Cardiovascular Adverse Events Associated With Cancer Therapy

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Abstract

The increasing use of more complex multiagent treatments and multimodal delivery of antineoplastic therapies has resulted in a growing number of cardiovascular complications resulting in cardiotoxicity. These complications may manifest as a relatively benign cardiac dysrhythmia to potentially life-threatening conditions such as hypertensive crisis, myocardial infarction, and heart failure. Prevention, early detection, and continuous monitoring should be the guiding principles in the management of cancer patients receiving these therapies.

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Advances in technology and the development of novel cancer therapies have resulted in increased successful outcomes, with more than 11 million cancer survivors in the United States today (Altekruse, 2009). However, increased survivorship does not come without a price. The increasing use of more complex, intensive multiagent and multimodal delivery of antineoplastic therapies has resulted in a growing number of cardiovascular complications. Antineoplastic therapy—including chemotherapeutic agents, antibody-based therapy, tyrosine kinase inhibitors, and radiation—can affect the functioning of the cardiovascular system, resulting in cardiotoxicity. This toxicity encompasses a heterogeneous group of disorders, ranging from relatively benign cardiac dysrhythmias to potentially lethal conditions such as hypertensive crisis, myocardial infarction, and heart failure.

A wide range of chemotherapeutic agents have been associated with cardiotoxicity (Floyd et al., 2005; Monsuez, Charniot, Vignat, & Artigou, 2010), but the prevalence is not well known because most registries and studies (clinicaltrials.gov) have not analyzed chemotherapy-induced cardiotoxicity. Moreover, there is still no consensus definition of cardiotoxicity. The definitions vary from a spectrum of predefined laboratory findings in asymptomatic patients to changes in left ventricular ejection fraction (LVEF). The National Cancer Institute (NCI) defines cardiotoxicity as "toxicity that affects the heart" (NCI, 2011). The threshold value for LVEF measurement is not established in the definition. However, one of the most utilized clinical definitions of cardiotoxicity has been formulated by the Cardiac Review and

Evaluation Committee for supervising trastuzumab (Herceptin) clinical trials (Seidman et al., 2001). The following criteria were used in the trastuzumab clinical trials to confirm or revise the preliminary diagnosis of cardiac dysfunction: (1) cardiomyopathy characterized by a decrease in cardiac LVEF that was either global or more severe in the septum; (2) symptoms of congestive heart failure (CHF); (3) associated signs of CHF, including but not limited to S3 gallop, tachycardia, or both; and (4) decline in LVEF of at least 10% to below 55% without accompanying signs and symptoms (Seidman et al., 2001). Any one of the four criteria was sufficient to confirm a diagnosis of cardiac dysfunction.

The development of cardiotoxicity not only has a negative impact on the patient's quality of life, but also limits the choice of possible cancer treatments. The purpose of this article is to discuss the potential adverse cardiovascular effects that may result from cancer treatments, including hypertension, myocardial ischemia, venous thromboembolism (VTE), QTc prolongation, bradycardia, pericarditis, cardiomyopathy, and heart failure. The adverse effects associated with radiation therapy will also be discussed because of its major contributory effect on the development of the cardiovascular complications in cancer patients with prior history of therapy. Management of heart failure, which is usually a terminal end result of these cardiac complications in a cancer patient, will also be addressed.

Hypertension

Hypertension is a well-known side effect of angiogenesis inhibitors; it is highly debated as to whether this marker is a sign of clinical toxicity or in fact a therapeutic target predictive of treatment success (van Heeckeren, Ortiz, Cooney, & Remick, 2007). With five angiogenesis inhibitors (bevacizumab [Avastin], sorafenib [Nexavar], sunitinib [Sutent], pazopanib [Votrient], and vandetanib [Caprelsa]) currently approved by the US Food and Drug Administration for marketing and several others still in the pipeline, there is an increased need for advanced practitioners to recognize the proposed mechanisms for angiogenesis inhibitor–induced hypertension and use them to tailor treatment strategies.

PATHOGENESIS

One major pathway implicated in angiogenesis inhibitor–induced hypertension is decreased nitric oxide (NO) production in arteriole walls and other vessels via inhibition of vascular endothelial growth factor (VEGF) (Chen & Cleck, 2009). Nitric oxide is a naturally occurring vasodilator. Decreased production can result in vasoconstriction, an increase in systemic vascular resistance (SVR), and ultimately hypertension. Another mechanism that is not completely understood is vascular rarefaction, which is a functional decrease in the number of arterioles; this condition is thought to lead to a decrease in perfusion, resulting in an increase in SVR (Izzedine et al., 2009; Maitland et al., 2010). Anticancer medications that may cause hypertension are listed in Table 1.

Myocardial Ischemia

Myocardial ischemia is a condition caused by a partial or complete blockage of blood supply to the heart muscle, usually due to the atherosclerosis of the coronary arteries. The decrease in blood flow reduces the heart's oxygen supply, often resulting in chest pain. A number of chemotherapeutic agents are known to cause myocardial ischemia (Table 2).

Table 1. Cancer Drugs That Can Cause Hypertension

Drug	Overall incidence	Grade ≥ 3
Monoclonal antibody–based TKI		
Bevacizumab[a]	4%–35.9%	11%
VEGF Trap		
Aflibercept	46%	18%
Small-molecule TKIs		
Axitinib	30%	5%
Cediranib	72%	33%
Motesanib	56%	25%
Pazopanib[a]	40%–47%	8%
Sorafenib[a]	17%–43%	4%
Sunitinib[a]	5%–24%	8%
Vandetanib[a]	21%	2%

Note. TKI = tyrosine kinase inhibitor.
[a]FDA approved.
Information from Clinical Pharmacology 2010, Escudier et al. (2007); GlaxoSmithKline (2010), Miller et al. (2007), Thomson Reuters Micromedex (2011), and Yeh & Bickford (2009).

Table 2. Anticancer Drugs That Can Cause Myocardial Ischemia

Drug	Incidence
Antimetabolites	
Fluorouracil	1%–68%
Capecitabine	3%–9%
Antimicrotubule agents	
Paclitaxel	< 1%–5%
Docetaxel	1.7%
Monoclonal antibody–based TKIs	
Bevacizumab	0.6%–1.5%
Small-molecule TKIs	
Erlotinib	2.3%
Sorafenib	2.7%–3%
Pazopanib	5%

Note. TKI = tyrosine kinase inhibitor.
Information from Clinical Pharmacology (2010), Thomson Reuters Micromedex (2011), Pai & Nahata (2000), Sugrue et al. (2007), and Van Cutsem et al. (2002).

Table 3. Medications That Can Cause Thromboembolism

Drug	Incidence
Alkylating agent	
Cisplatin	8.5%
Angiogenesis inhibitors[a]	
Thalidomide	1%–58%
Lenalidomide	3%–75%
Histone deacetylase inhibitor	
Vorinostat	4.7%–8%
Small-molecule TKI	
Erlotinib	2.9%–11%
Monoclonal antibody-based TKI	
Bevacizumab	8.5%

Note. TKI = tyrosine kinase inhibitor.
[a]The incidence of venous thromboembolism for angiogenesis inhibitors reported in the literature varies considerably depending on the patients' disease status, concomitant use of high- or low-dose steroids, erythropoietin, or other chemotherapeutic agents, and whether or not proper thromboprophylaxis was employed during the study period.
Information from Clinical Pharmacology (2010), Czaykowski et al. (1998), Hirsh (2007), Nalluri et al. (2008), Rajkumar (2005), and Thomson Reuters Micromedex (2011).

PATHOGENESIS

The exact mechanism by which fluorouracil (5-FU) and capecitabine (Xeloda) induce ischemia is unknown, but coronary artery thrombosis, arteritis, and vasospasms have been accepted as the most probable causes (Yeh & Bickford, 2009). While some studies suggest that these agents cause direct myocardial ischemia through endothelial damage, changes in platelet aggregation, abnormalities of coagulation proteins, and significant decrease in protein-C activity may be contributory (Saif, Tomita, Ledbetter, & Diasio, 2008). Risk factors associated with ischemia include concomitant radiation therapy, continuous infusions rather than bolus dosing, and preexisting coronary artery disease (Saif et al., 2008; Yeh et al., 2004).

Paclitaxel-induced myocardial ischemia is thought to be precipitated by multifactorial conditions, such as advanced age and severe systemic illness; patients with impaired renal function are at the highest risk for complications (Rowinsky et al., 1991; Yeh & Bickford, 2009). Many believe that the Cremophor EL vehicle in which the drug is produced may also contribute to the toxicity by eliciting a cardiac histamine response (Rowinsky et al., 1991).

Anticancer therapies that target VEGF pathways may induce ischemia through a decrease in nitric oxide and prostacyclin formation, as well as through an increase in hematocrit and blood viscosity as a result of overproduction of erythropoietin (Kamba & McDonald, 2007).

Thromboembolism

Cancer is known to affect clotting pathways and induce a hypercoagulable state. In fact, the overall risk of VTE is increased 7- to 10-fold in patients with malignancy (Palumbo et al., 2008). As a result, it becomes increasingly challenging to treat patients with anticancer therapies known to cause thrombotic events (Table 3). It can also be difficult to delineate clear mechanisms by which the medications stimulate thrombus formation since baseline hemostasis abnormalities exist (Yeh & Bickford, 2009).

Cisplatin has been shown to induce platelet activation and aggregation when studied in the labo-

ratory. This may be due to monocyte procoagulate activity or an alteration in endothelial cell integrity (Czaykowski, Moore, & Tannock, 1998). Thromboembolic events caused by thalidomide (Thalomid) and lenalidomide (Revlimid) may also involve an interaction between platelets and the endothelium (Zangari, Elice, Fink, & Tricot, 2007). Increased levels of platelet aggregation and von Willebrand factor have been found in patients treated with thalidomide (Baz et al., 2005).

Bevacizumab is also known to be associated with an increase in thromboembolic events. This is thought to be attributable to an increase in endothelial cell apoptosis, disturbances in platelet–endothelial cell homeostasis, increase in platelet aggregation, and exposure of the extracellular matrix to blood cells (Chen & Cleck, 2009; Kamba & McDonald, 2007).

QTc Prolongation

QTc (heart rate–corrected QT) prolongation, which may occur as an adverse effect of a number of chemotherapeutic agents (Table 4), can result in serious consequences. The clinical diagnosis of QTc prolongation is based solely on interpretation of the electrocardiogram (ECG). Because of its inverse relationship to heart rate, the measured QT interval is routinely corrected by means of various formulas to a less heart rate–dependent value known as the QTc interval. QTc interval can be calculated using Bazzett's formula (the QT interval divided by the square root of the RR interval). The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the ECG, which represents the electrical depolarization and repolarization of the right and left ventricles. A prolonged QT interval is a biomarker for ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death. Torsades de pointes is a form of ventricular tachycardia associated with prolongation of the QT interval. A prospective population-based Rotterdam study found that prolongation of the QTc interval increased the risk of sudden cardiac death in adult patients by 60%, independent of other known risk factors (Straus et al., 2006).

A normal QTc interval is ≤ 440 ms; it is considered prolonged if it is greater than 450 and 470 ms in men and women, respectively. Clinicians should pay particular attention to increases in the QTc ≥ 60 ms from baseline or if the QTc prolongs to ≥ 500 ms following the administration of a medication. Both of these changes can put patients at risk of developing arrhythmias and torsades de pointes. If the patient should become symptomatic, the offending agents should be discontinued immediately (Vorchheimer, 2005; Yeh & Bickford, 2009).

Table 4. Cancer Drugs That Can Cause QTc Prolongation

Drug	Incidence
Miscellaneous	
Arsenic	26%–93%
Histone deacetylase inhibitors	
Vorinostat	3.5%–6%
Romidepsin	Unreported[a]
Small-molecule TKIs	
Lapatinib	16%
Nilotinib	1%–10%
Pazopanib	< 2%
Dasatinib	< 1%–3%
Sunitinib	< 0.1%

Note. TKI = tyrosine kinase inhibitor.
[a]While the exact incidence of QT prolongation with Romidepsin has not been reported in the literature, the package insert lists QT prolongation as a warning and reminds practitioners to ensure that both potassium and magnesium are within the normal range before administration.
Information from Clinical Pharmacology (2010), Thomson Reuters Micromedex (2011), and Yeh & Bickford (2009).

PATHOGENESIS

The mechanism underlying the QT prolongation associated with many cancer therapies remains unknown. When discussing drug-induced QT prolongation, it is understood that the blockade of delayed rectifier potassium current by medications is at least in part responsible for their proarrhythmic effect (Strevel, Ing, & Siu, 2007; Viskin, 1999). In addition, one or more risk factors in the presence of underlying long QT syndrome may lead to significant QT interval prolongation (Strevel et al., 2007). Many cancer patients are thought to be predisposed to QTc prolongation due to comorbid disease states, electrolyte disturbances as a result of malnutrition, nausea and vomiting, as well as increased use of medications such as antiemetics and azole antifungals

that are known to prolong the QTc interval (Strevel et al., 2007; Yeh & Bickford, 2009).

When initiating QTc-prolonging agents in this population it is important to conduct a pretreatment evaluation and to continue screening patients throughout the course of therapy. Baseline ECGs should be performed to evaluate the QTc interval prior to therapy, and patients at high risk of QTc prolongation should be identified. Some examples of high-risk groups include the elderly, women, patients with advanced heart failure, patients using concomitant medications that can prolong the QTc interval (i.e., antiemetics, antifungals, quinolones, selective serotonin receptor antagonists, and methadone), and patients receiving medications known to cause electrolyte abnormalities, specifically hypokalemia and hypomagnesemia (i.e., diuretics) (Strevel et al., 2007; Viskin, 1999). Patients with renal insufficiency, hepatic dysfunction, congenital QTc abnormalities, or a known family history of sudden cardiac death are also considered to be at high risk (Vorchheimer, 2005).

TORSADES DE POINTES

Torsades de pointes, mentioned previously, is a rare complication associated with QTc prolongation that can have life-threatening consequences if not properly managed. As an initial course of treatment, all patients should be given a 2-g IV bolus of magnesium sulfate, regardless of serum magnesium level. This can be followed by a continuous infusion at a rate of 2–4 mg/min (Viskin, 1999). Potassium levels should also be kept in the high normal range, targeting a potassium > 4.5 mmol/dL (Viskin, 1999). In addition, any medications that either prolong the QTc or inhibit the metabolism of QTc-prolonging agents should be discontinued immediately (Vukmir, 1991; Yeh & Bickford, 2009).

Another treatment strategy is to shorten the QTc interval by increasing the heart rate. This can be achieved by using either overdrive transvenous temporary pacing or a medication like isoproterenol titrated to a heart rate > 90 beats/min if pacing is not available. Isoproterenol should not be used in patients with congenital QTc prolongation, ischemic heart disease, and hypertension (Khan & Gowda, 2004). If the patient becomes unstable at any time or if torsades de pointes deteriorates into polymorphic ventricular fibrillation, unsynchronized defibrillation would be indicated (Viskin, 1999; Vukmir, 1991; Yeh & Bickford, 2009).

Bradycardia

Sinus bradycardia is a regular but unusually slow heart rate of less than 60 beats/min at rest, which results from certain medications (Table 5) and some forms of heart block. There are several underlying mechanisms for different conditions resulting in sinus bradycardia. Paclitaxel and thalidomide have been seen to precipitate the occurrence of sinus bradyarrhythmias.

PATHOGENESIS

Two possible mechanisms explaining the probable cause of conduction abnormalities seen during the administration of paclitaxel have been explored in the literature. First is the idea that selective stimulation of cardiac histamine receptors would increase myocardial oxygen demand in the heart, leading to coronary vasoconstriction and negative chronotropic effects (Rowinsky et al., 1991). Second is the thought that Cremophor EL, the vehicle the drug is suspended in, can trigger the histamine response pathway and lead to the conduction abnormalities (Arbuck et al., 1993; Rowinsky et al., 1991).

The mechanism by which thalidomide causes bradycardia remains unclear, but many hypotheses have been made. One thought is that thalidomide may actually induce hypothyroidism in some patients, which could lead to bradycardia (Kaur, Yu, Lee, & Chiao, 2003). Another thought is that the slow heart rate may be attributed to thalidomide's central sedative effect (Coutsouvelis & Corallo, 2004). There has also been some evidence suggesting that thalidomide can cause vagal inhibition through

Table 5. Medications That Can Cause Bradycardia

Drug	Incidence
Antimicrotubule agent	
Paclitaxel	< 0.1%–31%
Angiogenesis inhibitor	
Thalidomide	0.12%–55%

Note. Information from Clinical Pharmacology (2010), Fahdi et al. (2004), Rowinsky et al. (1991), and Yeh & Bickford (2009).

exposure to tumor necrosis factor–alpha (TNFα), leading to overactivity of the parasympathetic system and a decrease in heart rate (Tseng et al., 2001).

Pericarditis

Acute pericarditis is an inflammation of the pericardium characterized by chest pain, pericardial friction rub, and ECG changes. While uncommon, pericarditis is a known side effect of many anticancer therapies (Table 6). Case reports provide evidence of cytarabine-induced pericarditis developing in patients, but the mechanism behind it is unclear. One hypothesis is that the administration of cytarabine may trigger the event via an immune-mediated hypersensitivity reaction that can occur anywhere from 3 to 28 days after treatment (Reykdal, Sham, & Kouides, 1995). Anthracyclines have also been associated with pericarditis, more specifically acute fibrinous myopericarditis, although the mechanism behind this is not well understood. However, there are two distinct timeframes for pericarditis to develop: early acute pericarditis, which can occur during treatment and is usually the result of tumor lysis, or delayed onset acute pericarditis (Berry & Jorden, 2005). The mechanism by which the other therapies cause pericarditis is not well understood.

Table 6. Medications That Can Cause Pericarditis

Antimetabolite
Cytarabine
Anthracyclines
Doxorubicin
Daunorubicin
Folic acid antagonist
Methotrexate
Small-molecule tyrosine kinase inhibitor
Imatinib
Antitumor antibiotic
Bleomycin
Alkylating agents
Cyclophosphamide

Note. Information from Clinical Pharmacology (2010) and Thomson Reuters Micromedex (2011).

Radiation-Associated Cardiovascular Effects

Radiation therapy used either alone or in combination with other modalities is frequently a mode of treatment for different types of cancer. Patients who have received high-dose radiation to the chest involving a substantial volume of the heart can damage the cardiac structure including the pericardium, myocardium, heart valves, coronary arteries, capillaries, and the conduction system, resulting in cardiovascular complications (Table 7). The incidence of radiation-induced cardiac disease, which can occur 5 to 10 years after initial treatment, is 10% to 30% (Carver et al., 2007). Radiation pericarditis is the most common acute manifestation of radiation injury, while the late effects such as chronic pericardial disease, arrhythmias, cardiomyopathy, valvular disease, carotid artery disease, and conduction abnormalities may manifest years after the treatment is completed.

The pathophysiology of radiation injury is related to the damage to the capillary endothelial cells of the blood vessels. This injury results in inflammatory changes that lead to diffuse fibrosis in the interstitium of the myocardium, resulting in the narrowing of the capillary and arterial lumen (Cuzick et al., 1994). The ratio of capillaries to myocytes is reduced by 50%, and this leads to myocardial cell death, ischemia, and fibrosis (Hooning et al., 2006). Myocardial fibrosis can compromise

Table 7. Cardiovascular Complications of Radiation Therapy

Complication	Description
Pericardial disease	Constrictive pericarditis, pericardial effusion/tamponade
Coronary artery disease	Premature fibrosis/ atherosclerosis
Valvular disease	Aortic stenosis, mitral stenosis
Cardiomyopathy	Constrictive cardiomyopathy, diastolic dysfunction
Conduction abnormalities	A-V blocks, complete heart block

Note. Information from Adams & Lipschultz (2005) and Berry & Jorden (2005).

cardiac compliance resulting in diastolic dysfunction (Heidenreich, Hancock, Vagelos, Lee, & Schnittger, 2005), and fibrosis of cells in the conduction system can predispose to dysrhythmias (Larsen et al., 1992; Orzan et al., 1993).

The development of radiation-induced cardiotoxicity can be precipitated by a number of risk factors, including younger age at time of treatment, history of coronary artery disease, hypertension, smoking, total radiation dose received, volume of heart irradiated, and concomitant administration of cardiotoxic agents such as anthracyclines and trastuzumab.

Cardiomyopathy

Cardiomyopathy is defined by the World Health Organization as a disease of the myocardium associated with cardiac dysfunction (Richardson et al., 1996). The American Heart Association expounded the definition that cardiomyopathy is either confined to the heart or a part of generalized systemic disorders, often leading to cardiovascular death or progressive heart failure–related disability (Maron et al., 2006). Cardiomyopathies are divided into either primary or secondary, based on organ involvement (Maron & Thiene, 2008). Cardiomyopathies resulting from cancer therapy are considered secondary, and have been associated with a wide variety of cancer drugs (Table 8).

Anthracycline-based chemotherapy, which is frequently used in the treatment of many types of cancer, has been implicated with cardiotoxicity resulting in cardiomyopathy. The onset can be acute, chronic early, or chronic late, and the injury to the cardiomyocytes is not always reversible (Yeh, 2006) as shown in Table 9. When assessing a patient's risk for toxicity, advanced practitioners should focus on cumulative dose administered, schedule of administration, and concomitant administration of other cardiotoxic therapies.

PATHOGENESIS

While no clear mechanism for anthracycline-induced cardiomyopathy has been established, it is widely attributed to an increase in oxidative stress on the myocardium. This increase in oxidative stress leads to the formation of free radicals and superoxides and causes a decrease in the production of nitric oxide (Schimmel, Richel, van den Brink, & Guchelaar, 2004). Other hypotheses that have been discussed in the literature include apoptosis, inhibition of cardiac lipid peroxidation which affects the iron-oxygen complexes in the myocardium, alterations in mitochondrial calcium transport that lead to tissue damage and

Table 8. Anticancer Drugs That Can Cause Cardiomyopathy

Drug	Incidence
Anthracyclines	
Doxorubicin	3%–26%
Epirubicin	0.9%–3.3%
Idarubicin	5%–18%
Alkylating agents	
Cyclophosphamide	7%–28%
Ifosfamide	17%
Anthraquinone	
Mitoxantrone	2.6%–13%
Antitumor antibiotic	
Mitomycin	15.3%[a]
Antimetabolite	
Clofarabine	27%
Antimicrotubule agent	
Docetaxel	2.3%–8%
Proteosome inhibitor	
Bortezomib	2.5%
Monoclonal antibody–based TKIs	
Bevacizumab	1%–3.8%
Trastuzumab	2%–28%
Small-molecule TKIs	
Dasatinib	2%–4%
Imatinib	0.5%–1.7%
Lapatinib	0.2%–2.2%
Sunitinib	4%–11%
Sorafenib	< 1%

Note. TKI = tyrosine kinase inhibitor.
[a]When used in combination with doxorubicin.
Information from Clinical Pharmacology (2010), Guarneri et al. (2006), Khakoo et al. (2008), Swain et al. (2003), Thomson Reuters Micromedex (2011), Pai & Nahata (2000), and Yeh & Bickford (2009).

Table 9. Three Types of Anthracycline-Induced Cardiomyopathy

Type	Onset	Clinical manifestations
Acute onset	Any time from the initiation or within 2 weeks of therapy	ECG changes, arrhythmias (supraventricular and ventricular) ventricular dysfunction, increase in BNP, pericarditis/myocarditis syndrome to acute fulminant heart failure, death
Early-onset chronic progressive	Within 1 year of treatment	Subclinical decline in myocardial function or symptoms of clinical heart failure
Late-onset chronic progressive	After 1 year to decades after therapy	Subclinical decline in myocardial function or symptoms of clinical heart failure

Note. BNP = brain natriuretic peptide; ECG = electrocardiogram. Information from Bristow et al. (1978), Pai & Nahata (2000), Silber et al. (2004), and Wouters et al. (2005).

weakened cardiac contractility, as well as immune-mediated pathways triggered by anthracycline-induced damage of plasma membranes of cardiac myocytes (Schimmel et al., 2004). Several risk factors can predispose patients to the development of anthracycline-induced cardiomyopathy, as outlined in Table 10.

Alkylating agents such as cyclophosphamide, on the other hand, are thought to cause direct endothelial injury triggered by the accumulation of toxic metabolites that lead to cardiac myocyte damage, interstitial hemorrhage, and edema (Senkus & Jassem, 2011; Viale & Yamamoto, 2008; Yeh & Bickford, 2009). One of the characteristic signs of cyclophosphamide-induced toxicity found on autopsy is the thickening of left ventricular walls with hemorrhagic necrosis of the myocardium (Yeh et al., 2004). Cyclophosphamide may also trigger intracapillary microemboli or coronary vasospasm. It is important to note that, unlike anthracyclines, toxicity related to cyclophosphamide is thought to be a result of individual doses rather than a cumulative dose effect, with doses of greater than 1.5 mg/m^2 associated with the highest incidence of cardiomyopathy (Viale & Yamamoto, 2008; Yeh & Bickford, 2009). One could also hypothesize that since ifosfamide is structurally similar to cyclophosphamide, the mechanism for inducing heart failure would also be similar; however, no evidence of hemorrhagic myocarditis has been found in these patients (Yeh & Bickford, 2009).

Trastuzumab is a monoclonal antibody that targets the human epidermal growth factor receptor 2 (HER2) receptor signaling pathway in breast cells. It is this inhibition of HER2 that is

Table 10. Risk Factors for Anthracycline-Induced Cardiomyopathy

Risk factor	Description
Cumulative dose of chemotherapy	Higher incidence in cumulative dose > 300 mg/m^2 of doxorubicin or > 600 mg/m^2 of epirubicin (1% to 5% up to 550 mg/m^2, 30% at 600 mg/m^2, and 50% at 1 gm/m^2 or higher)
Age at time of exposure	Extremes of age (< 18 years or > 65 years), development of cardiotoxicity even at lower cumulative dose
Concomitant administration of other cardiotoxic drugs	Combination chemotherapy (paclitaxel, trastuzumab, cyclophosphamide, etoposide, melphalan, mitoxantrone, idarubicin)
Concurrent or prior chest irradiation	Radiation involving the left side of the chest
Preexisting cardiovascular disease	Presence of coronary artery disease, hypertension, or left ventricular dysfunction
Longer duration of survival	Chronic cardiotoxicity may occur even 30 years after treatment

Note. Information from Carver et al. (2007) and Swain et al. (2003).

most likely responsible for the medication's cardiotoxic effects. Blocking the HER2 pathway prevents important cell-protective, growth-promoting, antiapoptotic pathways in the myocardium from functioning and may lead to an increase in cell death (Schimmel et al., 2004; Senkus & Jassem, 2011). It is also believed that normal HER2 signaling is necessary to repair the oxidative damage anthracyclines can cause (Senkus & Jassem, 2011). This may be part of the reason why cardiotoxic effects of trastuzumab are thought to be additive when combined with anthracyclines (Senkus & Jassem, 2011).

Heart Failure

Heart failure (HF) can be the terminal end result of the cardiotoxic adverse effects of cancer therapy and other comorbid conditions. Similar to cancer, HF is a dreaded diagnosis characterized by clinical stages that predict survival and outcome, ultimately resulting in a terminal phase (Hoshijima & Chien, 2002). Heart failure is a complex clinical syndrome that can result from myocardial muscle dysfunction or loss and is characterized by left ventricular dilation or hypertrophy (Maitland et al., 2010). The most common cause of HF in the general population is coronary artery disease resulting from ischemic cardiomyopathy (Fadol, 2006; Macabasco-O'Connell, Rasmusson, & Fiorini, 2006). However, in cancer patients HF is usually of nonischemic etiology secondary to chemotherapy-induced cardiomyopathy. Moreover, several other comorbid conditions can potentially result in HF in a cancer patient (Table 11).

The prevalence of heart failure in cancer patients is not clearly established, but data from the oncology literature indicate that more than 50% of all patients exposed to anthracyclines will show some degree of cardiac dysfunction 10 to 20 years after treatment, and 5% of those patients will develop overt HF (Steinherz, Steinherz, Tan, Heller, & Murphy, 1991). The overall incidence of this diagnosis may be underestimated in the 11 million cancer survivors and the more than 60,000 patients in the United States who receive anthracycline every year (Silber et al., 2004). Compared to HF from other causes, cancer treatment–related heart failure is associated with a significantly poorer prognosis, with a 2-year mortality rate of up to 60% (Felker et al., 2000; Saini, Rich, & Lyss, 1987; Von Hoff et al., 1979).

Heart failure is often classified as either systolic HF or HF with preserved left ventricular function (diastolic HF) based on a normal LVEF value of ≥ 50% (Pfisterer, Battler, & Zaret, 1985). Systolic dysfunction is characterized by a decrease in LVEF (less than 50%) in contrast to diastolic dysfunction with normal LVEF (≥ 50%). Following chemotherapy, 50% of asymptomatic patients with normal LVEF have diastolic dysfunction on echocardiogram (Tjeerdsma et al., 1999).

PREVENTION

The best treatment for heart failure in cancer patients is prevention of its occurrence. Measures to prevent HF include the following: (1) maintaining adequate blood pressure control in patients on vascular endothelial growth factor (VEGF) inhibitors, (2) closely monitoring cardiac function while receiving chemotherapy with potential cardiotoxic adverse effect, (3) limiting the lifetime cumulative dose of anthracyclines and its analogs, (4) altering the anthracycline mode of administration (e.g., continuous infusion vs. bolus administration), (5) utilizing anthracycline analogs (e.g., liposomal anthracyclines), (6) adding cardioprotectants (e.g., dexrazoxane) to anthracycline treatment, (7) using cardiac biomarkers for early detection of cardiotox-

Table 11. Other Causes of Heart Failure in Cancer Patients

Amyloidosis
Cardiotoxic chemotherapy
Coronary artery disease
Endocarditis, myocarditis
Hemochromatosis
Hypertension
Mantle radiation to the chest
Persistent tachycardia
Pericardial disease
Stress induced (Takostubo cardiomyopathy)
Sepsis
Thyroid disorders

Note. Information from Boufidou et al. (2010), Murphy & Oudit (2010), Ewer & Lippman (2005), Giampaolo et al. (2011), Hunt et al. (2005), Martinelli et al. (2011), and Prasad et al. (2008).

icity, and (8) initiating the recommended pharmacologic heart failure regimen at the initial detection of ventricular dysfunction.

DIAGNOSIS

Heart failure is identified by the presence of cardinal symptoms of fatigue, edema, and shortness of breath resulting from ventricular dysfunction (Lenihan, 2006). The New York Heart Association (NYHA) functional classification (The Criteria Committee of the NYHA, 1994) is widely used to categorize heart failure patients based on clinicians' interpretation of patients' reported symptoms (Hurst, Morris, & Alexander, 1999). However, establishing a definitive diagnosis of HF in cancer patients based on symptoms alone is challenging because HF, cancer, and the adverse effects of cancer treatment share similar signs and symptoms. Advanced practitioners should perform a thorough history and physical examination to identify the exact etiology of HF to guide therapeutic intervention. Possible etiologic conditions outlined in Table 11 should be investigated. Certain specific tests described in Table 12, in addition to the standard HF diagnostic work-up, are needed to establish the diagnosis of heart failure in a cancer patient.

TREATMENT

The specific treatments of HF in cancer patients have not been extensively studied. To date, there is no consensus regarding which medications are recommended for chemotherapy-induced heart failure. The nationally accepted HF clinical practice guidelines published by the American College of Cardiology, American Heart Association, and Heart Failure Society of America are used in the management of these patients. The guidelines recommend a range of interventions from prevention to medical management based on stages A through D (Hunt et al., 2005). Stage A, which includes patients exposed to cardiotoxic chemotherapy, focuses on risk factor reduction such as controlling hypertension, diabetes,

Table 12. Diagnostic Tests to Evaluate for Heart Failure in Cancer Patients

Diagnostic test	Purpose
Electrocardiogram	To detect arrhythmias (premature ventricular contractions) or atrial fibrillation which may cause or exacerbate heart failure
Chest x-ray	To evaluate for pulmonary edema, pleural effusion, and cardiomegaly
Echocardiogram	To detect decrease in left ventricular ejection fraction, valvular problems, and wall motion abnormalities; longitudinal strain used for early detection of cardiotoxicity
Nuclear imaging	To detect the location and severity of coronary artery disease
Coronary arteriography	To evaluate for blockages in the coronary arteries
Endomyocardial biopsy	To diagnose anthracycline-induced CMP; endomyocardial biopsies demonstrate sarcoplasmic reticulum dilation, vacuole formation, myofibrillar dropout, and necrosis
Cardiovascular magnetic resonance imaging	To detect coronary artery calcification
Cardiac biomarkers (troponin I and N-terminal pro-BNP)	Elevated troponin level signals myocardial damage after chemotherapy; increased troponin level associated with increased incidence of cardiac events
Thyroid function	To evaluate for hypothyroidism/hyperthyroidism as the heart failure etiology
Viral titers	To evaluate causes of myocarditis, endocarditis, and pericarditis (cytomegalovirus, echovirus, parvovirus, and adenovirus)
Blood cultures	To define organisms in sepsis-related heart failure
Iron studies	To evaluate for hemochromatosis resulting in heart failure

Note. CMP = cardiomyopathy; BNP = brain natriuretic peptide. Information from Cardinale et al. (2004); Sawaya et al. (2011), Steinherz & Yahalom (2001), and Urbanova et al. (2006).

Table 13. Recommended Medications for Treatment of Heart Failure

Drug	Starting dose	Target dose	Maximum dose
ACE inhibitors			
Captopril	6.25–12.5 mg 3x/day	50 mg 3x/day	100 mg 3x/day
Enalapril	2.5 mg 2x/day	20 mg 2x/day	40 mg/day
Fosinopril	2.5–5 mg/day	20 mg/day	40 mg/day
Lisinopril	2.5–5 mg/day	20 mg/day	40 mg/day
Quinapril	5 mg 2x/day	20 mg 2x/day	20 mg 2x/day
Ramipril	1.25–2.5 mg/day	10 mg/day	10 mg/day
Trandolapril	1 mg/day	4 mg/day	8 mg/day
Angiotensin receptor blockers			
Candesartan	4 mg/day	32 mg/day	32 mg/day
Valsartan	40 mg 2x/day	160 mg 2x/day	320 mg/day
Beta blockers			
Carvedilol	3.125 mg 2x/day	25 mg 2x/day	50 mg/day (wt > 85 kg)
Carvedilol phosphate	10 mg/day	80 mg/day	80 mg/day
Metoprolol succinate	25 mg 2x/day	100 mg/day	100 mg/day
Bisoprolol	1.25 mg/day	10 mg/day	10 mg/day
Aldosterone antagonists			
Eplerenone	25 mg/day	50 mg/day	50 mg/day
Spironolactone	25 mg/day	50 mg/day	50 mg/day
Cardiac glycoside			
Digitalis	0.125 mg/day	0.25 mg/day	0.25 mg/day
Direct-acting vasodilator			
Hydralazine + isosorbide dinitrate	37.5 mg–20 mg (1 tablet) 3x/day	37.5 mg–20 mg (2 tablets) 3x/day	37.5 mg–20 mg (2 tablets) 3x/day

Note. Information from Hunt et al. (2005).

and hyperlipidemia. Patients in stages B, C, and D should receive recommended heart failure medications, which include ACE-I and beta-blockers, unless contraindicated. Multiple randomized trials have shown that these medications cause reverse remodeling and improve survival. Patients who are intolerant to ACE-I because of adverse effects should receive an angiotensin II receptor blocker (ARB). These recommended medications are listed in Table 13. Patients with advanced HF with frequent exacerbation episodes should receive additional medications, including digoxin, diuretics, and aldosterone antagonists. Those with end-stage heart failure who remain symptomatic despite maximum medical therapy should be considered for possible synchronized pacing or a ventricular assist device (Hunt et al., 2005). Cancer survivors with end-stage HF who are cancer-free for at least 5 years should be considered for heart transplantation.

To prevent worsening of the HF, the required pharmacologic therapy should be initiated as soon as the patient is diagnosed with asymptomatic or subclinical left ventricular dysfunction. In addition to the recommended HF medications, the treatment plan should include management of other comorbid conditions that could result in HF, as listed in Table 11.

Conclusions

The significant advances in the development of novel therapies have resulted in increased cancer survivorship; however, adverse treatment-related cardiotoxicities remain a major challenge. Prevention, early detection, monitoring, intervention, and long-term follow-up should continue to be the guiding principles in the management of this specific group of patients. Successful management demands a close interdisciplinary collaboration between oncology and cardiology to provide optimum care and meet the complex needs of these patients.

It is imperative for advanced practitioners involved in the management of cancer patients to be aware of the cardiovascular adverse events associated with cancer therapy. See Appendix A (available online at www.AdvancedPractitioner.com) to access a printable reference chart listing all of the agents mentioned in this article and their associated cardiovascular effects. Armed with this information, advanced practitioners can better identify, prevent, and effectively manage their patients' complications in the hopes of increasing overall survival and improving quality of life.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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