Cardiovascular Complications of Cancer Therapy
Diagnosis, Pathogenesis, and Management

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Abstract—The cardiotoxicity of anticancer agents can lead to significant complications that can affect patients being treated for various malignancies. The severity of such toxicity depends on many factors such as the molecular site of action, the immediate and cumulative dose, the method of administration, the presence of any underlying cardiac condition, and the demographics of the patient. Moreover, toxicity can be affected by current or previous treatment with other antineoplastic agents. Cardiotoxic effects can occur immediately during administration of the drug, or they may not manifest themselves until months or years after the patient has been treated. In this article we review commonly used chemotherapy agents, including several recently approved medications, for their propensity to cause cardiotoxicity. Further research will be required to more accurately predict which patients are at risk for developing cardiotoxicity. In addition, management plans, as well as strategies to reduce cardiotoxicity, need to be developed. (Circulation. 2004;109:3122-3131.)

Key Words: cardiomyopathy ■ chemotherapy ■ complications ■ drugs

Therapy for cancer has progressed dramatically in recent years, and tremendous progress has been made in reducing the morbidity and mortality from many forms of cancer. An emerging concept is that cancer is a manageable disease, similar to hypertension or diabetes, and requires early detection, periodic surveillance, and coordinated therapeutic decision making. It is therefore critical for cancer survivors to limit comorbid illnesses. Many cancer survivors will actually be at as great a risk from cardiac disease as from recurrent cancer.1 The therapeutic options for patients with cancer now include increasingly complex combinations of medications, radiation therapy, and surgical intervention. Many of these treatments have important potential adverse cardiac effects and are likely to have significant effects on patient outcomes. Therefore, understanding these effects is crucial to their effective management. The purpose of this review is to highlight medications commonly used in the treatment of cancer and their associated cardiovascular complications.

In reviewing the literature of a subject as complex as the cardiovascular complications of cancer treatment, several variables must be considered. Each chemotherapeutic agent has unique cardiac effects as well as the ability to potentiate the adverse effects of other agents. Radiation therapy also plays an important role in magnifying toxicity. It is important to bear in mind that cancer patients undergoing intensive therapy are often severely ill, and cause-and-effect relationships are often unclear. Therefore, in this review we attempt to summarize the current state of knowledge on the cardiovascular complications of cancer therapy on the basis of a review of the literature as well as the extensive clinical experience of the Department of Cardiology at The University of Texas M.D. Anderson Cancer Center.

Grading Cardiovascular Toxicity
Cardiovascular toxicity can be reflected in preclinical and clinical events. Preclinical toxicity may be detected by histopathological or biochemical techniques; for example, doxorubicin-induced myocardial damage may appear in endomyocardial biopsy specimens but may not produce any measurable rise in troponin T or I protein levels. The grading system proposed by the World Health Organization in 1981 to standardize the reporting of drug side effects2 does not consider laboratory cardiovascular changes. The National Cancer Institute developed a more comprehensive system, the common toxicity criteria, in which all of the important clinical and laboratory changes are considered.

Cardiovascular Complications of Chemotherapeutic and Other Anticancer Agents
Cardiotoxic effects associated with chemotherapy agents are listed in Tables 1 and 2, Table 1 according to drug class and
## CARDIOTOXICITY PROFILES OF CHEMOTHERAPEUTIC AGENTS

<table>
<thead>
<tr>
<th>Drug Class/Name, Generic (Brand)</th>
<th>Cardiac Adverse Events</th>
<th>Relative Frequency of Specific Adverse Effect*</th>
<th>Relative Frequency of Therapeutic Use†</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthracyclines/anthraquinolones</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin (Adriamycin)</td>
<td>CHF/LV dysfunction</td>
<td>+++</td>
<td>+++</td>
<td>Risk of CHF is cumulative dose and schedule dependent; LV dysfunction is secondary to free radical production; increased risk for young/elderly, after mediastinal XRT, female gender, history of cardiac disease; continuous infusion, liposomal delivery systems, or use of dexrazoxane can reduce toxicity; when appropriately administered, incidence of LV dysfunction is &lt;5%</td>
</tr>
<tr>
<td>Daunorubicin (Cerubidine)</td>
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<tr>
<td>Epirubicin (Ellence, Pharmorubicin)</td>
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<tr>
<td>Idarubicin (Idamycin)</td>
<td></td>
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</tr>
<tr>
<td>Mitoxantrone (Novantrone)</td>
<td>CHF/LV dysfunction</td>
<td>++</td>
<td>+</td>
<td>Anthraquinone derivative; low propensity for free radical production; myocarditis and arrhythmia can be seen acutely with infusion</td>
</tr>
<tr>
<td><strong>Alkylating agents</strong></td>
<td></td>
<td></td>
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<tr>
<td>Busulfan (Myleran)</td>
<td>Endomyocardial fibrosis</td>
<td>+</td>
<td></td>
<td>CHF risk is increased in elderly, after chest XRT, or after prior anthracyclines</td>
</tr>
<tr>
<td></td>
<td>Cardiac tamponade</td>
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<tr>
<td>Cisplatin (Platinol)</td>
<td>Ischemia</td>
<td></td>
<td></td>
<td>Rare cases of cardiomyopathy after experimental high-dose therapy in combination with cyclophosphamide</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>+++</td>
<td>+++</td>
<td>CHF risk is increased with cumulative dose, in elderly, after chest XRT, or after prior anthracyclines</td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cyclophosphamide</strong> (Cytoxan)**</td>
<td>Pericarditis/ myocarditis</td>
<td>+</td>
<td>+++</td>
<td>Rare incidence of hemorrhagic myocarditis, more common with high dose</td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td>+</td>
<td></td>
<td>CHF risk is increased with cumulative dose, in elderly, after chest XRT, or after prior anthracyclines</td>
</tr>
<tr>
<td>Ifosfamide (Ifex)</td>
<td>CHF</td>
<td>+</td>
<td>++</td>
<td>CHF risk is increased with cumulative dose, prior anthracyclines</td>
</tr>
<tr>
<td>Mitomycin (Mutamycin)</td>
<td>CHF</td>
<td>+</td>
<td>+</td>
<td>CHF risk is increased with cumulative dose, prior anthracyclines, chest XRT</td>
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<tr>
<td><strong>Antimetabolites</strong></td>
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<tr>
<td>Capecitabine (Xeloda)</td>
<td>Ischemia</td>
<td>+</td>
<td>+++</td>
<td>More common in those with CAD; mechanism is potentially vasospasm or thrombosis.</td>
</tr>
<tr>
<td>Cytarabine, Ara-C (Cytosar)</td>
<td>Pericarditis</td>
<td>+</td>
<td>+++</td>
<td>Rare cases of cardiomyopathy after experimental high-dose therapy in combination with cyclophosphamide</td>
</tr>
<tr>
<td>Fluorouracil (Adrucil)</td>
<td>Ischemia</td>
<td>+</td>
<td>+++</td>
<td>Risk increased for CAD, prior chest XRT, concomitant cisplatin therapy; rate and dose dependent; vasospasm is possible mechanism</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>+</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>CHF</td>
<td>+</td>
<td></td>
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<tr>
<td><strong>Antimicrotubules</strong></td>
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<tr>
<td>Paclitaxel (Taxol)</td>
<td>Sinus bradycardia, AV block, ventricular tachycardia</td>
<td>+</td>
<td>+++</td>
<td>Often seen with hypersensitivity; CHF possible if given with doxorubicin</td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td>+</td>
<td></td>
<td></td>
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<tr>
<td><strong>Biological agents</strong></td>
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<tr>
<td>Monoclonal antibodies</td>
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<tr>
<td>Alemtuzumab (Campath)</td>
<td>Hypotension</td>
<td>+++</td>
<td>+</td>
<td>In setting of infusion reactions LV dysfunction rarely seen in patients with mycosis fungoides</td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td>+</td>
<td></td>
<td>Severe hypertension (&gt;200/110 mm Hg) seen in 7% of patients in a recent trial</td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>Hypertension</td>
<td>+++</td>
<td>+</td>
<td>CHF occurred in 14% of patients receiving concurrent anthracyclines</td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td>+</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>DVT</td>
<td>+</td>
<td></td>
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</tr>
<tr>
<td>Cetuximab (Erbitux)</td>
<td>Hypotension</td>
<td>+</td>
<td>+++</td>
<td>In setting of severe infusion reactions (bronchospasm, stridor, urticaria)</td>
</tr>
<tr>
<td>Rituximab (Rituxan)</td>
<td>Hypotension</td>
<td>+++</td>
<td>+</td>
<td>Usually in setting of infusion reactions (hypotension, hypoxia, bronchospasm); severe hypotension and angioedema estimated at 1%</td>
</tr>
<tr>
<td></td>
<td>Angioedema</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arrhythmias</td>
<td>+</td>
<td></td>
<td>Rare fatal cardiac failure; patients with arrhythmias and CAD should be monitored during and after infusion</td>
</tr>
</tbody>
</table>

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patients are given doses of doxorubicin prevalence of cardiomyopathy increases significantly when among patients who actually develop late cardiotoxicity has ular (LV) dysfunction. The mechanism is thought to be direct can result in congestive heart failure (CHF) and left ventric-

cumulative, dose related, and, at sufficiently high dosages, late anthracycline cardiotoxicity is nonspecific ST-segment and T-wave abnormalities. In con-

Anthracyclines are the best studied of the anticancer drugs – approved anthracyclines, doxorubicin, daunorubi-

Acute cardiotoxicity may manifest as solid malignancies. Acute cardiotoxicity may manifest as congestive heart failure (CHF) and left ventric-

interleukins

IL-2

Hypotension

Arrhythmias

+ + + +

+ +

Usually seen at higher doses, associated with capillary leak syndrome (hypotension, hypoperfusion, edema, and effusions); severe hypotension 3%; transient LV dysfunction seen during infusion

Denileukin diftitox (Ontak)

Hypotension

Ischemia

LV dysfunction

+ + + +

+ +

In the setting of a vascular leak syndrome (hypotension, edema, hypoalbuminemia)

Interferon-α

Hypotension

Ischemia

LV dysfunction

+ + +

+ +

Increased risk with preexisting cardiac dysfunction or prior cardiotoxic therapy

Miscellaneous

All-trans retinoic acid (Tretinoin)

CHF Hypotension

Pericardial effusion

+ +

+ +

May occur in the setting of retinoic acid syndrome (respiratory distress, fever, pulmonary infiltrates)

Arsenic trioxide (Trisenox)

QT prolongation

+ + + +

Important to maintain normal electrolytes and to discontinue QT-prolonging drugs; fatal torsades de pointes has been reported

Imatinib (Gleevec)

Pericardial effusion, CHF

Edema

+ +

+ + +

Severe fluid retention can rarely be fatal

Dose related, occurring in 50–70% of patients receiving >300 mg/d

Pentostatin (Nipent)

CHF

Edema

+ +

Rare fatal cardiac toxicity reported after high-dose cyclophosphamide before bone marrow transplantation

Thalidomide (Thalomid)

Edema

Hypotension

DVT

Bradyarrhythmia

+ + + +

Known severe congenital defects in fetuses; prescribers should be registered in STEPS program; patients with multiple myeloma are routinely given low-dose warfarin for DVT prophylaxis

Etoposide (Vepesid)

Hypotension

+ +

+ +

Usually seen with rapid infusion

XRT indicates external beam radiation therapy; DVT, deep vein thrombosis; and STEPS, System for Thalidomide Education and Prescribing Safety.

*Relative frequency of specific adverse effect: + indicates rare (<1%); + +, uncommon (1–5%); + + +, common (6–10%); and + + + +, frequent (>10%).

†Relative frequency of therapeutic use: + indicates infrequent; + +, common; and + + + + , very frequent.

Table 2 according to types of potential cardiotoxic effects (eg, depressed myocardial function, ischemia, or hypotension). To facilitate cross-referencing, both generic and trade names are used.

**Cardiovascular Toxicity:**

Anthracyclines/Anthraquinolones

Anthracyclines are the best studied of the anticancer drugs with established cardiotoxicity. The Food and Drug Administration–approved anthracyclines, doxorubicin, daunorubicin, and epirubicin, are used to treat many hematologic and solid malignancies. Acute cardiotoxicity may manifest as nonspecific ST-segment and T-wave abnormalities. In contrast to early effects, late anthracycline cardiotoxicity is cumulative, dose related, and, at sufficiently high dosages, can result in congestive heart failure (CHF) and left ventricular (LV) dysfunction. The mechanism is thought to be direct myocardial injury due to formation of free radicals. The prevalence of cardiomyopathy increases significantly when patients are given doses of doxorubicin >550 mg/m². However, more recent studies have shown that lower cumulative doses can cause similar cardiomyopathy. The mortality rate among patients who actually develop late cardiotoxicity has been estimated to be high, but the dismal prognosis can be greatly altered by early recognition and treatment. Mitoxantrone, a derivative of the anthracyclines, can cause mild cardiotoxicity that is similar to that caused by anthracyclines at currently used dosages.

Alkylating Agents

Another commonly used class of chemotherapy agents is the alkylators, first used in the treatment of leukemia. A few cases of pericardial and endomyocardial fibrosis occurring 4 to 9 years after busulfan treatment have been reported, but the cumulative doses in these cases usually exceeded 600 mg.

Cyclophosphamide has been used in combination chemotherapy for several solid tumors and lymphomas. Although cyclophosphamide is relatively well tolerated at lower doses, high-dose regimens such as those given with bone marrow transplantation can be associated with a variety of adverse effects. However, the total dose of an individual course, rather than the cumulative dose, seems to be the best predictor of acute cardiotoxicity. Prior treatment with an anthracycline and mediastinal radiation therapy have also been proposed as contributing factors. Subsequent cardiac adverse
TABLE 2. Cardiotoxic Syndromes Associated With Chemotherapeutic Agents

<table>
<thead>
<tr>
<th>Agents associated with myocardial depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
</tr>
<tr>
<td>Mitoxantrone (Novantrone)</td>
</tr>
<tr>
<td>Cyclophosphamide (Cytoxan)—high dose</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin)</td>
</tr>
<tr>
<td>Ifosfamide (Ifex)</td>
</tr>
<tr>
<td>All-trans retinoic acid (Tretinoin)</td>
</tr>
</tbody>
</table>

| Agents associated with ischemia                |
| 5-FU (Adrucil)                                 |
| Cisplatin (Platinol)                           |
| Capcitabine (Keloda)                           |
| IL-2                                          |

| Agents associated with hypotension             |
| Etoposide (Vepesid)                            |
| Paclitaxel (Taxol)                             |
| Alectuzumab (Campath)                          |
| Cetuximab (Erbitux)                            |
| Rituximab (Rituxan)                            |
| IL-2                                          |
| Denileukin (Ontak)                             |
| Interferon-α                                   |
| All-trans retinoic acid (Tretinoin)            |
| Homoharringtonine                              |

| Agents associated with hypertension            |
| Bevacizumab (Avastin)                          |
| Cisplatin (Platinol)                           |

| Agents associated with other toxic effects     |
| Cardiac tamponade or endomyocardial fibrosis: busulfan (Myleran) |
| Hemorrhagic myocarditis: cyclophosphamide (Cytoxan) |
| Bradyarrhythmias: paclitaxel (Taxol), thalidomide (Thalomid) |
| Raynaud phenomenon: vinblastine (Velban) |
| Autonomic neuropathy: vincristine (Oncovin) |
| QT prolongation or torsades de pointes: arsenic trioxide (Trisenox) |
| Pulmonary fibrosis: bleomycin (Blenoxane) |

Events may include heart failure, myocarditis, or pericarditis. Gross changes at autopsy have included increased LV wall thickness with hemorrhagic myocardial necrosis. The mechanism of injury is thought to be related to endothelial and myocyte injury mediated through a toxic metabolite. Acute toxic effects can last up to 6 days, but long-term effects are not usually seen in those who survive. Quezado et al reported a significant, dose-related incidence of heart failure and arrhythmias in patients given ifosfamide. All of the patients who died were found to have increased heart weight and small pericardial effusions at autopsy; less common findings were subendocardial hemorrhage and petechial lesions in the epicardium.

Acute clinical syndromes associated with cisplatin infusion include chest pain, palpitations, and, occasionally, elevated cardiac enzymes indicative of myocardial infarction (MI). A subset of patients receiving cisplatin in combination with cyclophosphamide have developed heart failure; the risk was greatest among those of advanced age or with prior mediastinal irradiation. Cisplatin is unique in that it can cause late cardiovascular complications such as hypertension, LV hypertrophy, myocardial ischemia, and MI as long as 10 to 20 years after the remission of metastatic testicular cancer. Nephrotoxicity, experienced by up to 35% of patients receiving cisplatin, can lead to significant hypomagnesemia and hypokalemia, which in turn can cause cardiac arrhythmias.

Mitomycin has been used in the treatment of many solid tumors. It has been associated with the development of cardiomyopathy, especially when administered with or after an anthracycline. A cumulative dose effect has been suggested, with complications appearing later in the course of treatment. Superoxide radicals form when mitomycin is reduced to a semiquinone radical under aerobic conditions, and this process may play a role in the development of cardiotoxic effects.

**Antimetabolites**

The chemotherapeutic agent 5-fluorouracil (5-FU) is widely used in the treatment of many solid tumor treatment protocols. The most commonly described cardiotoxic effect is the ischemic syndrome, which varies clinically from angina pectoris to acute MI. A “rechallenge” with 5-FU frequently reproduces the clinical cardiotoxicity. The ischemia is usually reversible on cessation of the 5-FU and implementation of anti-ischemic medical therapy. Ischemia can occur in patients without underlying coronary artery disease (CAD) (incidence, 1.1%), but the incidence is higher in patients with CAD (4.5%). Capcitabine is currently used in the treatment of breast and gastrointestinal cancers and is believed to be less toxic than 5-FU. Other reported cardiotoxic effects associated with capcitabine include angina or MI, arrhythmias, ECG changes, and cardiomyopathy.

**Antimicrotubule Agents**

Paclitaxel is used extensively in the treatment of many solid tumors and has recently been used to coat stents for cardiovascular use. It has been reported to cause sinus bradycardia, heart block, premature ventricular contractions, and ventricular tachycardia. Thrombosis has also been reported with the use of paclitaxel. In a large study of approximately 1000 patients, the incidence of cardiac toxicity was 14%, and most incidents (76%) were grade I asymptomatic bradycardia.

Vinca alkaloids are used primarily in the treatment of leukemia and lymphoma. They have been reported to cause autonomic neuropathy, angina with ECG changes, and myocardial ischemia and MI. Vinorelbine-related cardiac events are more likely to occur in women than in men. The occasional clinical presentation of Prinzmetal’s angina and reversible ECG changes has led to the hypothesis of ischemia induced by coronary spasm.

**Monoclonal Antibodies**

Advances in cancer therapy have led to the use of monoclonal antibodies to manage certain hematologic malignancies and solid tumors. Infusion of these agents commonly causes...
hypotension caused by the massive release of cytokines, as well as fever, dyspnea, hypoxia, or even death.33,34 However, they also have unique toxicity profiles specific to the receptors they block.

Alemtuzumab,36 a humanized IgG1 directed against CD52, is used in the treatment of some hematologic malignancies. Alemtuzumab has been associated with infusion-related reactions including hypotension, bronchospasm, and rash, usually during the first week of therapy. LV dysfunction is rare but has been reported in patients with cutaneous T-cell lymphoma who had previously undergone multiple chemotherapy regimens.37 Careful monitoring for hypotension is recommended for patients with preexisting cardiac disease. Antihistamines, acetaminophen, steroids, and slow infusions have all been used to prevent or treat the infusion reactions.

Bevacizumab,38 a humanized monoclonal IgG1 antibody that binds to and inhibits the activity of human vascular endothelial growth factor, was recently approved for use in combination with 5-FU–based therapy for metastatic colorectal carcinoma. Newly developed or worsening hypertension is a commonly observed side effect. In clinical trials, severe hypertension occurred in up to 5% of patients, with rare cases of hypertensive crises of encephalopathy and subarachnoid hemorrhage. In patients previously given antracyclines or with a history of left chest wall irradiation, the incidence of CHF was 4%, and this incidence increased to 14% in patients undergoing concurrent antracycline therapy.39,40

Cetuximab, a human/mouse chimeric monoclonal antibody that binds to the human epidermal growth factor receptor, has been approved for treatment of metastatic colorectal carcinoma with or without irinotecan. Severe, potentially fatal infusion reactions characterized by bronchospasm, urticaria, and hypotension have been noted in approximately 3% of patients.41 Rare cases of interstitial pneumonitis with noncardiogenic pulmonary edema have also been reported.42

Rituximab,43 a chimeric murine/human monoclonal antibody against the CD20 antigen, is used in a wide spectrum of non-Hodgkin lymphoma. Most of the side effects of rituximab are infusion related and occur within the first few hours, especially during the first infusion. Less severe reactions such as hypotension, angioedema, hypoxia, or bronchospasm can be seen in up to 10% of cases.44 Supportive care measures including intravenous fluids, vasopressors, bronchodilators, diphenhydramine, and acetaminophen are usually effective.44

Trastuzumab,45 another recombinant humanized IgG1 monoclonal antibody that selectively binds to the human epidermal growth factor receptor 2 protein (HER2), has been approved for the treatment of breast cancer that overexpresses HER2, a variant that accounts for approximately 25% to 30% of breast cancer cases and is associated with a poorer prognosis.46 The reported incidence of cardiac dysfunction and CHF with trastuzumab has been higher than anticipated, especially when it is used in combination with other cardiotoxic chemotherapy.47 Preexisting cardiac disease, older age, prior cardiotoxic therapy, and radiation to the chest may increase the incidence of cardiotoxicity. However, the true incidence of trastuzumab-induced cardiac dysfunction is not clearly defined. In the initial clinical trials of trastuzumab, use of this agent alone was associated with up to a 2% risk of developing significant cardiac dysfunction (New York Heart Association class III to IV heart failure) and increased to 16% when trastuzumab was used in combination with antracyclines and cyclophosphamide.47 In more recent trials, monitoring LV function before and during treatment and not administering these drugs simultaneously have substantially reduced toxicity.48 The mechanism responsible for the cardiac dysfunction is not known but has been shown to be different from that of doxorubicin and may be secondary to a sequential stress mechanism.49 Animal data have suggested that signaling through HER2 in cardiac myocytes is essential for the prevention of dilated cardiomyopathy.50

Cytokines

Interleukins

Interleukin-2 (IL-2), a T-cell growth factor, has been approved for the treatment of metastatic renal cell carcinoma and melanoma. High-dose IL-2 treatment results in adverse cardiovascular and hemodynamic effects similar to septic shock51 and can lead to hypotension, vascular leak syndrome, and respiratory insufficiency requiring pressors and mechanical ventilation support.52 Severe cases may result in cardiac arrhythmias, MI, cardiomyopathy, and myocarditis.53 Improvements in patient selection and treatment protocols have substantially reduced IL-2 treatment–related toxicity.54 Denileukin diftitox (Ontak), an IL-2/diphtheria toxin fusion protein, is used in the treatment of T-cell lymphoma. It can cause vascular leak syndrome (hypotension, edema, hypoalbuminemia), as well as dyspnea, chest pain, dizziness, and syncope. Slowing or terminating the infusion and administering antihistamines, steroids, and epinephrine can relieve these reactions.55 Premedication with steroids can also prevent or ameliorate acute infusion events.56 Thrombotic events such as deep vein thrombosis, pulmonary embolism, and arterial thrombosis have been reported in approximately 11% of patients.57

Interferons

Interferon-α is produced by macrophages and lymphocytes and has been approved for the treatment of many types of cancer. Interferons usually cause acute symptoms during the first 2 to 8 hours after treatment, including flu-like symptoms, hypotension or hypertension, tachycardia, and nausea and vomiting.51 In severe cases, angina and MI have been reported.

Miscellaneous Agents

All-trans Retinoic Acid

All-trans retinoic acid, a vitamin A derivative, is used in the treatment of acute promyelocytic leukemia. The retinoic acid syndrome appears in approximately 26% of cases,58 typically within the first 21 days of treatment. This syndrome is manifested by fever, dyspnea, hypotension, and pericardial and pleural effusions.59 Other major manifestations of retinoic acid syndrome have included respiratory distress, pulmonary infiltrates, pulmonary edema, and acute renal failure.60 Approximately 17% of patients also showed substantial
Arsenic Trioxide
Arsenic trioxide is used in the treatment of refractory or relapsed acute promyelocytic leukemia. Arsenic is commonly known to cause ECG abnormalities, producing QT prolongation in >50% of patients. Other side effects include sinus tachycardia, nonspecific ST-T changes, and torsades de pointes. In one study, the most common acute side effect was fluid retention with pleural and pericardial effusions. In addition to prolonged QT interval, complete heart block and sudden death have also been reported. In these cases, the infusion of arsenic had been completed 7 to 22 hours before the event, underscoring the importance of continuous monitoring after the infusion has been completed.

Imatinib Mesylate
Imatinib mesylate, an important new agent used in the treatment of chronic myelogenous leukemia and other malignancies, is a specific inhibitor of the BCR-ABL tyrosine kinase found in several types of malignant cells. Imatinib mesylate is associated with a significant incidence of edema, which can progress to severe fluid retention and result in pericardial or pleural effusions or generalized third-space fluid accumulation.

Pentostatin
Pentostatin, a purine analogue used in the treatment of hairy cell leukemia and other hematologic malignancies, may have several cardiotoxic effects, including MI, CHF, and arrhythmias. Cardiotoxicity is particularly prominent when pentostatin is given with high doses of cyclophosphamide in preparation for bone marrow transplantation.

Thalidomide
Thalidomide currently is used to treat a variety of hematologic and solid malignancies. It is relatively safe with regard to cardiovascular complications and is generally well tolerated. Many of the common side effects can be managed by adjusting the dosage. There is evidence that thalidomide might be useful in the treatment of heart failure because of its ability to reduce tumor necrosis factor-α levels. The major cardiotoxic effects of thalidomide are edema and sinus bradycardia and, rarely, deep venous thrombosis.

Etoposide
Etoposide is used mainly in the treatment of refractory testicular tumors and small-cell lung carcinoma. The most common cardiac side effect is hypotension, although myocardial ischemia and MI have also been noted. Patients who have previously undergone chemotherapy or mediastinal radiation may be at increased risk for MI after etoposide treatment, and concomitant chemotherapy with other agents may also be a predisposing factor for MI.

Homoharringtonine
Homoharringtonine, most often used in the treatment of leukemia, can be associated with severe hypotension—a dose-related and occasionally rate-limiting effect that may be related to its calcium channel-blocking activity. Premature ventricular contractions, ventricular tachycardia, and atrial fibrillation have been reported after administration of homoharringtonine.

Risk Factors for Developing Cardiovascular Complications
The cardiotoxicity of a drug depends on many different factors related to the drug itself and to the individual patient. Understanding these factors may help to reduce the occurrence or severity of cardiovascular side effects. The dose of the drug administered during each session, cumulative dose, schedule of delivery, route of administration, combination of drugs given, and sequence of administration of these drugs are some important drug-related factors to consider. Patient-related factors include age, previous cardiovascular disease, radiation therapy, metabolic abnormalities, and hypersensitivity to the drugs given. Knowing the risk factors for chemotherapy-induced cardiovascular complication can help to focus preventive efforts to reduce cardiotoxicity.

Some chemotherapeutic agents evoke cardiotoxicity only when the drug is administered at high doses; examples include CHF and pericarditis with platinum drugs, atrial fibrillation with melphalan, systolic dysfunction and pericarditis with cyclophosphamide, and LV dysfunction with antracyclines. Ifosfamide causes low-grade arrhythmias at doses of 1.2 to 2 g/m² per day for 5 days, but it causes CHF at doses of 10 to 18 g/m². IL-2 causes weight gain when given as a continuous (low) dose of 9×10⁹ IU/m² per day, but it causes hypotension when given as bolus doses of 600 000 IU/kg every 8 hours. The cardiac side effects of antracyclines and cyclophosphamide also depend on the schedule of administration. Administering antracyclines by continuous infusion over 24 to 92 hours rather than by rapid intravenous infusion could reduce the cardiotoxicity of these drugs. Busulfan causes tachyarrhythmias, hypertension or hypotension, and LV dysfunction when injected but not when taken orally. Changing the sequence in which drugs are administered can also reduce cardiotoxicity. For example, the combination of IL-2 and interferon significantly increases hypotension, but delivering interferon alone for the first 2 weeks followed by IL-2 has much less cardiovascular toxicity. The combination of paclitaxel and doxorubicin caused CHF in 20% of cases if the interval between doxorubicin and paclitaxel was 15 to 30 minutes, but increasing the interval to 4 to 16 hours reduced the cardiotoxicity of this combination.

Advanced age is a known risk factor for anthracycline cardiotoxicity, as is previous cardiovascular disease. Infrequently, cardiovascular side effects from a particular drug occur in a specific subset of cancer patients; examples are cardiovascular complications from cisplatin only in patients with metastatic testicular cancer, episodes of cardiotoxicity from low-dose ifosfamide being more common in patients with lymphoma, and alemtuzumab being associated with LV dysfunction in patients with mycosis fungoides.

Cardiotoxicity Associated With Radiation Therapy
Radiation therapy is used in the treatment of many types of cancer. Radiation to the thorax can damage the pericardium, myocardium, valves, and coronary vessels, with the pericar-
Vascular injury from radiation therapy can be silent; approximately 50% of asymptomatic patients develop new myocardial perfusion defects. Clinically, most patients present with angina, dyspnea, or heart failure, although sudden death has been reported. Sudden death in patients given radiation therapy is thought to result from diffuse intimal hyperplasia of all coronary arteries or from significant left main stenosis. The mean interval for developing CAD after radiation therapy is approximately 82 months. Management of radiation-induced CAD is similar to that of atherosclerotic disease. Both percutaneous intervention and coronary artery bypass grafting have been used. Surgical bypass grafting may be more difficult in patients with radiation-induced atherosclerosis because of mediastinal fibrosis, which is associated with a high incidence of complications. Radiation-induced carotid disease produces carotid lesions that are more extensive than the traditional bifurcation stenosis and often involves atypical areas such as long segments of carotid artery.

Radiation therapy also causes fibrous thickening of the pericardium, with the right ventricle more often and more extensively involved. Pericardial disease after radiation therapy most commonly presents as pericardial effusion or pericarditis. The interval between radiation therapy and symptom development in patients with radiation-induced pericardial disease is variable, ranging from 2 to 145 months. Pericardial effusion is typically an early presentation, whereas pericardial constriction is a late manifestation, usually appearing after 18 months.

Myocardial fibrosis is also a side effect of radiation therapy. Fibrosis is characterized by marked alterations in collagen synthesis. Valvular heart disease is also common after radiation because radiation causes fibrous thickening of cardiac valves. Left-sided valves are more often involved than right valves, and only a minority of patients with radiation-induced valvular disease have clinically moderate or severe dysfunction. The mean time from radiation to onset of symptoms is approximately 98 months.

**Monitoring Cardiovascular Toxicity**

The experience with anthracycline cardiotoxicity proved that the early detection and treatment of cardiotoxicity could significantly reduce the development of clinical manifestations. Endomyocardial biopsy is the most sensitive and specific way to diagnose and monitor anthracycline cardiotoxicity, but the invasive nature of this procedure limits its use. Although guidelines have been developed for children receiving anthracyclines, no definite guidelines have been adopted for adults.

The most common noninvasive method of monitoring myocardial toxicity from anthracyclines and other chemotherapeutic agents has been the assessment of LV systolic function, with either radionuclide ventriculography or echocardiography. Fractional shortening and LV ejection fraction are the most commonly used measurements, but both depend on preload and afterload. LV ejection fraction measurements also are not sensitive for the early detection of preclinical cardiac disease.

Several studies have suggested that diastolic dysfunction is an early sign of anthracycline-induced cardiac dysfunction. Thus, measurements of diastolic function by Doppler echocardiography may be a sensitive method for early detection of toxicity. Provocative testing with exercise or dobutamine echocardiography has also been used to assess early anthracycline cardiotoxicity. Thus, these provocative-testing modalities may be sensitive for the early detection of subclinical cardiomyopathy and may provide an opportunity for therapeutic intervention before the development of overt LV dysfunction.

Biomarkers such as troponin I and T may be useful in early detection of doxorubicin cardiotoxicity before the appearance of changes in LV ejection fraction, especially in children. During the past 10 years, several studies have confirmed the usefulness of B-type natriuretic peptide (BNP), a neurohormone elevated in response to volume overload, in the diagnosis and treatment of CHF. Recent studies in patients with cancer have shown that high levels of BNP correlated with impairment of LV function during anthracycline therapy. BNP has also been shown to be elevated before the development of LV dysfunction in patients undergoing high-dose therapy and hematopoietic stem cell transplantation.

Monitoring for other anticancer drug–related cardiotoxic effects such as arrhythmias, ischemic cardiac events, and pericardial disease should be planned and specially tailored for each therapeutic protocol according to which anticancer agents are prescribed. Cardiac tests such as electrocardiography, rest and stress myocardial perfusion imaging, and troponin levels can be used to monitor ischemic cardiac complications. Twenty-four–hour Holter monitoring can be very helpful in detecting and evaluating suspected arrhythmias. Echocardiography has emerged as the test of choice for the noninvasive evaluation of cardiac disease as related to cancer therapy. This tool is essential in the evaluation of LV systolic and diastolic function, pericardial disease, and detailed evaluation of valvular heart disease. Doppler echocardiography can also be used to assess hemodynamic status, including the presence of pulmonary hypertension.

In patients with chemotherapy-induced cardiomyopathy, a decrease in BNP levels after dobutamine stress echocardiography correlated with the presence of contractile reserve. This finding also correlated with long-term improvement in LV systolic function and New York Heart Association class rating when patients were given β-blockers and angiotensin-converting enzyme (ACE) inhibitors.

**Strategies to Reduce Cardiovascular Toxicity and Manage Complications**

Once cardiac toxicity is anticipated, strategies to control these adverse events can be developed, as evidenced by the
changing patterns of anthracycline administration over time. Anthracycline toxicity can be minimized by reducing the total dose to <400 mg/m² and changing the administration from a rapid infusion to a continuous infusion. Newer liposomal formulations also may reduce cardiotoxicity. Dexrazoxane, a derivative of EDTA, can reduce the amount of free iron in myocytes by producing free radicals that decrease oxidized iron levels during anthracycline infusion. Generally, dexrazoxane has been recommended for patients with metastatic breast cancer who have received cumulative anthracycline doses of >300 mg/m²; dexrazoxane is not recommended at the beginning of therapy because of the possibility of reducing the anticancer effect of the anthracyclines. Dexrazoxane has led to improved survival in some studies, but whether this improvement was due to improved cardiac status is unclear. What is known, however, is that dexrazoxane can worsen thrombocytopenia and granulocytopenia.

The evolution of management strategies for trastuzumab-related cardiac toxicity is following a progression similar to that of the anthracyclines. After initial reports that the combination of trastuzumab, anthracyclines, and cyclophosphamide led to severe heart failure in up to 16% of patients with breast cancer undergoing this treatment, the administration strategy was changed to avoid giving these drugs simultaneously, and more stringent cardiac monitoring was instituted. These modifications have considerably reduced toxicity rates. Current studies of trastuzumab for a variety of breast cancer populations will further define the risk of LV dysfunction from such treatment. Trastuzumab-related cardiomyopathy seems to be largely reversible with appropriate therapy. Such therapy would include ceasing the drug, treating cardiac risk factors, and administering appropriate therapy for LV dysfunction. These principles apply to any cardiac toxicity discussed in this review but especially to the management of LV dysfunction. ACE inhibitors and β-blockers are the cornerstones of therapy for LV dysfunction and should be administered to patients with cancer as aggressively as to any other patient population. Interestingly, rechallenge with trastuzumab does not necessarily lead to redevelopment of LV dysfunction or CHF, thus allowing important anticancer therapy to be continued without compromising the patient’s cardiac status.

Much cardiac toxicity can be managed best by removing the offending agent. Unfortunately, in the case of newly developed LV dysfunction, chemotherapy may not be the only explanation for the reduced function, and thus all possible reversible causes should be investigated. In patients with cancer, ischemia is still a reversible cause of LV dysfunction. Cardiac reserve and subsequent improvement after aggressive CHF-based therapy can be predicted by results from dobutamine stress echocardiography. More importantly, once therapy is established, it may need to be continued because withdrawal of therapy in some patients has been associated with serious adverse events.

References


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