reported. However, most often the toxicity is mild and resolves after stopping the cyclophosphamide, with no long-term sequelae.
Ifosfamide (Ifex) belongs to the same class of drugs and in one series is reported to have had significant cardiotoxicity in 17% of patients treated with the drug [51].

**Prevention and management.** There are no established guidelines for prevention or treatment of cyclophosphamide-associated cardiomyopathy. We recommend close clinical monitoring of patients for signs and symptoms of congestive heart failure. For those patients who develop such symptoms and are suspected to have cardiomyopathy, further therapy should be stopped and a complete evaluation, including ECG and an echocardiogram, performed to assess LVEF. These patients should be treated symptomatically for congestive heart failure. Repeat treatment with an alkylating agent can be instituted once LVEF returns to ≥ 50%.

**Paclitaxel**

Treatment with paclitaxel (or docetaxel [Taxotere]) has been associated with infusion-related hypotension (12% of patients) and asymptomatic bradycardia (3% of patients). Rhythm abnormalities (including supraventricular tachycardia and atrial fibrillation), hypertension, syncope, and myocardial infarction also have been reported with paclitaxel therapy.

**Prevention and management.** Currently, there are no standard guidelines for monitoring of patients on trastuzumab. We recommend that patients with underlying cardiac disease should be closely monitored for signs and symptoms of cardiac dysfunction. Patients who develop congestive heart failure or are suspected of developing cardiac dysfunction should be evaluated by an ECG and an echocardiogram. Further chemotherapy should be stopped, and management is supportive depending on the degree of myocardial dysfunction.

**Rituximab**

Rituximab is a chimeric murine/human monoclonal antibody directed against the CD20 antigen expressed on the surface of B lymphocytes. Rare cardiovascular adverse effects associated with rituximab include reversible or transient infusion-related hypotension and arrhythmia, as well as acute myocardial infarction, ventricular fibrillation, and cardiogenic shock. Most of these reactions (80%) occur during the first infusion and may be associated with a cytokine-release phenomenon.

**Prevention and management.** Rituximab should be discontinued in patients who develop significant arrhythmia or other severe cardiotoxicity. Careful monitoring during and after infusion is warranted, especially in patients with pre-existing cardiac disease. With respect to possible rituximab-associated hypotension, it is recommended that...
patients avoid anti-hypertensive medication the morning of rituximab infusion and delay taking these drugs until all transient cardiac side effects of rituximab have completely resolved.

**ARSENIC TRIOXIDE**

Arsenic trioxide is a novel agent currently used in various hematologic malignancies [33]. It is associated with prolongation of the QT interval and potentially serious cardiac arrhythmia [34]. Cardiotoxicity associated with arsenic trioxide is usually acute and occurs during or immediately after infusion. Hypokalemia or hypomagnesemia predisposes patients to the cardiotoxic effects of arsenic trioxide.

**Prevention and management.** A baseline ECG should be done before starting therapy to assess the rhythm pattern and QT interval. This monitoring should be repeated weekly during induction and biweekly during consolidation. If the QT interval is > 500 ms, the patient should be evaluated for potential risk versus benefit with further therapy. Prior to each infusion, electrolytes should be checked and corrected if low. Recommended levels of potassium and magnesium are > 4 mEq/L and > 1.8 mg/dL, respectively. Patients who develop cardiac symptoms should be hospitalized with close cardiac monitoring and correction of electrolytes. Arsenic trioxide can usually be restarted once the QTc interval is < 460 ms.

**THALIDOMIDE**

Thalidomide is an immunomodulatory agent currently used in the treatment of multiple myeloma and other malignancies. It is rarely associated with any cardiovascular side effects, but recently, pulmonary hypertension has occurred in a patient receiving thalidomide [32]. Two patients at our institute were noted to have symptoms of pulmonary hypertension while on thalidomide and had elevated pulmonary artery pressures on echocardiogram. Both symptoms and pulmonary pressure resolved after cessation of thalidomide. The exact etiology of this phenomenon remains unclear. Patients typically complain of shortness of breath and dyspnea on exertion.

**Prevention and management.** High-resolution computed tomography (CT) and D-dimer should be performed to rule out pulmonary embolism. Diagnosis is made by echocardiogram with Doppler studies to assess pulmonary artery pressure. Further therapy with thalidomide should be stopped, as this is a reversible phenomenon.

**Conclusions**

In conclusion, cardiotoxicity is an important dose-limiting side effect of various anticancer agents. In this review, we have identified some of the important and commonly used chemotherapeutic and biologic agents that have been reported to be associated with cardiovascular side effects. Identifying these side effects early on may prevent irreversible cardiac damage and long-term morbidity. Although cardiotoxicity can occur without any predisposing factors, various risk factors are now known and should be considered while treating our patients. We hope that recognition of these risk factors can aid clinicians in choosing the optimal and safest anticancer regimen suitable for their patients’ specific needs.

**References**


Preventing cardiotoxicity remains an important challenge in oncology for several reasons. The development of better supportive care strategies has expanded the number of patients who receive intensive chemotherapy. The introduction of a large number of novel agents with unique mechanisms of action produces a risk of unexpected drug interactions and toxicities. Advances in the field have resulted in an overall improvement in long-term survival, making late sequelae of treatment an increasingly common management issue. In short, although many acute side effects of cancer therapy, such as nausea, have faded as critical issues, cardiotoxicity remains a relevant concern and necessitates careful pre-clinical evaluation of drug action and animal toxicities and then ongoing clinical attention with a high index of suspicion [1].

For anthracycline-associated cardiotoxicity, the clinical manifestations are pleiomorphic, but the pathogenesis is common and distinct from the antiproliferative mechanism of action. The initial insult is the formation of semiquinone free radicals that are detoxified slowly. These free radicals result from the disequilibrium between energy-producing enzymes like NADH oxidase and P450 reductase and a lack of reducing enzymes such as catalase that convert H$_2$O$_2$ free radicals to H$_2$O. The anthracyclines tend to form highly toxic free radicals after binding to iron. In addition, the C-13 alcohol anthracycline metabolites delocalize iron from the cytoplasmic aconitase. This process results in impaired energy production, disruption of the ionic gradient, and calcium translocations. Failing or ischemic myocardium is less capable of dealing with the membrane lipid peroxidation, the defective binding of calcium to the sarcoplasmic reticulum, the reduced energy production, and the decreased production of contracting filaments. As a result, programmed cell death ensues [1, 2].

**PREDISPOSING FACTORS AND OPTIONS FOR ANTHRACYCLINE THERAPY**

Aging of the myocardium, preexisting cardiac dysfunction, long-standing hypertension, intercurrent cardiotoxic medicines, and prior irradiation confer higher risk of cardiotoxicity, especially when anthracyclines are given in high cumulative doses and with bolus administration. In this setting, monitoring should be more aggressive and cardiac function should be checked following the delivery of every 100 mg/m$^2$ of doxorubicin. Patients with preexisting congestive heart failure and older patients with metastatic disease who have received more than 300 mg/m$^2$ of doxorubicin should be given dexrazoxane (Zinexcard) in combination with doxorubicin [3, 4].

Alternatively, a related but different drug could be used: Idarubicin, mitoxantrone (Novantrone), and epirubicin (Ellence) are less cardiotoxic than doxorubicin, and epirubicin is at least as effective as doxorubicin for breast cancer. Infusional doxorubicin also is an alternative, but its administration requires a programmable portable pump. Liposomal-encapsulated doxorubicin (Doxil) is another option; it is comparable to or perhaps even more efficacious than doxorubicin for myeloma, Kaposi’s sarcoma, ovarian cancer, and possibly breast cancer [5]. Its reduced cardiotoxicity may be attributed to better distribution of drug to the tumor or to its prolonged half-life, which mimics the infusional administration of doxorubicin in terms of tissue distribution. Unfortunately, its use is limited by cost, mucositis, and the hand-foot syndrome.

The cardiomyopathy related to anthracycline use is associated with a poorer prognosis than idiopathic cardiomyopathies. Aggressive treatment with beta blockers, angiotensin-converting enzyme (ACE) inhibitors, diuretics, and digoxin (for symptomatic improvement) is indicated. Serious consideration should be given to implantation of an automatic cardiac defibrillator for patients with recurrent arrhythmia and also enrollment in the heart transplant list for patients cured of their cancer but with serious cardiac sequelae. Aldosterone-receptor blockers, especially eplerenone (Inspra), may reduce the rate of myocardial apoptosis, although studies confirming their efficacy are limited.

**5-FLUOROURACIL AND OTHER AGENTS**

Although 5-fluorouracil (5-FU) is even older than doxorubicin, it remains a mainstay of treatment for many common tumors. Its mechanism of action is well characterized, but the basis for damage to the heart is less clear. Electron microscopy has demonstrated direct endothelial cell damage, with subsequent thrombus formation...
and vasospasm. This finding may explain why the efficacy of coronary vasodilators such as calcium channel blockers is controversial in the prevention/treatment of fluoropyrimidine-induced ischemia. Telemetry should be considered during the administration of the initial doses of 5-FU for patients with coronary artery disease.

Once cardiotoxicity develops, the medication should be discontinued immediately, and an antianginal regimen and electrocardiographic monitoring should be instituted. Rechallenge in a patient who experienced coronary ischemia from 5-FU can be fatal and is contraindicated, despite a few reports of its success after a change from infusional to bolus administration.

Hemorrhagic myopericarditis and myocardial necrosis have been reported with cyclophosphamide and, very rarely, with ifosfamide (Ifex). This complication generally occurs at the high doses used for bone marrow transplantation. A poor correlation with peak plasma concentrations of the parent drug, coupled with the identification of acrolein in the aorta and myocardium in animal models, implicates acrolein as the probable culprit. Cyclophosphamide probably exacerbates the cardiotoxicity from doxorubicin and trastuzumab (Herceptin).

Vinca alkaloids, bleomycin, and cisplatin have potential vasospastic effects, and cisplatin may predispose the myocardium to significant arrhythmia secondary to electrolyte wasting from the kidneys. Vinca alkaloids can cause autonomic neuropathy, which is usually irreversible. Busulfan (Myleran) is associated with endocardial fibrosis.

Occasionally, paclitaxel causes bradycardia as well as conduction problems. It is possible that most of these events are related to the cremaphor vehicle in paclitaxel. At any rate, paclitaxel should be given cautiously to patients with severe cardiomyopathy who may not be able to tolerate bradycardia, patients with established conduction defects, and patients receiving paclitaxel in combination with doxorubicin because it lowers the threshold dose for cardiomyopathy. Docetaxel (Taxotere) causes fluid retention, so patients with congestive heart failure should be monitored closely when receiving this agent.

Cardiotoxicity associated with etoposide, cytarabine (injection), pentostatin (Nipent), and gemcitabine (Gemzar) is rare and in the case of etoposide can be prevented by longer infusion time. Biologic agents, such as the interferons and interleukin-2, novel agents like arsenic trioxide (Trisenox), and putative antiangiogenic agents may also directly or indirectly cause cardiotoxicity.

**BALANCING EFFICACY AND TOXICITY**

The discovery of critical signal transduction and growth pathways in cells has produced an explosion in the development of new anticancer agents. Each component of these signaling pathways is a potential therapeutic target. Furthermore, a large body of data indicates that for many targeted drugs, efficacy is enhanced when they are administered in combination with traditional cytotoxic drugs. The basis for this synergy may be that interruption of selected signaling pathways reduces the likelihood that a cell will repair the damage caused by a cytotoxic drug, thus leading to the initiation of apoptosis. Of course, this synergy may also lead to unintended toxicity to normal organs.

Clinical experience with trastuzumab, a monoclonal antibody that binds the HER2 receptor, is instructive. HER2 is one of four known members of the human epidermal growth factor receptor family involved in the control of the downstream activity of the neuregulins and possibly the epidermal growth factor itself. HER2 was identified as a potential therapeutic target for anticancer therapy because it is frequently overexpressed and is a poor prognostic feature for a number of different malignancies. Less well appreciated prior to the development of trastuzumab, HER2 is also important for the development and defense of the myocardium [6]. Besides playing an essential role in myocardial development, neuregulins also protect the myocytes from toxins like doxorubicin. The mechanism of this protective effect has not been fully characterized but appears to be mediated by activation of the Akt/PKB and Erk1/2 pathways following the heterodimerization of HER2/HER4 [7, 8].

**DOXORUBICIN PLUS TRASTUZUMAB CAN BE LETHAL**

Trastuzumab alone can cause a reduction in the cardiac ejection fraction, but this result is usually of limited clinical significance. However, when trastuzumab is given with potentially cardiotoxic chemotherapy, the damage can be dra-
matic [9]. As a result, the combination of doxorubicin and trastuzumab should be avoided. Clinicians need to be vigilant when a patient is taking trastuzumab, and formal cardiac function testing should be promptly initiated if symptoms of congestive heart failure or an increase in the baseline heart rate is detected. Guidelines for the discontinuation of trastuzumab are similar to those for doxorubicin, and, in most cases, there is improvement in cardiac function with discontinuation of the medication [10].

THE NEED FOR LONG-TERM VIGILANCE

Overall, the population of cancer patients is aging. Aggressive treatment programs that were once reserved for the young are now frequently administered to the elderly. Many of these patients have subclinical cardiac dysfunction. Although novel therapeutics offer unprecedented hope to better manage the malignancy, they may produce heart damage in some cases, either independently or when combined with other agents. Better therapies are also associated with prolonged survival, which means the long-term risks of treatment should be more fully considered and managed. A baseline cardiac assessment and monitoring for complications during chemotherapy have become a standard of care.

Since the cardiotoxicity of many agents does not become evident for years, longitudinal assessment will become an increasingly important component of management. There are limited data to guide the plan for such long-term assessment, however, and as a result, management is not standardized and often sporadic. Nevertheless, a few recommendations can be made:

- Patients should be educated so that additional risk factors, such as tobacco use, hypertension, and hyperlipidemia, are controlled.
- Endocarditis prophylaxis should continue throughout life.
- Primary care physicians should be made aware of risk factors and the early signs of delayed toxicity.
- Periodic monitoring by echocardiography to detect a subclinical decline in pump function seems reasonable.

In brief, cancer therapy is improving, but it is not benign. Chanak-Khan and colleagues remind us that the cardiotoxic complications of therapy are as important today as when doxorubicin was introduced nearly 30 years ago and that we in the medical community need to remain vigilant.

Lazaros J. Lekakis, MD
Fellow in Medical Oncology
Marianne Davies, APRN
Medical Oncology
John R. Murren, MD
Associate Professor of Medicine
Medical Oncology
Yale University
New Haven, Connecticut

REFERENCES

Commentary by Joseph Sparano, MD

Chanen-Khan and colleagues provide an overview of the prevention and management of cardiotoxicity from antineoplastic therapy. They provide a literature review that is supplemented by their own personal approach to specific clinical situations.

The two most commonly used agents associated with cardiac toxicity remain the anthracyclines and trastuzumab (Herceptin). However, some of the newer agents that have recently entered the clinic (eg, arsenic trioxide [Trisenox] and depsipeptide) also have been associated with cardiac conduction abnormalities that may require attention in regard to electrolyte replenition and electocardiographic monitoring of electrical conduction.

Both the anthracyclines and trastuzumab may produce cardiac dysfunction resulting in a clinical syndrome consistent with congestive heart failure. The anthracyclines (eg, doxorubicin, epirubicin [Ellence], and daunorubicin) are frequently used with curative intent in patients with acute leukemia, lymphoma, and breast cancer. Trastuzumab is a humanized version of the murine monoclonal antibody 4D5 that is directed against the extracellular domain of HER2 (human epidermal growth factor receptor 2), which is overexpressed by approximately 20%–30% of human breast cancers. It is approved for the treatment of HER2-overexpressing metastatic breast cancer [1] and is currently being evaluated in operable breast cancer in ongoing clinical trials [1].

**TIMING AND NATURAL HISTORY DIFFER**

Although the type of cardiotoxicity associated with these agents manifests itself similarly, the timing of presentation and natural history of cardiac dysfunction associated with these agents are very different. Anthracycline-induced toxicity usually presents within 1 year of the patient’s completing therapy and tends to have a more chronic course that may not respond well to medical therapy [1]. A delayed form of subclinical toxicity also can occur years later [1].

Trastuzumab-associated cardiac dysfunction usually occurs earlier, generally during treatment, and is more likely than anthracycline-induced cardiotoxicity to respond to medical therapy. The patient is more likely than the anthracycline-treated patient to fully recover, and in some cases, such recovery will permit rechallenge with trastuzumab. Factors associated with an increased risk of trastuzumab-associated cardiac toxicity include current anthracycline use, past anthracycline use, and age more than 60 years [1]. Although early studies indicated that trastuzumab should not be used concurrently with anthracyclines, recent reports have suggested that trastuzumab may be used safely with liposomal anthracyclines [2, 3].

**PATHOGENESIS**

The pathogenesis of cardiac toxicity associated with these agents also is different. The anthracyclines mediate their cardiac effects via reactive free-radical intermediates (eg, superoxide, hydrogen peroxide, and hydroxyl radicals) that are produced by chemical reduction via iron-catalyzed pathways [4], resulting in typical histological changes, such as myofibril loss, vacuolar swelling of the sarcoplasmic reticulum, loss of contractile elements and organelles, and mitochondrial and nuclear degeneration [5]. Agents that chelate iron, such as dexrazoxane (Zincard), prevent the generation of oxygen free radicals and protect against anthracycline-induced cardiomyopathy [6].

Hydrogen peroxide is inactivated by catalase (which converts hydrogen peroxide to water and oxygen) and glutathione peroxidase (which uses glutathione to reduce hydrogen peroxide to water and oxidized glutathione). Possible explanations for why cardiac muscle is prone to doxorubicin-induced injury include its relative deficiency of catalase and doxorubicin-induced depletion of glutathione peroxidase in cardiac muscle [7].

Cardiac imaging studies (eg, echocardiograms or nuclear scans) may identify subclinical evidence of myocardial dysfunction, and it is reasonable to routinely perform such studies prior to initiating anthracycline therapy to exclude subclinical cardiac dysfunction. However, there is conflicting evidence regarding the utility of such studies in predicting cardiac dysfunction when used serially in monitoring asymptomatic patients who are undergoing anthracycline therapy [8, 9]. Other diagnostic modalities, such as nuclear medicine scintigraphy with indium 111-labeled monoclonal antimyosin antibody [10, 11] and endomyocardial biopsy [12–14], may
identify early cardiac damage, but their routine clinical use is limited by practical considerations, such as feasibility and cost.

In contrast to the anthracyclines, the pathogenesis of trastuzumab-associated cardiac dysfunction is unknown. It does not share the histologic characteristics of doxorubicin-associated cardiotoxicity. Evidence suggests that the epidermal growth factor receptor (EGFR) family (and some of its ligands) plays an important role in myocardial cell physiology and development [15]. For example, mice with loss-of-function mutations of the neuregulin gene (Nrg-1) or of either of its receptors (erbB2 and erbB4) exhibit aborted development of myocardial trabeculae in ventricular muscle [16]. ErbB3 knockouts exhibit cardiac cushion abnormalities, leading to defective heart valves [17]. Finally, ErbB4 is the predominant neuregulin 1 receptor in postnatal rat ventricular muscle, and its expression in adult animals is limited to cardiac myocytes [18]. Burstein and colleagues [19] have recently proposed that performing a nuclear cardiac scan at week 16 of therapy is useful for identifying individuals at risk of trastuzumab-associated cardiac toxicity.

IMPORTANT QUESTIONS

The authors address or allude to several important questions regarding anthracycline use in patients with cardiac dysfunction or a prior history of anthracycline exposure:

• Can anthracyclines be used in individuals who have a subnormal left ventricular ejection fraction (LVEF)? Chanan-Khan et al recommend that patients with an LVEF between 30% and 50% may be safely treated with anthracyclines as long as these patients are closely monitored. The authors cite a report by Schwartz et al (reference 31 in their paper) to support this conclusion. Personally, I would caution against the use of anthracyclines in this setting because of the lack of safety information and would consider anthracycline use an option only under unusual circumstances in patients who had an LVEF in the upper range of that proposed by Chanan-Khan et al.

• Should the cardioprotective agent dexrazoxane be used in conjunction with anthracyclines in patients with a subnormal baseline LVEF or in patients with other cardiac risk factors, such as age > 50 years, hypertension, prior chest wall irradiation, or underlying cardiac disease? No, the American Society of Clinical Oncology’s technology assessment panel for cryoprotectants concluded that there was insufficient evidence to recommend dexrazoxane in this setting [20].

• Are liposomal anthracyclines equivalent to conventional anthracyclines? No, there are substantial differences between conventional anthracyclines and pegylated forms of liposomal anthracycline preparations, such as liposomal doxorubicin (Doxil). Clinicians should not use these agents interchangeably. The liposomal formulations have been approved for the treatment of ovarian carcinoma and Kaposi’s sarcoma. Although pegylated and nonpegylated forms of liposomal doxorubicin appear to be comparable in efficacy to conventional anthracyclines in metastatic breast cancer [21, 22], these agents have not been adequately tested in other disease types or as a component of adjuvant breast cancer therapy [23].

• Can liposomal anthracyclines be used safely in patients with a history of prior anthracycline exposure? There is some safety information on this matter. In one study comparing liposomal doxorubicin with either vinorelbine or mitomycin/vinblastine, most of the patients had had prior anthracycline therapy in the adjuvant or metastatic setting [24]. Cardiac toxicity was infrequent in patients treated with liposomal doxorubicin in this trial, demonstrating that liposomal forms of anthracyclines may be safely used in patients with a history of anthracycline exposure.

There are clearly more therapeutic options now than a decade ago for administering anthracyclines in a safe manner. Ten years ago, infusional administration of anthracyclines and weekly low-dose drug administration were commonly used to minimize the risk of anthracycline cardiotoxicity, and these modalities still may be of value in certain settings. Other means for more effectively monitoring patients receiving anthracycline therapy and predicting cardiac toxicity are currently being evaluated [25].

Joseph Sparano, MD
Professor of Medicine
Albert Einstein College of Medicine
Director, Breast Medical Oncology
Montefiore Medical Center
Bronx, New York
Cardiotoxicity

REFERENCES