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STATE-OF-THE-ART PAPERS

Cardiovascular Complications of Cancer Therapy

Incidence, Pathogenesis, Diagnosis, and Management

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Cancer treatment today employs a combination of chemotherapy, radiotherapy, and surgery to prolong life and provide cure. However, many of these treatments can cause cardiovascular complications such as heart failure, myocardial ischemia/infarction, hypertension, thromboembolism, and arrhythmias. In this article we review the incidence of cardiotoxicity caused by commonly used chemotherapeutic agents as well as discuss the pathogenesis, diagnosis, management, and prevention of these cardiovascular side effects. Cardiotoxicity related to anticancer treatment is important to recognize as it may have a significant impact on the overall prognosis and survival of cancer patients, and it is likely to remain a significant challenge for both cardiologists and oncologists in the future due to an increasing aging population of patients with cancer and the introduction of many new cancer therapies. (J Am Coll Cardiol 2009;53:2231–47) © 2009 by the American College of Cardiology Foundation

Antineoplastic therapy is frequently complicated by the development of cardiotoxicity. This subject is of rising concern for both cardiologists and oncologists since many of these adverse effects are likely to have significant consequences on patient outcomes. Therefore, identifying and understanding these effects is crucial to the successful management of cancer patients with cardiovascular complications.

The purpose of this review is to attempt to summarize the current state of knowledge of common cardiovascular complications, such as heart failure (HF), myocardial ischemia, hypertension (HTN), thromboembolism, QT prolongation, and bradycardia associated with frequently used anticancer medications at the University of Texas M. D. Anderson Cancer Center (MDACC). A MEDLINE search for each of the aforementioned cardiovascular side effects and associated chemotherapeutic agents was performed. The most recent review articles and key research papers establishing the chemotherapy's incidence, diagnosis, pathophysiology, and management of its cardiovascular complications were included. For anticancer therapies in which the incidence of a particular cardiotoxicity was considered rare, or when there were only case reports available, these agents were excluded from this review. During the literature search conducted for this report, we found that in many cases primary literature was lacking in regard to the rate of these side effects reported in the package insert, particularly for newer targeted therapies. In these instances, the package insert was the only published information available to report the incidence of cardiotoxicity. In addition, scientific abstracts presented at national conferences, the Food and Drug Administration (FDA) website, as well as the extensive clinical experience of the Department of Cardiology at MDACC were utilized to comprise this review. The reported rates of cardiotoxicity were obtained from available published literature and they apply to the follow-up periods for each agent, which were variable. Therefore, in this report, incidence should be understood as the number of new cases of cardiotoxicity described over the variable follow-up period studied.

For every cardiotoxic side effect discussed, a table was created. In each of the tables presented, the incidence of the cardiotoxic side effect being discussed is listed. In addition, the frequency of use for each chemotherapeutic agent in the past year (January 1, 2007 to December 31, 2007) at MDACC is represented. If >5,000 doses per year were dispensed, then the agent was assigned +++; if 1,000 to 5,000 doses per year were dispensed, the agent was assigned ++; lastly, if <1,000 doses were dispensed per year, then + was assigned to correspond to its frequency of use.

HF

Several therapies for cancer have been associated with the development of left ventricular dysfunction (LVD) and/or HF. The cumulative dose, the administration schedule, and the concomitant use of other cardiotoxic therapies determine the likelihood of cardiomyopathy (CMP). Table 1 highlights the incidences of LVD associated with selected chemotherapeutic agents.

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
ACS = acute coronary syndrome
ATE = arterial thrombotic event
ATP = adenosine triphosphate
CMP = cardiomyopathy
CTCL = cutaneous T-cell lymphoma
DVT = deep vein thrombosis
FDA = Food and Drug Administration
HF = heart failure
HTN = hypertension
LMWH = low-molecular-weight heparin
LVD = left ventricular dysfunction
LVEF = left ventricular ejection fraction
MI = myocardial infarction
MUGA = multigated acquisition scan
PE = pulmonary embolism
VEGF = vascular endothelial growth factor
VTE = venous thromboembolism
5-FU = 5-fluorouracil

Incidence. ANTHRACYCLINES. Anthracycline-induced cardiotoxicity has been categorized into acute, early-onset chronic progressive, and late-onset chronic progressive (1,2). Acute cardiotoxicity occurs in <1% of patients immediately after infusion of the anthracycline and manifests as an acute, transient decline in myocardial contractility, which is usually reversible (3). The early-onset chronic progressive form occurs in 1.6% to 2.1% of patients, during therapy or within the first year after treatment (3). Late-onset chronic progressive anthracycline-induced cardiotoxicity occurs at least 1 year after completion of therapy in 1.6% to 5% of patients (3). Early- and late-onset chronic progressive cardiotoxicity typically presents as dilated CMP in adults, which can be progressive (2). Late-occurring cardiotoxicity may not become clinically evident until 10 to 20 years after the first dose of cancer treatment. In addition, the Childhood Cancer Survivor study demonstrated that 30 years after therapy, 73% of pediatric cancer survivors will develop at least 1 chronic physical health condition and 42% a severe, life-threatening or disabling condition, or die of a chronic condition (4). The risk of clinical cardiotoxicity increases with a cumulative dose of anthracycline. Studies that have looked at the cumulative probability of doxorubicin-induced HF have found that it occurs in 3% to 5% with 400 mg/m^2, 7% to 26% at 550 mg/m^2, and 18% to 48% at 700 mg/m^2 (3,5,6). However, in a retrospective review of 3 trials, the incidence of HF was found to be 26% with cumulative doses of 550 mg/m^2 (7). For this reason, the maximum lifetime cumulative dose for doxorubicin is 400 to 550 mg/m^2 (3). However, epirubicin or idarubicin appears to have less incidence of HF (8–10). Risk factors for anthracycline toxicity include cumulative dose; intravenous bolus administration; higher single doses; history of prior irradiation; the use of other concomitant agents known to have cardiotoxic effects such as cyclophosphamide, trastuzumab, and paclitaxel; female gender; underlying cardiovascular disease; age (young and old age); and increased length of time since anthracycline completion (1,2,7).

Table 1 Chemotherapy Associated With Left Ventricular Dysfunction

Chemotherapy Agents	Incidence (%)	Frequency of Use
Anthracyclines		
Doxorubicin (Adriamycin) (6,7)	3–26*	+++
Epirubicin (Ellence) (10)	0.9–3.3	++
Idarubicin (Idamycin PFS) (8)	5–18	+
Alkylating agents		
Cyclophosphamide (Cytoxan) (8,11–13)	7–28	+++
Ifosfamide (Ifex) (8,14)	17	+++
Antimetabolites		
Clofarabine (Clolar) (10)	27	+
Antimicrotubule agents		
Docetaxel (Taxotere) (10,15,16)	2.3–8	++
Monoclonal antibody-based tyrosine kinase inhibitors		
Bevacizumab (Avastin) (10,18,19)	1.7–3	++
Trastuzumab (Herceptin) (20–28)	2–28	++
Proteasome inhibitor		
Bortezomib (Velcade) (10,17)	2–5	++
Small molecule tyrosine kinase inhibitors		
Dasatinib (Sprycel) (10)	2–4	++
Imatinib mesylate (Gleevec) (34,35)	0.5–1.7	+
Lapatinib (Tykerb) (32)	1.5–2.2	+
Sunitinib (Sutent) (36,37)	2.7–11	+++

If 5,000 doses per year were dispensed, then the agent was assigned +++; if 1,000 to 5,000 doses per year were dispensed, the agent was assigned ++; lastly, if 1,000 doses were dispensed per year, then + was assigned to correspond to its frequency of use. *At a cumulative dose of 550 mg/m^2. Medication manufacturers (and locations): Adriamycin, Pharmacia & Upjohn SpA, Milano, Italy; Ellence, Idamycin, and Sutent, Pfizer Inc., New York, New York; Cytoxan, Ifex, and Sprycel, Bristol-Myers Squibb, Princeton, New Jersey; Clolar, Genzyme Oncology, Cambridge, Massachusetts; Taxotere, Sanofi-Aventis U.S. LLC, Bridgewater, New Jersey; Avastin and Herceptin, Genentech Inc., South San Francisco, California; Velcade, Millenium Pharmaceuticals, Cambridge, Massachusetts; Gleevac, Novartis Pharmaceuticals Corp., East Hanover, New Jersey; Tykerb, GlaxoSmithKline, Research Triangle Park, North Carolina.

ALKYLATING AGENTS. *Cyclophosphamide.* HF has been associated with cyclophosphamide therapy in 7% to 28% of patients (8,11–13). Clinical manifestations of cardiotoxicity range from asymptomatic pericardial effusions to HF and myopericarditis (11,13). The risk of cardiotoxicity appears to be dose related (>150 mg/kg and 1.5 g/m^2/day) and occurs within 1 to 10 days after the administration of the first dose of cyclophosphamide (8). Besides total dose, risk factors for cardiotoxicity include prior anthracycline or mitoxantrone therapy and mediastinal radiation (8,12).
Ifosfamide. In a retrospective review of patients treated with ifosfamide combination chemotherapy, cardiotoxicity developed in 17% of patients (8,14). Acute onset of HF occurred within 6 to 23 days after the first dose of ifosfamide, and a dose-response trend was observed (doses ≥12.5 g/m^2) (8).

ANTIMETABOLITES. *Clofarabine.* According to the package insert, LVD was noted in 27% of pediatric acute lymphoblastic leukemia patients. In most cases, LVD appeared to be transient (10).

ANTIMICROTUBULE AGENTS. *Docetaxel.* The incidence of HF associated with docetaxel ranges from 2.3% to 8% (10,15,16). In a trial comparing docetaxel plus doxoru-