Chemotherapy and Cardiotoxicity

Howard Broder, MD,* Roberta A. Gottlieb, MD,† Norman E. Lepor, MD, FACC, FAHA, FSCAI‡

*Cedars-Sinai Medical Center, Los Angeles, CA; †BioScience Center, San Diego State University, San Diego, CA; ‡The David Geffen School of Medicine at UCLA, Cedars-Sinai Medical Center, Los Angeles, CA

Newer cancer therapies have improved the survival of patients with cancer and, in some cases, turned cancer into a chronic disease. Patients are now surviving long enough for the adverse cardiovascular effects of some cancer therapies to become apparent. The anthracyclines are perhaps the most notorious offenders. Acute reactions include chest discomfort and shortness of breath consistent with a myopericarditis. Toxicity can also develop months after the last chemotherapy dose and typically presents as new onset heart failure with left ventricular systolic dysfunction. Late reactions are seen years after presentation as new-onset cardiomyopathy, often in patients who were treated for childhood neoplasms. 5-Fluorouracil, its prodrug capecitabine, and trastuzumab, a tumor-specific antibody, have also been associated with cardiotoxicity. Until adequate predictive models, prevention modalities, and treatments can be identified, the clinician's focus should be on aggressive monitoring for early signs of cardiac dysfunction in order to prevent severe systolic dysfunction and its concomitant morbidity and mortality.
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Cancer is the second leading cause of mortality in the United States, where it is responsible for 1 of every 4 deaths.[1] This impact has driven efforts to detect cancers earlier and to develop more aggressive antineoplastic regimens, including newer biologic and immunologic therapies. Some of these therapies, while leading to remission and cure, are also associated with serious cardiovascular complications that in themselves adversely affect patient survival. As these newer therapies improve survival and turn cancer into a

chronic disease, patients are now surviving long enough for adverse cardiovascular effects, including cardiomyopathy, to become apparent. It is important for cardiologists to be familiar with cancer treatments that have cardiovascular toxicity, to recognize predisposing factors so that adverse events can be prevented, and to optimally treat manifestations of cardiovascular toxicity. Research examining these toxicities is giving the cardiology community new insights into the cardiomyocyte and its life cycle.

Anthracycline Antibiotics

Perhaps the most notorious offenders for chemotherapeutic cardiotoxicity are the anthracyclines. These agents prevent cell division by disrupting the structure of the DNA and terminating its function. The anthracyclines include the parent compound daunorubicin, which early on was found to have significant toxicities. However, because daunorubicin was an effective antineoplastic agent, daughter compounds were sought. They include doxorubicin, epirubicin, idarubicin, and mitoxantrone.

Doxorubicin was thought to have an increased therapeutic index compared with daunorubicin.[2] It has a somewhat reduced risk of cardiotoxicity and broad effectiveness in the treatment of acute leukemia and multiple soft tissue tumors. It went into widespread clinical use for a variety of tumors, including leukemias and lymphomas, and for breast, uterine, ovarian, and lung cancers. In 1973, Lefrak and colleagues[3] assembled a comprehensive case series detailing the cardiotoxicity of doxorubicin. Of 399 patients who had received doxorubicin at their institutions, there were 11 cases (3%) of acute cardiac decompensation, with 8 deaths within 3 weeks. During and after treatment with doxorubicin, 45 patients (11%) had electrocardiogram (EKG) changes. Most of these EKG changes were transient; they included sinus tachycardia, nonspecific ST segment and T-wave changes, frank ST-segment elevation, and a decrease in voltage consistent with a myocarditis or diffuse edema throughout the myocardium. Scanning electron microscopy showed a marked decrease in the number of myocardial fibrils, mitochondrial distortion, nuclear degeneration, disorganized sarcoplasmic reticulum, and glycogen granule depletion. In this early study, the authors noted that there was certainly a dose effect, with 0.27% of patients developing heart failure at doses of less than 550 mg/m^2, but 30% of patients developing refractory congestive heart failure with doses greater than 550 mg/m^2. Findings on biopsy included ruptured cristae, swollen mitochondria with dense deposits, myofibril disruption and disorganization, vacuolization, and replacement of myocardium with fibrous tissue.[3,4]

There are established risk factors for the development of cardiomyopathy with anthracycline treatment. The most predictive is cumulative dose. From the earliest experience, there has been a clear dose response, with a sharp increase in the events of cardiac toxicity with doses greater than 550 mg/m^2. Other factors, such as age, are also important. Children and patients older than 70 appear to be more susceptible to the development of cardiac toxicity.[5] Patients who have received chest irradiation or who are currently receiving it are at increased risk, as are those who are receiving other chemotherapies, which may act in a synergistic effect with doxorubicin. The most notable chemotherapeutic agents that can add to anthracycline toxicity include trastuzumab, paclitaxel, and cyclophosphamide. In a review of 3 trials of doxorubicin, Swain and colleagues[6] identified cardiac events in 9% to 65% of patients receiving doxorubicin and cyclophosphamide, as a function of the doxorubicin dose. (Cardiac events were defined as a drop in left ventricular [LV] ejection fraction from baseline of at least 20% or of at least 10% if the level decreased below 50%.)

Types of Reactions

Cardiovascular toxicities related to anthracyclines can be categorized as acute, early, or late. Acute reactions typically present during or shortly after intravenous infusion with the chemotherapeutic agent. Initial symptoms can include chest discomfort and shortness of breath consistent with a myopericarditis. Echocardiography may show LV dysfunction. In 2005, Nakamae and colleagues[7] showed that valsartan, an angiotensin receptor blocker, can mitigate the effects of acute cardiotoxicity. Any link to subsequent development of systolic dysfunction is unclear because patients typically recover uneventfully from this acute toxic presentation. Early toxicity develops months after the last chemotherapy dose and typically presents as new onset heart failure with LV systolic dysfunction. Treatment of these patients includes all of the standard heart failure medications, including angiotensin-converting enzyme inhibitors, beta blockers,

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aldosterone antagonists, and diuretics. Patients with evidence of LV dyssynchrony may also benefit from cardiac resynchronization therapy.

Late reactions are seen years after presentation as new-onset cardiomyopathy, often in patients who were treated for childhood neoplasms. A survey by the Pediatric Cardiomyopathy Registry shows that more than 15% of adult patients with cardiomyopathy were treated for cancer during childhood or adolescence.[8] In patients with late, severe, refractory cardiotoxicity, as long as the cancer has been cured, orthotopic heart transplantation is an option.

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Cell Biology of Anthracycline Cardiotoxicity

Because anthracyclines are such effective anticancer drugs, their mechanisms of action have been under intense investigation for many years. Multiple mechanisms have been proposed, including free radical formation, apoptosis, disruption in DNA replication, and transcription by interaction with the DNA-topoisomerase complex or direct interaction with the DNA.[9] Cardiac myocytes are not proliferating, so the mechanism for doxorubicin-induced cardiotoxicity has been attributed, at least in part, to reactive oxygen species (ROS)–mediated damage to cardiac myocytes. Treatment with antioxidants can protect isolated cardiac myocytes and intact hearts from doxorubicin toxicity,[10-13] which suggests that production of ROS and damage to mitochondria play an important role in doxorubicin-mediated cardiotoxicity and that limiting oxidative stress can mitigate these effects.

There is evidence implicating cardiac mitochondria as key intracellular targets, both as sites of generation of ROS and as direct targets. Mitochondrial swelling and vacuolization have been identified in human cardiac tissue.[14] Doxorubicin can accumulate in the mitochondria, where it forms a complex with cardiolipin in the inner membrane.[15,16] The cycling of doxorubicin between the quinone and semiquinone forms can generate large amounts of superoxide, which can be converted to hydrogen peroxide and hydroxyl radical. Excess levels of ROS can result in oxidative modification of mitochondrial proteins, lipids, and mitochondrial DNA (mtDNA), culminating in mitochondrial dysfunction and cell death. It has been suggested that mitochondrial bioenergetic failure plays a critical role in doxorubicin-induced cardiotoxicity. Patients treated with anthracyclines during childhood showed impaired myocardial high-energy phosphate metabolism in adulthood even in the absence of cardiomyopathy.[17] Doxorubicin treatment decreased levels of respiratory chain subunits encoded by mtDNA in rat and human hearts.[18-19] Although a decrease in mitochondrial functional deficits may not be apparent in the nonstressed heart, these hearts will be more susceptible to additional bioenergetic stress under increased workload and would have limited functional reserve.

Recent investigations have revealed that progenitor cells residing in the heart have the ability to differentiate into cardiac myocytes.[20-24] These cells are thought to participate in cardiac growth during adolescence and to provide a mechanism for replacement of damaged cells within the adult heart. It is possible that doxorubicin targets the cardiac stem cells, thus limiting future regenerative potential. This effect would be exacerbated by concomitant chest irradiation. Tomita and colleagues[25] reported that granulocyte-colony stimulating factor (G-CSF) enhanced migration of bone marrow cells to the heart and attenuated cardiotoxicity by doxorubicin. Similarly, Hou and coworkers[26] found that administration of G-CSF inhibited cardiomyocyte apoptosis and improved cardiac function in a mouse model of doxorubicin-induced cardiomyopathy. These studies suggest that future management of anthracycline cardiotoxicity may involve promoting repair and regeneration through therapeutic administration of stem cells or their growth factors.

Detection of Cardiotoxicity

Despite the identification of risk factors, there are very few convincing data regarding the identification of which patients will develop cardiotoxicity from doxorubicin. From early experience, we understand that if the condition is allowed to progress to congestive heart failure with severe systolic dysfunction, then the chance for recovery is low and the mortality rates are high. Therefore, much emphasis has been placed on early identification of cardiotoxicity in the hope of preventing the development of severe irreversible systolic dysfunction. Traditionally, an assessment of ejection fraction is performed prior to each cycle of doxorubicin, and typically after doses of 100, 300, and 400 to 450 mg/m^2, depending on risk factors. This assessment can be performed with a multiple gated acquisition scan or 2-dimensional echocardiography. If the baseline ejection fraction (EF) is less than 30% or if the EF drops to less than

50% with a decrease of 10% since the previous cycle, the doxorubicin treatment is withheld. With close monitoring, most cases of serious doxorubicin toxicity can be avoided. Unfortunately, ejection fraction remains a rather crude and late measure of cardiotoxicity.

In 2006, Civelli and colleagues[27] reported on their experiences using low-dose dobutamine echocardiography during and after anthracycline administration to measure LV contractile reserve (LVCR). They postulated that LVCR, which is the difference in ejection fraction between the peak dobutamine effect and the basal state, is potentially an early measure of myocardial dysfunction and a predictor of late cardiac dysfunction. In this study, 49 women with advanced breast cancer were studied. Any patient with known cardiac disease or risk factors such as diabetes or advanced age was excluded. These patients underwent stress echocardiography prior to chemotherapy, after each of 3 cycles of epirubicin, cyclophosphamide, and docetaxel, and then at 1, 4, and 7 months after chemotherapy. Resting echocardiography was performed between 12 and 18 months after therapy for all the surviving participants. Seventeen percent of patients developed systolic dysfunction with a drop in EF of at least 10%, and with a final EF of less than 50%. Prior to and during chemotherapy, resting echocardiography showed no significant differences between the groups that did and did not go on to develop systolic dysfunction. However, with dobutamine, there were significant decreases in peak LVEF and LVCR in those patients who did go on to develop systolic dysfunction at rest ($P < .0001$). The differences can be identified as early as after the first cycle of chemotherapy, but become significant prior to the third cycle. Diastolic dysfunction was identified in both groups and was not found to be a predictive factor for the development of systolic dysfunction in this patient population. Although dobutamine echocardiography can be somewhat cumbersome and expensive, it stratified patients at low risk and at higher risk for developing systolic dysfunction. This distinction is important because the levels of systolic dysfunction identified in this trial fulfill the guidelines to withhold further anthracycline chemotherapy, as even asymptomatic reductions in LVEF lead to severe congestive heart failure if anthracyclines are continued.[28,29]

Although dobutamine echocardiography can be somewhat cumbersome and expensive, it can stratify patients at low risk and at higher risk for developing systolic dysfunction.

In regard to diastolic dysfunction, in as early as 1989, Marchandise and colleagues[30] documented changes in LV filling dynamics in patients who had received doxorubicin as compared with controls. These changes were typified by mitral flow patterns of a prolonged LV cavity isovolumic relaxation period, a reduced E velocity, and a decreased E/A ratio. These findings are seen in as many as 80% of patients who receive doxorubicin and are not correlated to systolic dysfunction. In fact, there have been many studies documenting diastolic dysfunction using a variety of measures in patients receiving anthracyclines.[31] Only 1 study found a significant association between diastolic dysfunction and subsequent systolic dysfunction.[32]

Other, more sensitive methods for measuring LV function have also been sought. Eidem and coworkers[33] have investigated the use of the myocardial performance index (MPI) in children receiving doxorubicin. MPI is defined as the sum of the isovolumic relaxation time and isovolumic contraction time divided by the ventricular ejection time. Measured from the 5-chamber view, an increase in the MPI is interpreted as a decrease in myocardial performance. For example, a weaker heart will have a lengthened isovolumic contraction time and a decreased ejection time. In this study of 29 pediatric patients, significant toxicity, as defined by an increase in MPI, was seen in those with increased doses of doxorubicin before the occurrence of LV systolic dysfunction. In this study, the 4 patients who developed overt LV systolic dysfunction had elevated MPI prior to the drop in EF. With discontinuation of therapy, these patients' ejection fractions returned to normal, but the MPI remained persistently elevated.

Transient and more sustained release of troponin I after high-dose chemotherapy can identify cancer patients at progressively increased risk of LV systolic dysfunction and combined cardiac morbidity and mortality. In a recent analysis, LVEF remained within 15% of baseline among the 483 of 495 patients (97.6%) with troponin I levels that remained normal after chemotherapy.[34] However, EF decreased by more than 15% in 94 of the 145 patients (64.8%) in whom troponin I increased early but normalized 1 month after chemotherapy, and in 53 of the 63 patients (84.1%) in whom troponin I remained elevated at 1 month.

Prevention of Cardiotoxicity

There has been a significant effort on the part of the medical community to identify protocols or medications that mitigate the adverse effects of anthracycline antibiotics. The compound with the most evidence is dexrazoxane (DZR). An antioxidant that chelates iron in a fashion similar to ethylenediaminetetraacetic acid has been shown to reduce iron-dependent free radical formation and lipid peroxidation. Other antioxidants that act following the formation of free radicals have not shown any effectiveness in mitigating anthracycline-induced cardiotoxicity.[6,35] DZR has been evaluated in multiple trials. A recent meta-analysis by van Dalen and colleagues[36] showed a significant reduction of risk for heart failure, with a relative risk of 0.28. However, because of fears of reduced efficacy of the anthracycline antitumor response, DZR is often withheld until patients have already received 300 mg/m^2 of doxorubicin in the treatment of primary breast cancer. In regard to adjuvant treatment for breast cancer or other malignancies, DZR is often withheld altogether.[37] Liposomal formulations of daunorubicin and doxorubicin that appear to be somewhat less toxic to cardiac tissue have been approved.

In a study by Cardinale and colleagues,[38] 473 cancer patients who had received high-dose chemotherapy and had a significant elevation of troponin I were randomized to an angiotensin-converting enzyme (ACE) inhibitor or control. These investigators found that the incidence of the primary endpoint (worsening LV function) was significantly higher in control subjects than in the ACE-inhibitor group (43% vs 0%; $P < .001$). Results from a small study that aimed to determine the protective effect of carvedilol in anthracycline-induced cardiomyopathy suggested that the prophylactic use of carvedilol in patients receiving anthracyclines may protect both systolic and diastolic functions of the left ventricle.[39]

Treatment of Cardiotoxicity

Once systolic dysfunction develops, patients with doxorubicin-associated congestive heart failure should receive comprehensive medical management with device therapy as indicated by guidelines for nonischemic cardiomyopathy. In particular, ACE inhibitors have been shown to improve cardiac function in a small study of patients with anthracycline cardiotoxicity.[40] Patients who fail standard medical management for dilated cardiomyopathy, and whose tumors are considered "cured," may be candidates for orthotopic heart transplantation. Until adequate predictive models, prevention modalities, and treatments can be identified, the clinician's focus should be on aggressive monitoring for early signs of cardiac dysfunction in order to prevent severe systolic dysfunction and its concomitant morbidity and mortality.

Non-Anthracycline Agents

5-Fluorouracil and its prodrug capecitabine are the next most common causes of chemotherapy-related cardiotoxicity after the anthracyclines. Depending on the study, rates of toxicity range from 1% to 19%.[41,42] Most studies have found rates of toxicity of less than 8%. Risk factors for the development of cardiotoxicity include underlying coronary artery disease, concurrent anthracycline administration, and radiation therapy. It is thought that the toxicity is related to endothelial effects and vasospasm leading to coronary spasm.[43] Toxicities of 5-fluorouracil can include angina, myocardial infarction, arrhythmias, and pulmonary edema, as well as cardiac arrest and pericarditis.

Treatment of 5-fluorouracil toxicity consists of discontinuation of the offending agent. Symptoms of angina typically resolve with medical therapy. If therapy is to be resumed, stress testing can be used to identify any underlying coronary artery disease. In the uncommon case in which therapy is not discontinued, the infusions may be switched to bolus form, or if there is significant coronary disease on stress testing, the patient may benefit from revascularization prior to resumption of chemotherapy.[44] Because the basis of cardiac ischemia with 5-fluorouracil is related to intense coronary spasm, calcium antagonists and/or nitrates may be useful in those patients who have exhibited this cardiovascular toxic effect and in whom it is imperative to continue 5-fluorouracil therapy. (Note there is no clinical trial experience to support this approach.)

Paclitaxel belongs to an important new class of anticancer agents: the taxanes used in the treatment of patients with advanced ovarian and breast cancer. Paclitaxel promotes the polymerization of tubulin, leading to the development of dysfunctional microtubules. These dysfunctional microtubules interfere with normal cell division and may eventually lead to cellular death. Transient asymptomatic bradycardia appears to be the most frequent cardiovascular adverse effect, reported in up to 29% of the patients treated with paclitaxel.[45] Paclitaxel may potentiate the development of heart failure when used in combination with anthracyclines.

Biologic Therapies

In the past decade, anti-tumor therapies have grown increasingly into the realm of targeted biologic therapies. Tumor-specific antibodies are one such example. In addition to being

one of the most exciting developments in oncology, this field has also begun to elucidate some basic mechanisms in cardiomyocyte biology.

In the 1980s, work by Slamon and colleagues[46] brought to light the role of the HER2/neu (ERBB2) proto-oncogene in many breast cancers. HER2, or human epidermal growth factor receptor 2, codes for a transmembrane tyrosine kinase receptor. Overexpression of the HER2 protein, which occurs in approximately 25% of breast cancers, leads to cell proliferation, angiogenesis, and resistance to apoptosis.[47] Slamon and colleagues[46] showed that patients whose tumors over-express HER2 have a worse prognosis than patients whose tumors do not. Investigation of HER2 eventually led to the development of a monoclonal antibody against HER2. Trastuzumab was approved by the US Food and Drug Administration in 1998 as both adjunctive therapy and monotherapy for women with HER2-positive breast cancer. Early in its development, trastuzumab demonstrated effectiveness against HER2-expressing tumors, with relatively few apparent side effects. Early studies showed that trastuzumab improved response rates and survival of patients with advanced metastatic breast cancer.[48] Later studies showed that patients with operable tumors also benefited, with a 33% relative risk reduction in mortality.[49] Trastuzumab also worked as a monotherapy, reducing recurrence by up to 50%.[50]

These early studies did not identify cardiotoxicity as a side effect of trastuzumab. Many of these patients typically had received large doses of anthracycline chemotherapy, and some had received radiation to the chest, so cardiac events were not readily assigned to trastuzumab. It was not until phase 3 studies that cardiotoxicity as a potential side effect was identified.[51] The concern regarding cardiotoxicity, as well as the presence of multiple confounding factors, led to the development of the Cardiac Review and Evaluation Committee (CREC) to review the data gathered in all previous phase 2 and 3 trials. Cardiac events were defined as the development of congestive heart failure symptoms and signs, including an S3 or tachycardia associated with a drop in EF of more than 5% to less than 55%, or an asymptomatic drop in EF of more than 10% to less than 55%.[52] In perhaps its most significant finding, the CREC looked at the multinational phase 3 study led by Slamon and colleagues[46] comparing chemotherapy plus trastuzumab versus chemotherapy alone. In this trial of 469 patients, there were both anthracycline/cyclophosphamide and paclitaxel arms. The greatest risk for developing cardiac events was in the group receiving trastuzumab plus anthracycline and cyclophosphamide, of whom 27% developed heart failure. This rate is in comparison to only 8% in the patients who received anthracycline plus cyclophosphamide without trastuzumab. Cardiac toxicity occurred in 13% of patients who received paclitaxel and trastuzumab, 4% of patients who received trastuzumab monotherapy, and 1% of patients who received paclitaxel monotherapy. In addition, patients who received anthracyclines in combination with trastuzumab had greater functional impairment and more severe cardiomyopathies.[52]

The risk factors identified for trastuzumab-related cardiomyopathy were concomitant use of an anthracycline, previous exposure to an anthracycline, chest wall irradiation, pre-existing cardiac dysfunction, and age. The cardiotoxicity does not appear to be dose-related, in contrast to anthracycline.[53] In a recent study by Rastogi,[54] the risk of cardiomyopathy did not seem to increase with time from exposure to trastuzumab, and some patients who had developed myocardial injury had recovery of function with time. The association between trastuzumab and heart failure was stronger in women who were older, used hypertensive medications, and had a low normal baseline LV ejection fraction.

Treatment for trastuzumab-related cardiotoxicity has been with the standard heart failure regimen, including beta blockers, ACE inhibitors, and diuretics. A small observational study by Ewer and colleagues[55] examined 38 patients with trastuzumab-related cardiomyopathy. Sixteen percent received no specific treatment and 84% received standard heart failure treatment as described above. All recovered function, with a mean time to recovery of 6 weeks. Additionally, upon re-administration of the agent, 88% remained free of heart failure.

Investigation into the pathophysiology of trastuzumab-related cardiotoxicity has brought forth some interesting findings related to cardiomyocyte biology. ERBB2 knockout mice were viable, but displayed early signs of dilated cardiomyopathy, including wall thinning, decreased contractility, and chamber dilation. These mice were also more susceptible to anthracycline toxicity.[56] Use of polymerase chain reaction DNA fragmentation assays showed that ERBB2 knockout mice displayed increased apoptosis as compared with controls. In order to determine whether apoptosis plays a role in the development of heart failure in the ERBB2 knockout mice, they were transfected with an anti-apoptosis gene, basal cell lymphoma-extra large (Bcl-xL). In the ERBB2 knockout mice, the addition of Bcl-xL prevented chamber dilation

and reduction of fractional shortening, suggesting that chamber dilation is at least in part due to apoptosis. ERBB2 knockout cardiomyocytes in culture also demonstrated increased sensitivity to doxorubicin. Trastuzumab, therefore, provides an elegant example of the failure of tyrosine-kinase activity to cause apoptosis-induced heart failure. This finding has important implications, as many new therapies that are being used for a variety of disorders are targeting various tyrosine-kinase enzymes, and the side effects of these agents can be various and unpredictable. Results from one trial suggest that in patients who require treatment with both an anthracycline and trastuzumab, treatment with trastuzumab first may reduce the risk of cardiotoxicity.[57]

There have also been reports of heart failure symptoms in patients taking imatinib mesylate. Imatinib inhibits the function of bcr-abl, a constitutively active tyrosine kinase. Kerkelä and colleagues[58] reported 10 cases of congestive heart failure in patients taking imatinib. Electron microscopies from biopsies of these patients show myocyte membrane whorls, pleomorphic mitochondria with effaced cristae, scattered cytosolic lipid droplets and vacuoles, and glycogen accumulation in the cardiomyocytes. These changes have been described in cases of toxic cardiomyopathy. In mice treated with imatinib, the same findings were seen by electron microscopy. In this mouse model, imatinib caused a decrease of mitochondrial membrane potential. This reduction in turn caused a release of cytochrome C into the cytosol and subsequent lipid droplet formation, cytosolic vacuolization, and cell death. Gene transfer of c-Abl inhibited release of cytochrome C and prevented cell death.[58] Other tyrosine kinase inhibitors, such as sunitinib malate, have also been reported to have cardiotoxicity. It was postulated by Mann[59] that the cardiotoxicity could be an effect of sustained stress response of the endoplasmic reticulum. Oxidative stress has also been associated with translocation of c-Abl to the mitochondria and with the enzyme catalase that breaks down H_2O_2, a potential modulator of mitochondrial collapse and cell death.[59,60]

Bevacizumab is a therapeutic antibody that is believed to work by targeting and inhibiting the function of vascular endothelial growth factor. It is approved for use in combination with intravenous 5-fluorouracil-based chemotherapy as first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum and in combination with carboplatin and paclitaxel for the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic, nonsquamous, non–small cell lung cancer. In randomized, active-controlled studies, the overall incidence of arterial thromboembolic events was increased with the use of bevacizumab in combination with chemotherapy (4.4% vs 1.9%). The incidences of both cerebrovascular arterial events (1.9% vs 0.5%) and cardiovascular arterial events (2.1% vs 1.0%) were increased in patients receiving bevacizumab in combination with chemotherapy. In addition, there was a correlation between older age (at least 65 years) and increase in risk of thromboembolic events.[61]

Prostate cancer and its anti-androgen therapies are not typically thought of as high-risk chemotherapies. In fact, they are considered well-tolerated therapies that are relatively safe. An analysis by D'Amico and colleagues[62] examined fatal myocardial infarctions in patients who were enrolled in 1 of 3 randomized controlled trials of androgen suppression therapy (AST). They found that men older than 65 years who were given AST for longer than 6 months had a shorter time to fatal myocardial infarction than those who did not receive AST ($P = .017$). There was some suggestion that time

Main Points

- Perhaps the most notorious offenders for chemotherapeutic cardiotoxicity are the anthracyclines. They include daunorubicin and its daughter compounds, doxorubicin, epirubicin, idarubicin, and mitoxantrone.
- The most predictive risk factor for the development of cardiomyopathy with anthracycline treatment is cumulative dose.
- Treatment of patients with anthracycline cardiotoxicity includes all of the standard heart failure medications, such as angiotensin-converting enzyme inhibitors, beta blockers, aldosterone antagonists, and diuretics.
- 5-Fluorouracil and its prodrug capecitabine are the next most common causes of chemotherapy-related cardiotoxicity after the anthracyclines. Rates of toxicity range from 1% to 19%.
- Trastuzumab was associated with cardiotoxicity in phase 3 studies.

to fatal myocardial infarction was shorter in patients with as little as 3 months of AST. Other ancillary data suggest that antiandrogen therapies are associated with metabolic syndrome and that androgens may actually have a protective effect on the development of atherosclerosis. Although the risk of cardiovascular disease progression with AST has not been evaluated prospectively, current data suggest that risk assessment and aggressive therapy of coronary disease may be warranted prior to the initiation of AST.

Conclusion

Cancer is an aggressive disease with a wide variety of powerful treatments. The cellular processes that these therapies affect, however, are not limited to neoplastic tissue, and many therapies have significant cardiotoxicities that clinicians must be more familiar with. ■

References

1. Cancer Facts and Figures 2006. American Cancer Society Web site. http://www.cancer.org/docroot/STT/content/STT_1x_Cancer_Facts__Figures_2006.asp. Accessed April 20, 2008.
2. DeMarco A, Gaetani M, Scarpinato B. Adriamycin (NSC-123,127): a new antibiotic with antitumor activity. *Cancer Chemother Rep*. 1969;53:33-37.
3. Lefrak EA, Pitha J, Rosenheim S, Gottlieb JA. A clinicopathologic analysis of adriamycin cardiotoxicity. *Cancer*. 1973;32:302-314.
4. Elliott P. Pathogenesis of cardiotoxicity induced by anthracyclines. *Semin Oncol*. 2006;33 (3 suppl):S2-S7.
5. Kremer LC, Caron HN. Anthracycline cardiotoxicity in children. *N Engl J Med*. 2004; 351:120-121.
6. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. *Cancer*. 2003;97:2869-2879.
7. Nakamae H, Tsumura K, Terada Y, et al. Notable effects of angiotensin II receptor blocker, valsartan, on acute cardiotoxic changes after standard chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone. *Cancer*. 2005;104:2492-2498.
8. Giantris A, Abdurrahman L, Hinkle A, et al. Anthracycline-induced cardiotoxicity in children and young adults. *Crit Rev Oncol Hematol*. 1998;27:53-68.
9. Minotti G, Menna P, Salvatorelli E, et al. Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. *Pharmacol Rev*. 2004;56:185-229.
10. Doroshow JH, Locker GY, Ifrim I, Myers CE. Prevention of doxorubicin cardiac toxicity in the mouse by N-acetylcysteine. *J Clin Invest*. 1981;68:1053-1064.
11. Dhalla AK, Singal PK. Antioxidant changes in hypertrophied and failing guinea pig hearts. *Am J Physiol*. 1994;266(4 Pt 2):H1280-H1285.
12. Siveski-Iliskovic N, Hill M, Chow DA, Singal PK. Probucol protects against adriamycin cardiomyopathy without interfering with its antitumor effect. *Circulation*. 1995;91:10-15.
13. Siwik DA, Tzortzis JD, Pimental DR, et al. Inhibition of copper-zinc superoxide dismutase induces cell growth, hypertrophic phenotype, and apoptosis in neonatal rat cardiac myocytes in vitro. *Circ Res*. 1999;85:147-153.
14. Unverferth DV, Fertel RH, Altschuld R, et al. Biochemical measurements of endomyocardial biopsies. *Cathet Cardiovasc Diagn*. 1981;7:55-64.
15. Nicolay K, Timmers RJ, Spoelstra E, et al. The interaction of adriamycin with cardiolipin in model and rat liver mitochondrial membranes. *Biochim Biophys Acta*. 1984;778:359-371.
16. Goormaghtigh E, Huart P, Praet M, et al. Structure of the adriamycin-cardiolipin complex. Role in mitochondrial toxicity. *Biophys Chem*. 1990;35:247-257.
17. Eidenschink AB, Schröter G, Müller-Weihrich S, Stern H. Myocardial high-energy phosphate metabolism is altered after treatment with anthracycline in childhood. *Cardiol Young*. 2000;10:610-617.
18. Lebrecht D, Kokkori A, Ketelsen UP, et al. Tissue-specific mtDNA lesions and radical-associated mitochondrial dysfunction in human hearts exposed to doxorubicin. *J Pathol*. 2005;207: 436-444.
19. Lebrecht D, Setzer B, Rohrbach R, Walker UA. Mitochondrial DNA and its respiratory chain products are defective in doxorubicin nephrosis. *Nephrol Dial Transplant*. 2004;19:329-336.
20. Beltrami AP, Barlucchi L, Torella D, et al. Adult cardiac stem cells are multipotent and support myocardial regeneration. *Cell*. 2003;114:763-776.
21. Oh H, Bradfute SB, Gallardo TD, et al. Cardiac progenitor cells from adult myocardium: homing, differentiation, and fusion after infarction. *Proc Natl Acad Sci U S A*. 2003;100:12313-12318.
22. Martin CM, Meeson AP, Robertson SM, et al. Persistent expression of the ATP-binding cassette transporter, Abcg2, identifies cardiac SP cells in the developing and adult heart. *Dev Biol*. 2004;265:262-275.
23. Messina E, De Angelis L, Frati G, et al. Isolation and expansion of adult cardiac stem cells from human and murine heart. *Circ Res*. 2004; 95:911-921.
24. Laugwitz KL, Moretti A, Lam J, et al. Postnatal isl1+ cardioblasts enter fully differentiated cardiomyocyte lineages. *Nature*. 2005;433:647-653.
25. Tomita S, Ishida M, Nakatani T, et al. Bone marrow is a source of regenerated cardiomyocytes in doxorubicin-induced cardiomyopathy and granulocyte colony-stimulating factor enhances migration of bone marrow cells and attenuates cardiotoxicity of doxorubicin under electron microscopy. *J Heart Lung Transplant*. 2004;23:577-584.
26. Hou XW, Son J, Wang Y, et al. Granulocyte colony-stimulating factor reduces cardiomyocyte apoptosis and improves cardiac function in adriamycin-induced cardiomyopathy in rats. *Cardiovasc Drugs Ther*. 2006;20:85-91.
27. Civelli M, Cardinale D, Martinoni A, et al. Early reduction in left ventricular contractile reserve detected by dobutamine stress echo predicts high-dose chemotherapy-induced cardiac toxicity. *Int J Cardiol*. 2006;111:120-126.
28. Rosenthal DS, Braunwald E. Cardiac effects of radiation therapy and chemotherapy. In: Braunwald E, ed. *Heart Disease: A Textbook of Cardiovascular Medicine*. Philadelphia, PA: WB Saunders Company; 2001:1746-1751.
29. Schwartz RG, McKenzie WB, Alexander J, et al. Congestive heart failure and left ventricular dysfunction complicating doxorubicin therapy. Seven-year experience using serial radionuclide angiocardiography. *Am J Med*. 1987;82:1109-1118.
30. Marchandise B, Schroeder E, Bosly A, et al. Early detection of doxorubicin cardiotoxicity: interest of Doppler echocardiographic analysis of left ventricular filling dynamics. *Am Heart J*. 1989;118:92-98.
31. Tassan-Mangina S, Codorean D, Metivier M, et al. Tissue Doppler imaging and conventional echocardiography after anthracycline treatment in adults: early and late alterations of left ventricular function during a prospective study. *Eur J Echocardiogr*. 2006;7:141-146.
32. Stoddard MF, Seeger J, Liddell NE, et al. Prolongation of isovolumetric relaxation time as assessed by Doppler echocardiography predicts doxorubicin-induced systolic dysfunction in humans. *J Am Coll Cardiol*. 1992;20:62-69.
33. Eidem BW, Sapp BG, Suarez CR, Cetta F. Usefulness of the myocardial performance index for early detection of anthracycline-induced cardiotoxicity in children. *Am J Cardiol*. 2001;87: 1120-1122.
34. Cardinale D, Sandri MT, Colombo A, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. *Circulation*. 2004;109: 2749-2754.
35. Myers CE, McGuire WP, Liss RH, et al. Adriamycin: the role of lipid peroxidation in cardiac toxicity and tumor response. *Science*. 1977;197:165-167.
36. van Dalen EC, Caron HN, Dickinson H, Kremer L. Cardioprotective interventions for cancer patients receiving anthracyclines. *Cochrane Database Syst Rev*. 2005;CD003917.
37. Schucter LM, Hensley ML, Meropol NJ, Winer EP, for the American Society of Clinical Oncology Chemotherapy and Radiotherapy Expert Panel. 2002 update of recommendations for the use of chemotherapy and radiotherapy protectants: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol*. 2002;20:2895-2903.
38. Cardinale D, Colombo A, Sandri MT, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. *Circulation*. 2006;114:2474-2481.
39. Kalay N, Basar E, Ozdogru I, et al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. *J Am Coll Cardiol*. 2006;48:2258-2262.

40. Jensen BV, Skovsgaard T, Nielsen SL. Functional monitoring of anthracycline cardiotoxicity: a prospective, blinded, long-term observational study of outcome in 120 patients. *Ann Oncol*. 2002;13:699-709.
41. Anand AJ. Fluorouracil cardiotoxicity. *Ann Pharmacother*. 1994;28:374-378.
42. de Forni M, Malet-Martino MC, Jaillais P, et al. Cardiotoxicity of high-dose continuous infusion fluorouracil: a prospective clinical study. *J Clin Oncol*. 1992;10:1795-1801.
43. Kuropkat C, Griem K, Clark J, et al. Severe cardiotoxicity during 5-fluorouracil chemotherapy: a case and literature report. *Am J Clin Oncol*. 1999;22:466-470.
44. Cianci G, Morelli MF, Cannita K, et al. Prophylactic options in patients with 5-fluorouracil-associated cardiotoxicity. *Br J Cancer*. 2003;88: 1507-1509.
45. Rowinsky EK, Donehower RC. Paclitaxel (taxol). *N Engl J Med*. 1995;332:1004-1014.
46. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science*. 1987;235:177-182.
47. Pietras RJ, Arboleda J, Reese DM, et al. HER-2 tyrosine kinase pathway targets estrogen receptor and promotes hormone-independent growth in human breast cancer cells. *Oncogene*. 1995;10:2435-2446.
48. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001;344: 783-792.
49. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*. 2005;353:1673-1684.
50. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al for the Herceptin Adjuvant (HERA) Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med*. 2005;353:1659-1672.
51. Keefe DL. Trastuzumab-associated cardiotoxicity. *Cancer*. 2002;95:1592-1600.
52. Seidman A, Hudis C, Pierri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol*. 2002;20:1215-1221.
53. Routledge HC, Rea DW, Steeds RP. Monitoring the introduction of new drugs—Herceptin to cardiotoxicity. *Clin Med*. 2006;6:478-481.
54. Rastogi P. Five year update of cardiac dysfunction on NSABP B-31, a randomized trial of sequential doxorubicin/cyclophosphamide (AC)→paclitaxel (T) vs. AC→T with trastuzumab(H). Abstract presented at: 43rd Annual Meeting of the American Society for Clinical Oncology; June 1-5, 2007; Chicago, IL.
55. Ewer MS, Vooletich MT, Durand JB, et al. Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. *J Clin Oncol*. 2005;23:7820-7826.
56. Crone SA, Zhao YY, Fan L, et al. ErbB2 is essential in the prevention of dilated cardiomyopathy. *Nat Med*. 2002;8:459-465.
57. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al for the FinHer Study Investigators. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *N Engl J Med*. 2006;354:809-820.
58. Kerkelä R, Grazette L, Yacobi R, et al. Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. *Nat Med*. 2006;12:908-916.
59. Mann DL. Targeted cancer therapeutics: the heartbreak of success. *Nat Med*. 2006;12:881-882.
60. Strebhardt K, Ullrich A. Another look at imatinib mesylate. *N Engl J Med*. 2006;355:2481-2482.
61. Avastin [package insert]. South San Francisco, CA: Genentech, Inc; 2008.
62. D'Amico AV, Denham JW, Crook J, et al. Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. *J Clin Oncol*. 2007; 25:2420-2425.