Cardiovascular Toxicity Associated With Cancer Treatment

Pamela Hallquist Viale, RN, MS, CS, ANP, AOCNP®, and Deanna Sanchez Yamamoto, RN, MS, CS, ANP, AOCNP®

Cardiotoxicity is a well-described and potentially lethal side effect of certain chemotherapeutic agents. Cardiotoxicity is a broad term used to depict conditions ranging from benign forms of arrhythmias to potentially fatal conditions, such as myocardial ischemia or infarction and heart failure. Anthracyclines (daunorubicin, doxorubicin, and epirubicin), mitomycin, and monoclonal antibodies such as trastuzumab have been associated with cardiotoxicities, but other chemotherapeutic agents, such as fluorouracil, cyclophosphamide, interferons, and interleukin-2 and other targeted agents, also can cause this side effect. Although several theories exist about the process that leads to cardiotoxicity from some chemotherapeutic agents, the exact mechanism of action is unknown. Oncology nurses should know the agents associated with cardiotoxicity, including newer targeted therapy drugs. Knowledge of the potential mechanism of action, as well as the possible reversibility of cardiotoxicity with specific agents, is important.

Specific chemotherapy treatments have long been associated with cardiovascular toxicity in patients who receive the agents and oncology nurses are familiar with many of them (Yeh et al., 2004). Additional risk factors can place patients at an increased threat for toxicity, including the cumulative effects of multiple chemotherapeutic agents that increase toxicity risk as well as existing medical conditions that can predispose a patient to cardiovascular damage. Cancer occurs more frequently in older adults and, because cardiac disease is more prevalent in this population, cardiotoxicity associated with cancer therapies are an increased concern (Chanan-Khan, Srinivasan, & Czuczman, 2004). In addition, many patients now have a prolonged survival or life expectancy after cancer therapy and clinicians should view cardiovascular toxicity as a long-term side effect (Meinardi et al., 2000). Serious long-term cardiotoxic effects, such as congestive heart failure (CHF), have been noted with several specific types of cancer after therapy, including breast and testicular. According to Pinder, Duan, Goodwin, Hortobagyi, and Giordano (2007), women aged 66–70 years who received anthracyclines in the adjuvant setting, presented with significantly higher incidences of CHF over 10 years of follow-up. Therefore, decisions regarding initial adjuvant therapies should take into account potential long-term cardiotoxic effects of the treatment (Partridge, Burstein, & Winer, 2001).

Patients present in many different ways with cardiovascular effects associated with the various agents used in cancer treatment. Some of the effects include myocardial infarction, myocarditis or pericarditis, cardiomyopathy, arrhythmias or changes in cardiac conduction, hypertension, and changes in electrocardiographic readings (Chanan-Khan et al., 2004).

Changes can be acute or chronic and may appear years after therapy is completed (Chanan-Khan et al.). Oncology nurses should increase their awareness of the cardiac toxicities that are associated with standard chemotherapeutic...
agents and targeted therapies, including monoclonal antibodies and small molecule tyrosine kinase inhibitor (TKI) and multi-
kinease inhibitor (MKI) agents. This article will review the
mechanism of action for cardiotoxicity associated with selected
chemotherapy and targeted therapy agents as well as the implica-
tions for nursing in the management of heart failure. Although
radiation therapy also can cause cardiac issues, they will not be
reviewed in this article.

**Mechanism of Action for Cardiotoxicity Associated With Cancer Therapy**

Chemotherapy-associated cardiotoxicity may have two mark-
edly different mechanisms of action, depending on the agent
(Safra, 2007). Anthracycline-associated cardiotoxicity, which
causes cumulative damage to the cardiac myocytes leading
to CHF, has been labeled type I chemotherapy-related cardiac
dysfunction (CRCD). The specific damage associated with tras-
tuzumab is type II CRCD (Safra, 2007).

**Anthracycline Cardiotoxicity**

Cardiotoxicity is a well-known risk of anthracycline agents.
Medications include doxorubicin, daunorubicin, idarubicin,
and epirubicin. Liposomal versions of several of the agents
now exist. Both doxorubicin and daunorubicin have been in
use for several decades to treat breast cancer, leukemia, lym-
phomas, and a variety of other cancers. The exact mechanism
of action for the myocardial damage is unknown, but it is
believed that free radical-mediated myocyte damage, adren-
ergic dysfunction, free radical-induced oxidative stress, and
intracellular calcium overload may play a role (Safra, 2007;
Shan, Lincoff, & Young, 1996). In addition, evidence suggests
that the release of cardiotoxic cytokines may contribute to
the toxicity. Although the anthracycline cardiac toxicity may
be labeled type I CRCD (differentiating the damage from tras-
tuzumab), three distinct subtypes of cardiotoxicity related to
this drug class exist (Jones, Swanton, & Ewer, 2006; Shan et
al.) (see Table 1).

Although anthracyclines are valuable agents for treating vari-
ous cancers, the class of agents has a definitive dose-response
relationship in many of the regimens in which they are used;
therefore, survival and remission rates may be affected if
reduced doses are used (Shan et al., 1996). Chronic cardiotoxic-
ity is dose-limiting and usually occurs as CHF within a year
of treatment (Youssef & Links, 2005). The incidence of CHF
is approximately 3% in patients receiving a cumulative dose
of 400 mg/m² of doxorubicin, rising to 7% at 550 mg/m², and
18% at 700 mg/m² (Youssef & Links). Reports exist of fatal
cardiotoxicity with anthracyclines at cumulative doses less
than 400 mg/m² when given to patients receiving multiple
chemotherapy agents, such as high-dose methotrexate, bleo-
mycin, cyclophosphamide, dactinomycin, and cisplatin (Watts,
1991). Data suggest that cardiotoxicity may be exacerbated
by combination therapies, and the standard doses considered
to be cumulative limits for anthracyclines may need adjusted
on a case-by-case basis (Watts). Oncology nurses and other
clinicians should monitor cumulative doses of these agents
carefully; once maximum doses are reached, retreatment usu-
ally is not possible.

One strategy for reducing anthracycline cardiotoxicity is to
change the infusion method to a continuous administration
instead of a bolus administration (Hortobagyi et al., 1989).
Hortobagyi et al. treated 135 patients with doxorubicin by bolus
IV and 141 patients with either a 48- or 96-hour continuous
infusion schedule and found 75% or greater decrease in the
frequency of clinical CHF at cumulative doses less than 450
mg/m² (p = 0.04). The continuous method of infusion required
a central venous catheter.

Another strategy is to use the pegylated liposomal version of
the drug; however, clinicians must be aware of the indications
for each of the three liposomal anthracycline formulations:
daunorubicin, liposomal doxorubicin, and pegylated liposomal
doxorubicin (Hortobagyi, 1997; Safra, 2003, 2007). Pegylated
liposomal doxorubicin can reduce the risk of cardiotoxicity, al-
lowing for a significantly higher cumulative maximum tolerated
dose (Safra, 2003; Simpson, Herr, & Courville, 2004). The lipo-
osomal drug delivery provides for a prolonged circulation time
but a reduced concentration of medication to the cardiac muscle
itself (Simpson et al.). Liposomal daunorubicin has been found
to have a better cardiac safety profile than standard daunoru-
bicin in early studies; however, when patients have received
higher cumulative doses (600–900 mg/m²), cardiotoxicity has
occurred (Gill et al., 1995; Safra, 2003).

Epirubicin has been reported to have less cardiotoxicity than
other anthracycline agents, such as doxorubicin. The cardiac
 toxicity associated with epirubicin seems to occur at a higher
cumulative dose (more than 900 mg/m²) compared to 550 mg/
m² with standard doxorubicin (Safra, 2005). Bonneterre et al.
(2004) reported data from more than eight years of observation
of patients following epirubicin chemotherapy treatment. The
150 patients received either fluorouracil 500 mg/m², epirubi-
cin 50 mg/m², and cyclophosphamide 500 mg/m² (FEC 50)
(n = 65) or fluorouracil 500 mg/m², epirubicin 100 mg/
m², and cyclophosphamide 500 mg/m² (FEC 100) (n = 85)
for a median follow-up time of 102 months. In the FEC 100
group, left ventricular ejection fraction (LVEF) was less than
50% in five patients (normal LVEF is 50% or more [Aronow,
Ahn, & Kronzon, 1998]), two patients experienced CHF, and
18 patients had asymptomatic left ventricular dysfunction.

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**Table 1. Types of Anthracycline Toxicity**

<table>
<thead>
<tr>
<th>TYPE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occurring immediately after therapy</td>
<td>Rare acute or subacute cardiac injury may manifest as transient arrhythmia, pericarditis, or myocarditis syndrome.</td>
</tr>
<tr>
<td>Chronic cardiotoxicity</td>
<td>More common; early onset of progressive chronic heart failure or cardiomyopathy</td>
</tr>
<tr>
<td>Late-onset cardiotoxicity</td>
<td>Late-onset ventricular dysfunction and arrhythmias occurring years to decades after treatment ends</td>
</tr>
</tbody>
</table>

*Note. Based on information from Jones et al., 2006; Safra, 2007; Shan et al., 1996.*
One patient suffered left ventricular dysfunction after FEC 50 (Bonneterre et al.). The researchers concluded that the benefits of treatment with FEC 100 outweighed the risks of therapy and recommended careful evaluation of cardiac risk factors in patients selected for therapy (Bonneterre et al.). However, that conclusion was challenged by Ventura (2005) who cited a lack of supportive clinical data for the outcome and the potential for heart failure with either doxorubicin or epirubicin when given at equimolar doses.

Van Dalen, Michiels, Caron, and Kremer (2006) reviewed the different anthracyclines with regard to cardiotoxicity and concluded that no direct evidence suggested any difference between tumor response and survival for doxorubicin or epirubicin when given at the same dosages. Although a reduced rate of clinical heart failure may have been seen with epirubicin-treated patients, the researchers felt that neither drug was better than the other. However, they did report that liposomal-encapsulated doxorubicin has a lower rate of clinical and subclinical heart failure for patients receiving the drug without change in tumor response or survival when compared to standard doxorubicin (van Dalen et al.). The authors reported that, in patients with solid tumors, the liposomal preparation could be favored over traditional anthracyclines; however, more research was needed.

### Other Chemotherapeutic Agents Associated With Risk of Cardiotoxicity

#### 5-Fluorouracil and Capecitabine

Additional chemotherapy agents have been implicated in cardiovascular toxicities. The use of 5-fluorouracil (5-FU) is standard in many treatments for various tumor types, including colorectal cancer. Some researchers list this agent as the second-most common cause of cardiotoxicity with a reported incidence of 1.2%–7.6%, although reports exist of greater than 20% incidence with 5-FU (Alter, Herzum, Soufi, Schaefer, & Abt, and Osterwalder, 2002). However, reports such as myocardial ischemia and dysrhythmias and changes in electrocardiograph readings (Robben, Pippas, & Moore, 1993; Yeh et al.). In a study by Canale et al. (2006), 5-FU reportedly caused acute myocardial infarction during infusion in a patient. Severe cardiac failure associated with 5-FU also has been reported in the literature and, after endomyocardial biopsy, the damage was found to be similar to doxorubicin cardiotoxicity in one patient (Kuropkat et al., 1999). Capecitabine, as an oral produg of 5-FU, is believed to have the same risk for cardiotoxicity. In a retrospective study of 1,189 patients by Van Cutsem, Hoff, Blum, Abt, and Osterwalder (2002), the incidence was 3%, with 0.8% experiencing grade 3 toxicity (see Table 2).

#### Cyclophosphamide and Ifosfamide

Cyclophosphamide is a very common alkylating agent given in different regimens for many cancers and is known to cause acute cardiac toxicity in smaller doses. Damage from this agent typically occurs in the myocarditis and pericarditis, and heart failure can occur. The etiology of the damage is not completely understood but may be related to direct endothelial injury, which promotes leakage of plasma proteins and erythrocytes (Taniguchi, 2005). Patients may experience wall thickening from the edema, as well as hemorrhage, which combines to reduce left ventricular diastolic function and causes restrictive cardiomyopathy (Taniguchi). In addition, doses greater than 1.5 mg/m² per day are known for an increased risk of cardiotoxicity, with a reported incidence of 25%–28% at higher doses (Chanan-Khan et al., 2004; Gottsdiener, Appelbaum, Ferrans, Deisseroth, & Ziegler, 1981; Jones & Ewer, 2006). The damage seems to be related to the total dose delivered in a single administration rather than the cumulative dose seen with anthracyclines (Taniguchi, Yeh et al., 2004). In addition, patients who have received radiation therapy to the chest or

### Table 2. Selected Cardiac General Toxicities From the National Cancer Institute Common Terminology Criteria for Adverse Events

<table>
<thead>
<tr>
<th>ADVERSE EVENT</th>
<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3</th>
<th>GRADE 4</th>
<th>GRADE 5</th>
<th>GRADE 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular diastolic function</td>
<td>Asymptomatic diagnostic finding; intervention not indicated</td>
<td>Asymptomatic, intervention indicated</td>
<td>Symptomatic CHF responsive to intervention</td>
<td>Refractory CHF; poorly controlled; intervention such as ventricular assist device or heart transplantation indicated</td>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>Left ventricular systolic dysfunction</td>
<td>Asymptomatic, resting EF &lt; 50%–60%; SF &lt; 15%–30%</td>
<td>Asymptomatic, resting EF &lt; 40%–50%; SF &lt; 15%–24%</td>
<td>Symptomatic CHF responsive to intervention; EF &lt; 20%–40%; SF &lt; 15%</td>
<td>Refractory CHF or poorly controlled; EF &lt; 20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplantation indicated</td>
<td>Death</td>
<td></td>
</tr>
</tbody>
</table>

CHF—congestive heart failure; EF—ejection fraction; SF—shortening fraction

*Note.* Based on information from National Cancer Institute, 2006.
had previous treatment with an anthracycline are at higher risk for cardiotoxicity (Jones & Ewer, Kamezaki, Fukuda, Makino, & Harada, 2005; Yeh et al.). In one series, patients undergoing bone marrow transplantation had a 20% incidence of acute heart failure and a mortality rate of approximately 8% related to cyclophosphamide (Taniguchi). Ifosfamide, which is structurally related to cyclophosphamide, also has been linked to arrhythmias and death in some patients (Chanen-Khan et al.; Jones & Ewer; Kandylis, Vassilomanolakis, Tsoussis, & Efremidis, 1989; Quezado et al., 1993; Yeh et al.).

### Taxanes

Taxanes, including paclitaxel and docetaxel, can cause cardiotoxicity, with paclitaxel linked to a higher incidence. Although the cause of cardiotoxicity is not completely known, possible etiologies include the use of the glycerol-polymethylene glycol-containing solution (to provide solubility), agents used in premedication to prevent hypersensitivity reactions, and the action of the drug on the microtubules of the cells (Jones & Ewer, 2006). Paclitaxel is reported to have caused sinus bradycardia, heart block, and premature ventricular contractions (Yeh et al., 2004). The incidence was approximately 0.5% for grade 4 or 5 toxicities in one analysis of more than 3,400 patients by Arbuck et al. (1993). Supraventricular tachycardia and other rhythm abnormalities also have been observed, including atrial fibrillation (Chanen-Khan et al., 2004). In early reports, asymptomatic bradycardia was reported in 29% of patients with ovarian cancer treated in a phase II study as well as more significant effects, including heart block and cardiac ischemia, observed in a small group of patients (Rowinsky et al., 1991). Hypertension, infusion-related hypotension, and reports of myocardial infarction also have occurred (Chanen-Khan et al.). In one study of epirubicin in combination with paclitaxel, the incidence of CHF was low until a cumulative epirubicin dose of 990 mg/m² was reached (Gennari et al., 1999). The authors concluded that the regimen was safe even in the adjuvant setting, but the risk increases with doses exceeding 990 mg/m² and, if an additional cardiovascular risk factor is present, reduction of epirubicin may be appropriate (Gennari et al.). Most of the changes associated with paclitaxel ended once the agent was discontinued (Jones & Ewer).

The evidence for docetaxel-induced cardiotoxicity is less compelling (Floyd et al., 2005). Shimoyama, Murata, Sumi, Hamazoe, and Komuro (2001) studied 10 patients with breast cancer and found that docetaxel significantly increased the serum concentration of brain natriuretic peptide (a protein secreted by the ventricles of the heart and believed to be a sensitive measure of CHF) the day after docetaxel administration. After assessment of left ventricular systolic and diastolic functions, Shimoyama et al. concluded that, although fractional shortening and ejection fraction were not affected by docetaxel, the results did suggest that docetaxel induced left ventricular diastolic dysfunction and an increase in serum brain natriuretic peptide concentration without increasing preload or afterload.

### Miscellaneous Chemotherapy Agents

Cisplatin, mitomycin, and busulfan all have been implicated in cardiotoxic effects (Gharib & Burnett, 2002; Pai & Nahata, 2000; Yeh et al., 2004). Cisplatin can cause an acute cardiac syndrome in which patients report chest pain, exhibit increases in cardiac enzymes, and develop a syndrome where hypertension and left ventricular hypertrophy or myocardial ischemia may occur many years after treatment (Yeh et al.). The nephrotoxicity associated with cisplatin and the resulting changes in electrolytes for some patients is believed to intensify cardiac arrhythmias (Berliner et al., 1990; Jones & Ewer, 2006). Meinardi, Gietema, van der Graaf, et al. (2000) studied the long-term risk in 87 patients treated with cisplatin-containing chemotherapy for testicular cancer and found a significantly increased risk for occurrence of cardiac toxicity in the group. The cardiac events seen were myocardial infarction and angina pectoris with myocardial ischemia. The authors concluded that follow-up and intervention were important for this patient group (Meinardi, Gietema, van der Graaf, et al.).

Mitomycin C has long been believed to be cardiotoxic and that toxicity is dose dependent, occurring at dose levels of 30 mg/m² or more, and that patients previously or simultaneously treated with doxorubicin were at greater risk (Verweij, Funk-Kupper, Teule, & Pinedo, 1988). Cumulative dosing and effects related to combined therapies have been reported to contribute to cardiotoxicity with mitomycin C (Yeh et al., 2004).

Busulfan has been reported to cause pericardial fibrosis in at least one case report (Terpstra & de Maat, 1989; Yeh et al., 2004). Bleomycin has been linked to cardiotoxic effects, including pericarditis, acute chest pain syndrome, coronary artery disease, and myocardial infarction (Floyd et al., 2005).

Mitoxantrone, an anthraquinone, has been reported to cause toxicity in cardiac cells with doses greater than 160 mg/m², putting patients at increased risk for cardiac failure (OSI Oncology, 2007). The incidence of cardiac failure is 2.6%, with a 13% incidence of subclinical moderate to severe decline in LVEF (OSI Oncology). Reports of cardiotoxicity with this agent have surfaced in patients receiving the drug for multiple sclerosis (Paul, Dorr, Wurfel, Vogel, & Zipp, 2007). Etoposide, a podophyllotoxin, has caused cardiac effects such as myocardial infarction and vasospastic angina in some patients (Floyd et al., 2005).

Other agents that work as microtubule inhibitors include the vinca alkaloids, which have been reported to cause many different cardiac effects, including hypertension, myocardial infarction, or other vaso-occlusive complications (Floyd et al., 2005).

### Targeted Therapy Agents With Risk of Cardiotoxicity

Targeted therapies, including both monoclonal antibodies and the small-molecule TKI and MKI agents, are increasingly used in clinical practice. The agents work differently than standard chemotherapeutic agents and selectively target key
aspects of both intracellular and extracellular function. This selectivity changes their side-effect profile and, although toxicities exist with these agents, the type of side effects may differ from traditional chemotherapy (Viale, 2007). However, cardiotoxicity is a known effect of several of the targeted therapy agents.

**Trastuzumab**

Trastuzumab has changed treatment for patients with breast cancer who are HER2/neuregulin-positive. The agent was first approved by the U.S. Food and Drug Administration (FDA) in 1998 in the metastatic setting and later approved in 2006 in the adjuvant setting (Genentech, 2008). The HER2 gene is amplified or the receptor is overexpressed in about 15%–25% of patients with breast cancer and confers a poorer prognosis and shorter overall survival for patients (Suter, Cook-Bruns, & Barton, 2004). The exact mechanism of action for cardiotoxicity is unknown, but several possible mechanisms exist, with one theory describing the damage as type II CRCD (Safra, 2007). Type II CRCD involves the endothelial growth factor receptor pathway that normally maintains cardiac contractility and function. When blocked by trastuzumab, the pathway is unable to provide regulation of the growth of cardiomyocytes and interferes with repair of those cells (Safra, 2007). The pathway and ErbB2 signaling in the cardiac myocytes are critical in the prevention of dilated cardiomyopathy (Safra, 2007). Although no ligand exists for HER2, signaling occurs through heteromers with other receptors (Carlson & Perez, 2006). HER2/neuregulin is a critical component of cardiac development, with HER2 located in the T-tubule system of cardiomyocytes. However, the exact mechanism of action is unknown (Carlson & Perez). Others have postulated that damage occurs from drug-drug interactions or the induction of immune-mediated destruction of cardiomyocytes (Gonzalez-Angulo, Hortobagyi, & Esteva, 2006).

A critical difference between type I and II CRCD is that type II appears to be mostly reversible, with improvement seen in cardiac function after discontinuation of treatment (Safra, 2007). Certain factors also increase the risk for cardiotoxicity. Statistically significant increases were seen as patients aged and with concurrent use of anthracycline. Other factors are previous anthracycline use, prior chest wall irradiation, and preexisting cardiac dysfunction (Floyd et al., 2005).

Although clinically effective as a monotherapy, trastuzumab combined with chemotherapy enhances its activity (Suter et al., 2004). Clinical trials with trastuzumab in the metastatic setting identified cardiac dysfunction as the most significant adverse event, with a retrospective analysis showing the greatest amount of toxicity in patients who received trastuzumab and an anthracycline (27%) (Smith, 2001; Suter et al.) compared to a 7% rate in patients who received anthracycline alone (Smith). Risk factors for the cardiotoxicity identified in the clinical trials are similar to the risk factors for patients receiving doxorubicin, and an independent cardiac review committee concluded that the two most significant risk factors were age of the patient (older than 50) and the combination of anthracycline with trastuzumab treatment (Seidman et al., 2002; Suter et al.).

Patients receiving paclitaxel in combination with trastuzumab also had an increased risk of cardiotoxicity compared to patients on paclitaxel alone (12% versus 1%, respectively) (Smith, 2001). Cardiac dysfunction included asymptomatic decrease in LVEF. Symptomatic heart failure occurred in 16% of patients receiving trastuzumab with anthracycline/cyclophosphamide combinations, which is typical of toxicity associated with trastuzumab (Smith). This cardiac dysfunction was reversible in most patients with a very low rate of residual heart failure after treatment, and death occurred in less than 1% of patients. The reversibility is a hallmark of trastuzumab cardiotoxicity compared to the type of damage seen with anthracycline agents (Jones & Ewer, 2006; Smith). In fact, because of the reversible nature of cardiotoxicity associated with trastuzumab, reintroduction of the agent after improvement in individual patients may be possible (Ewer et al., 2005).

With the recent approval of trastuzumab in the adjuvant setting, the cardiovascular risks are of considerable interest. Although the drug is well tolerated and has shown tremendous clinical benefit for HER2/neuregulin-positive patients in both metastatic and adjuvant settings, the CHF that can occur in patients receiving the agents is concerning. The results from the adjuvant trials report that about 5% of all patients treated with adjuvant trastuzumab, either combined with nonanthracycline chemotherapy or given after all treatment is finished, will exhibit systolic cardiac dysfunction, with 1% developing symptomatic CHF (Hayes & Picard, 2006). An analysis by Suter et al. (2007) of the trastuzumab adjuvant trial showed that out of 1,693 patients receiving one year of trastuzumab therapy versus 1,693 on observation alone, the incidence of drug discontinuation because of cardiac issues was 4.3%. The researchers concluded that, because of the significant benefit in disease-free survival of the patients combined with the low incidence of cardiotoxicity and its reversibility, treatment with trastuzumab in the adjuvant setting should be considered for appropriate patients, although the women participating in this trial were, on average, about 50 years old with 22% having a history of cardiovascular disease or active cardiovascular disease (Suter et al., 2007).

Because the anthracycline combination with trastuzumab appears to act as a potentiator of cardiotoxicity, the agents should not be given together (Smith, 2001). Researchers have explored the use of liposomal doxorubicin in conjunction with trastuzumab to permit concomitant therapy with the two agents. Theodoulou et al. (2002) studied 39 patients with metastatic breast cancer and found that one patient had an asymptomatic decrease in LVEF and one patient experienced CHF. Chia et al. (2006) studied 30 patients receiving the two agents together and reported no patients with CHF, but three developed protocol-defined cardiotoxicity, which was considered to be an absolute decline in LVEF of 15% in an asymptomatic state, despite the absolute value (Chia et al.). The three patients had received prior adjuvant anthracyclines.

The Protocol B-31 (a pivotal trial which studied trastuzumab) recommendations for monitoring guidelines have been used by many clinicians for managing the drug and its cardiotoxic effects (see Table 3).

The black box warning for trastuzumab calls for evaluation of cardiac function prior to and during treatment, and discontinuing therapy for cardiomyopathy (Genentech, 2008). In addition, the warning calls for discontinuation of therapy in patients receiving adjuvant therapy and a strong consideration of discontinuation of trastuzumab in patients with metastatic breast cancer when a
Clinically significant decrease in LVEF is seen (Genentech). The package insert also calls for withholding of the drug after a 16% or greater absolute decrease in LVEF from pretreatment values or an LVEF value below institutional limits of normal and a 10% or greater absolute decrease in LVEF from pretreatment values. Continuing or resuming the drug in patients with cardiac dysfunction has not been adequately studied.

Additional recommendations are to conduct a thorough cardiac assessment and evaluation of LVEF by echocardiogram or multigated acquisition scan prior to starting therapy, with serial LVEF measurements every three months during and upon completion of trastuzumab, with repeat LVEF measurements at four-week intervals when the drug is held for measurable dysfunction (Genentech, 2008). Ongoing measurements of LVEF should be conducted every six months for at least two years following drug completion in the adjuvant setting.

**Lapatinib**

Lapatinib, an oral tyrosine kinase EGFR inhibitor, recently was approved for use in trastuzumab-treated patients with metastatic breast cancer with disease progression. Lapatinib also appears to have activity in patients with metastatic brain cancer (Moy & Goss, 2006). A study of lapatinib-associated cardiotoxicity by Perez et al. (2006) found that out of 2,812 patients with a variety of cancers receiving the drug, a decrease in LVEF was seen in 1.3%, and they were rarely symptomatic. The cardiotoxicity usually was reversible and did not progress (Perez et al.). Many patients with nonbreast cancer diagnoses in the clinical trials had not received prior anthracycline therapy compared to the participants with breast cancer, which also could have influenced the low incidence of cardiac failure in the data analysis (Moy & Goss, 2006).

The current package insert for lapatinib warns that decreases in LVEF have been reported and that normal LVEF should be confirmed prior to starting therapy with this agent while continuing evaluations during therapy (GlaxoSmithKline, 2007). Dose modification guidelines for this agent call for lapatinib to be discontinued in patients with a decreased LVEF that is grade 2 or greater by National Cancer Institute’s Common Terminology Criteria for Adverse Events and in patients with an LVEF that is less than the institution’s lower limit of normal (GlaxoSmithKline). The drug may be restarted at a reduced dose of 1,000 mg per day if the LVEF recovers to normal and the patient is asymptomatic. Studies are needed to determine further information regarding lapatinib, although it appears to have a very low incidence of cardiotoxicity (Moy & Goss, 2007).

**Sunitinib**

Sunitinib is an oral MKI, approved by the FDA in January 2006 to treat gastrointestinal stromal tumors after progression or intolerance to imatinib mesylate, and in patients with advanced renal cell carcinoma. Sunitinib targets several receptor TKI implicated in tumor growth, pathologic angiogenesis, and metastatic progression of cancer (Rock et al., 2007). A retrospective review by Chu et al. (2007) examined all cardiovascular events in 75 patients with gastrointestinal stromal tumors who had participated in a phase I and II trial with sunitinib. The review showed that 11% had a cardiac event (one patient died from cardiovascular causes, one had myocardial infarction, and six developed CHF); 28% of the patients had reductions in their LVEF of at least 10%, and 19% had reductions of 15% or more. This agent also caused increases in blood pressure, with 47% developing hypertension (greater than 150/100 mmHg) (Chu et al.). The authors hypothesized that the LVEF changes could be caused by direct toxicity to cardiomyocytes, influenced by the development of hypertension, and called for close monitoring of both hypertension and LVEF in the patients, particularly those with a history of coronary artery disease or other cardiac risk factors (Chu et al.).

Cardiac safety of sunitinib in patients with preexisting cardiac conditions remains unknown in part because patients with significant history of cardiac issues were excluded from clinical studies. Therefore, patients with a cardiac condition should be monitored carefully for clinical signs and symptoms of CHF while receiving sunitinib. A baseline evaluation of the ejection fraction is recommended for all patients as well as additional periodic evaluation ejection fraction studies for patients with known cardiac conditions receiving sunitinib (Pfizer Inc., 2006; Rock et al., 2007). The time between evaluations should be determined on a case-by-case basis. Hypertension can develop

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**Table 3. Protocol B-31 Rules for Suspension of Trastuzumab**

<table>
<thead>
<tr>
<th>RELATIONSHIP OF LVEF TO THE LLN</th>
<th>DECREASE OF &lt; 10 PERCENTAGE POINTS</th>
<th>DECREASE OF 10–15 PERCENTAGE POINTS</th>
<th>DECREASE OF ≥ 15 PERCENTAGE POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within radiology facility’s normal limits</td>
<td>Continue trastuzumab</td>
<td>Continue trastuzumab</td>
<td>Hold trastuzumab and repeat MUGA scan after four weeks</td>
</tr>
<tr>
<td>1–5 percentage points below the LLN</td>
<td>Continue trastuzumab</td>
<td>Hold trastuzumab and repeat MUGA scan after four weeks</td>
<td>Hold trastuzumab and repeat MUGA scan after four weeks</td>
</tr>
<tr>
<td>&gt; 6 percentage points below the LLN</td>
<td>Continue trastuzumab and repeat MUGA scan after four weeks</td>
<td>Hold trastuzumab and repeat MUGA scan after four weeks</td>
<td>Hold trastuzumab and repeat MUGA scan after four weeks</td>
</tr>
</tbody>
</table>

LLN—lower limit of normal; LVEF—left ventricular ejection fraction; MUGA—multigated acquisition

during therapy and should be monitored closely. The mechanism for this, however, is unclear and may be caused by increasing extracellular volume or decreasing vascular compliance. Sunitinib-induced hypertension should be managed aggressively to prevent the long-term effects or the worsening of cardiac conditions (Wood, 2006).

**Sorafenib**

Sorafenib, like sunitinib, is an MKI used in the treatment of advanced renal cell carcinoma, and similar cautionary warnings about cardiovascular events should apply regarding the development and management of hypertension. Rare but serious life-threatening or fatal outcomes of cardiac events were reported with the use of sorafenib and include myocardial ischemia, myocardial infarction, CHF, hypertensive crisis, and arrhythmia (Bayer Pharmaceuticals, 2006; Wood, 2006).

**Rituximab**

Rituximab is a chimeric murine/human monoclonal antibody directed against the CD20 antigen on B lymphocytes and used to treat a variety of malignant and nonmalignant conditions. Rituximab-associated cardiac events are rare, with the greatest incidence occurring during the first infusion, and may include infusion-related hypotension, arrhythmia, acute myocardial infarction, ventricular fibrillation, and cardiogenic shock. The proposed mechanism for these first infusion events are possibly related to a cytokine release phenomenon (Chanan-Khan et al., 2004; Floyd et al., 2005).

Prevention and management of potential cardiac events should include monitoring patients during and after a rituximab infusion with special attention paid to patients with a known history of cardiac disease and hypertension. To avoid infusion-related hypotension, patients should delay taking antihypertensive medications until after the infusion is completed (Chanan-Khan et al., 2004).

**Imatinib Mesylate**

Imatinib mesylate is a potent selective inhibitor of the BCR-ABL tyrosine kinase and is used in the treatment of chronic myelogenous leukemia, acute lymphoblastic leukemia, myelodysplastic or myeloproliferative diseases, aggressive systemic mastocytosis, hypereosinophilic syndrome, chronic eosinophilic leukemia, dermatofibrosarcoma protubersans, and gastrointestinal stromal tumor (Novartis Pharmaceuticals, 2006). Approximately 2%–6% of patients with chronic myelogenous leukemia receiving imatinib mesylate develop peripheral edema, pleura effusion, pericardial effusion, pulmonary edema, and ascites (Cohen et al., 2002; Novartis Pharmaceuticals). In clinical trials that led to FDA approval of imatinib mesylate for chronic myelogenous leukemia, one patient was reported to have died with pleural effusion, CHF, and renal failure (Cohen et al., 2002). The incidence of edema in the trials was dose- and age-dependent, with the incidence 20% higher for patients older than age 65 and for those taking a 600 mg per day dose of imatinib mesylate (Cohen et al., 2002). Therefore, when Kerkela et al. (2006) reported that 10 patients without a prior history of heart disease developed severe CHF while taking imatinib mesylate, changes occurred to the drug label.

**Bevacizumab**

A recombinant humanized monoclonal antibody, bevacizumab blocks the activity of vascular endothelial growth factor and is approved as first- and second-line therapy with 5-FU-based chemotherapy for patients with metastatic colon and lung cancer. A number of cardiovascular adverse effects have been associated with bevacizumab, including hypertension, CHF, and arterial thromboembolic events. About 14% of patients treated with bevacizumab while concurrently receiving anthracyclines and 4% of patients with prior anthracycline exposure treated with bevacizumab developed CHF. Serious and sometimes fatal cardiac events with bevacizumab use include arterial thromboembolic events, hypertensive crisis, and CHF (Cohen, Gootenberg, Keeegan, & Pazdur, 2007). Acute hypertension in as many as 1.7% of patients has been associated with initial or subsequent infusions of bevacizumab and can last after discontinuation, leading to central nervous system hemorrhage and, in some cases, fatal encephalopathy and reversible posterior leukoencephalopathy (Ozcan, Wong, & Hari, 2006). Based on evidence that bevacizumab has increased cardiac toxicity (2% increase in ventricular dysfunction when used alone, 14% increase in CHF when used concurrently with anthracyclines, and 4% in patients who had a prior history of anthracycline exposure), the FDA issued a warning regarding the risk of stroke, myocardial infarction, angina, reversible posterior leukoencephalopathy, and fatal heart disease (Floyd et al., 2005; Jones & Ewer, 2006). Prominent risk factors for a cardiac event include patients being 65 years or older and a prior arterial thromboembolic event (Floyd et al.). Patients developing uncontrolled hypertension with aggressive medical management will require temporary suspension and bevacizumab must be discontinued permanently for hypertension crisis (Genentech, 2007).

**Interferons or Interleukins**

Interferons are a set of glycoproteins that display antitumor properties in the treatment of melanoma, hairy cell leukemia, follicular lymphoma, and AIDS-related Kaposi sarcoma (Skeel & Khleif, 2003). Interferons can cause flu-like symptoms, hypotension or hypertension, tachycardia, and nausea and vomiting two to eight hours after treatment (Yeh et al., 2004). The cardiotoxicities associated with interferons are ischemia and infarction, arrhythmias, and cardiomyopathy. Patients with a previous history of coronary artery disease may be at risk for...
ischemic changes because the interferon flulike reaction with fever causes an increased myocardial oxygen demand, but the exact mechanism is not understood clearly. Risk factors for interferon-induced cardiotoxicity are not understood clearly and are not associated with age or dose because toxicity can occur with low and high daily doses. Only a prior history of coronary artery disease has been identified as a possible risk factor to interferon-induced arrhythmia and ischemia (Jones & Ewer, 2006). If myocardial ischemia develops, the interferon should be discontinued and standard therapy initiated for myocardial ischemia. Interferon-induced cardiomyopathy may improve once the drug has been discontinued (Floyd et al., 2005; Jones & Ewer).

**Interleukin-2:** Interleukin-2 (IL-2) is a T-cell growth factor with multiple immunomodulating effects and is approved for the treatment of metastatic renal cell carcinoma, malignant melanoma, and T-cell lymphoma (Skeel & Khleif, 2003; Yeh et al., 2004). IL-2 has well-recognized cardiac toxicities, including sinus tachycardia, arrhythmias, ischemia, or fatal myocardial infarction, without a clearly understood mechanism. From 14%–21% of patients will have ventricular and supraventricular arrhythmias. Supraventricular tachycardia should be treated with standard antiarrhythmic therapy (Floyd et al., 2005; Jones & Ewer, 2006). Patients receiving IL-2 commonly develop a capillary leak syndrome associated with vascular permeability and hypotension (Floyd et al.; Jones & Ewer). High-dose therapy can cause adverse cardiovascular and hemodynamic effects similar to septic shock and can lead to vascular leak syndrome (hypotension, edema, or hypoalbuminemia) and respiratory insufficiency requiring aggressive medical management with fluid resuscitation, vaspressors, and mechanical ventilation support. The septic shock symptoms can peak four hours after each dose and worsen with further treatment (Floyd et al.; Yeh et al.). Establishment of treatment protocols, including premedication with steroids, slowing or discontinuing infusions with the administration antihistamine, steroids and epinephrine, fluid resuscitation with infusion reactions, and careful patient selection are necessary to reduce toxicities because, in severe cases, cardiac arrhythmias, myocardial infarction, cardiomyopathy, and myocarditis can occur (Skeel & Khleif; Yeh et al.). About 11% of patients can develop thrombotic events, including deep vein thrombosis, pulmonary embolism, and arterial thrombosis (Yeh et al.).

**Arsenic trioxide:** Arsenic trioxide is a novel agent approved in September 2000 by the FDA and currently is used in various hematologic malignancies. It is associated with prolongation of the QT interval and potentially serious cardiac arrhythmia; more than 50% of patients will have electrocardiogram abnormalities (Yeh et al., 2004). Cardiotoxicity associated with arsenic trioxide usually is acute and occurs during or immediately after infusion. Hypokalemia or hypomagnesemia predisposes patients to the cardiotoxic effects of arsenic trioxide. A baseline electrocardiogram should be done before starting therapy to assess the rhythm pattern and QT interval. This monitoring should be repeated weekly during induction and biweekly during consolidation. If the QT interval is greater than 500 msec, the patient should be evaluated for the potential risk versus benefit of further therapy. Prior to each infusion, electrolytes should be checked and corrected if low. Recommended levels of potassium and magnesium are greater than 4 mEq/l and greater than 1.8 mg/dl, respectively. Patients who develop cardiac symptoms should be hospitalized with close cardiac monitoring and correction of electrolytes. Arsenic trioxide usually can be restarted once the QTc interval is less than 460 msec (Cell Therapeutics, 2000; Floyd et al., 2005).

**Nursing Implications for the Diagnosis and Management of Cardiotoxicity**

Oncology nurses should be aware of preexisting cardiovascular disease because it may predispose patients to develop heart failure or other cardiac issues while being treated with chemotherapeutic agents. For the purpose of this article, the management of heart failure will be the focus because this chronic condition has the widest implications for nursing care.

**Developing Heart Failure**

Heart failure is a multifaceted condition that results from either systolic or diastolic dysfunction impairing ventricular ejection or filling. The most common cause is coronary artery disease resulting in myocardial infarction and the loss of myocardial function or ischemic cardiomyopathy (Fadol, 2006; Macabasco-O’Connell, Rasmusson, & Fiorini, 2006). Patients can present with dyspnea, orthopnea, paroxysmal nocturnal dyspnea, activity intolerance, rapid weight gain, fatigue, and edema. Patients also may complain of upper-right quadrant pain, loss of appetite and nausea caused by alterations in liver and gastrointestinal perfusion, and a persistent nonproductive cough that is worse in a recumbent position (Bashore, Granger, & Hranitzky, 2007). The symptoms can be mistaken easily for other conditions, such as cancer progression or side effects of cancer treatment. To help categorize patients with heart failure, the New York Heart Association functional classification is used widely (see Table 4). However, the classification system relies on patients’ subjective reporting of symptoms. Therefore, some researchers have proposed that biomarker evaluation, specifically B-type natriuretic peptide assay, and echocardiography should be used to identify the development of heart failure (Khakoo et al., 2008).

Patients with symptoms of heart failure should have a thorough history and physical examination. A patient’s medical history should focus on health conditions, including pulmonary, renal, thyroid, liver, and cardiovascular diseases; uncontrolled hypertension; cardiac arrhythmias; anemia; exposure to radiation therapy; chemotherapy and targeted therapies; alcohol use, diabetes; and compliance with medications and diet. Physical findings specific to heart failure are the presence of jugular venous distention and a third heart sound, but the examination will help to identify other causes, such as pleural effusion, pulmonary embolism, or an infection (e.g., pneumonia) (Bashore et al., 2007; Fadol, 2006; Macabasco-O’Connell et al., 2006).

**Diagnostic Testing and Monitoring for Heart Failure**

A number of laboratory and diagnostic studies are used to confirm heart failure and consist typically of an electrolyte panel, a complete blood count, thyroid and liver function,
Table 4. New York Heart Association Functional Classification

<table>
<thead>
<tr>
<th>FUNCTIONAL CAPACITY</th>
<th>OBJECTIVE ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause fatigue, palpitation, dyspnea, or anginal pain.</td>
<td>No objective evidence of cardiovascular disease</td>
</tr>
<tr>
<td>Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.</td>
<td>Objective evidence of minimal cardiovascular disease</td>
</tr>
<tr>
<td>Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.</td>
<td>Objective evidence of moderately severe cardiovascular disease</td>
</tr>
<tr>
<td>Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.</td>
<td>Objective evidence of severe cardiovascular disease</td>
</tr>
</tbody>
</table>


a chest x-ray, electrocardiogram, B-type natriuretic peptide assay, and echocardiogram or radionuclide ventriculography (gated blood pool imaging or multigated acquisition scan) to determine left ventricle function (see Table 5). Cardiac troponins, creatine phosphokinase, creatine kinase-MB, and myoglobin, commonly used to determine the extent and degree of cardiac muscle necrosis, have been proposed as biomarkers for early detection and diagnosis of chemotherapy-induced cardiac toxicity (Urbanova, Urban, Carter, Maasova, & Mladosievicova, 2006). However, their use in this setting remains controversial.

Monitoring a patient with heart failure should consist of assessing signs and symptoms that indicate a worsening of the condition. Changes in the patient’s functional status or fluid volume status excess are clues that the patient’s condition is not responding to medical management and, for that reason, the patient’s weight should be checked at least three times a week. Additional reviews of electrolyte, blood urea nitrogen, creatinine, and therapeutic drug levels should be done for patients on pharmacologic therapy (National Guideline Clearinghouse, 2008). Oncology nurses should monitor weight and appropriate laboratory tests and assess for the development of edema or swelling of the lower limbs.

**Heart Failure Treatment**

Treatment should be initiated once a heart failure diagnosis has been established. No established guidelines exist regarding chemotherapy or targeted therapy modifications. A consultation with a cardiologist should be considered. Patients should be encouraged to discontinue cigarette smoking and alcohol use and maintain an optimal blood pressure and weight while making dietary changes. Patients with mild to moderate heart failure should be encouraged to participate in regular physical activities such as walking to improve functional status, and a formal cardiac rehabilitation should be considered for patients who are dyspneic at rest.

Pharmacologic management of heart failure is dependent on the presenting signs and symptoms. Diuretic therapy is effective in relieving symptoms such as dyspnea and edema in patients with moderate to severe CHF (Bashore et al., 2007; Macabasco-O’Connell et al., 2006). High doses of diuretics can lead to hypotension and hypokalemia from volume depletion. Angiotensin-converting enzyme inhibitors are used to reduce mortality and improve symptoms, quality of life, and exercise tolerance. In addition, beta blockers reduce mortality in patients with heart failure and reduced ejection fraction (Bashore et al.).

Angiotensin receptor blockers can be used in patients who are intolerant of angiotensin-converting enzyme inhibitors and present with cough, rash, or angioneurotic edema. Heart failure also can be worsened by nonsteroidal anti-inflammatory drugs, cyclooxygenase inhibitors, calcium channel blockers, antiarrhythmics except for digoxin, beta blockers, and amiodarone (Bashore et al., 2007; Macabasco-O’Connell et al., 2006).

**Implications for Nursing**

Oncology nurses should be aware that multiple reasons exist as to why patients with cancer are at risk for developing heart failure. Patients must be assessed for risk factors, such as prior or current use of cardiotoxic agents (anthracyclines) and other chemotherapeutic and targeted therapies, current or past history of radiation therapy to the chest, or preexisting cardiovascular disease. At-risk patients should be monitored for signs and symptoms of early heart failure and, when appropriate, undergo monitoring or diagnostic studies. Basic monitoring procedures, such as vital signs and weight measurements, are important tools that should not be overlooked or undervalued. Some chemotherapy and targeted therapy agents, such as anthracyclines and trastuzumab, require baseline and ongoing cardiovascular assessment to continue safe administration of the therapy. Oncology nurses have a duty to not only administer chemotherapy...
safely but to be ever vigilant regarding the long-term sequelae of patients exposed to cardiotoxic agents.

**Conclusion**

A number of cancer treatments can cause cardiotoxicities that range from minor events to life-threatening conditions. Some treatments require no more than discontinuation of the agent to reverse the cardiotoxic event, whereas others need careful selection of patients and ongoing monitoring. As the population of the United States ages, more patients needing cancer treatment will have comorbidities. The comorbidities, particularly heart disease, may put patients at increased risk for cardiotoxic events. Oncology nurses should be aware of the cardiovascular risks of specific agents, their monitoring guidelines, and signs and symptoms of cardiovascular toxicity.

**Author Contact:** Pamela Hallquist Viale, RN, MS, CS, ANP, AOCNP®, can be reached at p.viale@comcast.net, with copy to editor at CJONEditor@ons.org.

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