Treatment with the humanized monoclonal antibody trastuzumab can significantly improve outcomes for patients with early or metastatic HER2-positive breast cancer. In a small proportion of patients, trastuzumab is associated with an increased risk of cardiac dysfunction. Although the mechanisms have yet to be fully established, trastuzumab may block HER2 signaling in cardiomyocytes, which is believed to be important for protecting the cardiomyocytes from stress such as that induced by treatment with anthracyclines. The risk of trastuzumab-associated cardiac dysfunction can be reduced if patients are evaluated thoroughly for risk factors before treatment (e.g., hypertension, low ejection fraction at onset, hyperglycemia, prior congestive heart failure). In addition, cardiac function must be assessed before and during the treatment period. If cardiac dysfunction occurs during treatment, early intervention can expand the possibilities of reinstitution of trastuzumab treatment. The integration of nonanthracycline adjuvant regimens offers opportunities for cardiac-compromised patients.

At a Glance

- Trastuzumab is the standard of care for treatment of patients with early or metastatic HER2-positive breast cancer. Its use can be associated with cardiac dysfunction, the nature of which is believed to be different than that of anthracycline-related cardiac toxicity.
- Optimal cardiac safety is achieved when patients are evaluated thoroughly for cardiac risk factors before receiving trastuzumab and closely monitored for cardiac function throughout the treatment period and subsequently for at least two years.
- One way nurses can help minimize the risk of cardiac dysfunction is by educating patients about lifestyle changes that promote cardiac health.

Table 1 summarizes the potential risks associated with some adjuvant systemic therapies used in breast cancer. Most notable are the long-term effects associated with anthracycline therapy, namely a progressive decline in left ventricular (LV) function and congestive heart failure (CHF) (Jones et al., 2007). Trastuzumab treatment also has been associated with LV dysfunction and CHF; however, distinct differences exist between the clinical characteristics of and biologic mechanisms associated with the cardiovascular adverse effects of anthracyclines and those of trastuzumab (Ewer & Lippman, 2005).

Although they are the mainstay of treatment for early breast cancer, anthracyclines are associated with cardiac dysfunction (CD) (Bird & Swain, 2008). It can manifest acutely as arrhythmias and chest pain shortly after administration of an anthracycline or as heart failure months or years after administration (referred to as subacute and long-term toxicity, respectively) (Love & Steingart, 2007; Pinder, Duan, Goodwin, Hortobagyi, & Giordano, 2007). The risk of a patient experiencing cardiotoxic effects from anthracycline therapy is influenced by a number of treatment- and patient-related factors, including cumulative dose (doxorubicin 300 mg/m² or higher or epirubicin 600 mg/m² or higher), associated therapy (mediastinal radiation therapy or...
Clinical Journal of Oncology Nursing  •  Volume 14, Number 5  •  Trastuzumab Cardio-Oncology: Lessons Learned

Table 1. Potential Short- and Long-Term Cardiovascular Risks of Adjuvant Systemic Therapy for Breast Cancer

<table>
<thead>
<tr>
<th>ADJUVANT THERAPY AND POLYCHEMOTHERAPY</th>
<th>SHORT-TERM EFFECTS</th>
<th>LONG-TERM EFFECTS</th>
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</thead>
<tbody>
<tr>
<td><strong>Alkylating agents</strong></td>
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<tr>
<td>Cisplatin</td>
<td>Myocardial ischemia or infarction</td>
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<td></td>
<td>Hypertension</td>
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<td></td>
<td>Heart failure</td>
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<td></td>
<td>Arrhythmias</td>
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<td>Heart block</td>
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<td></td>
<td>Endocardial fibrosis</td>
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<td>Cyclophosphamide</td>
<td>Pericarditis or myocarditis</td>
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<td></td>
<td>Heart failure</td>
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<td></td>
<td>Atrial ectopy</td>
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<td></td>
<td>Bradycardia</td>
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<td><strong>Angiogenesis inhibitors</strong></td>
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<td>— bevacizumab (not yet evaluated in the adjuvant breast cancer setting)</td>
<td>Hypertension</td>
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<td></td>
<td>Myocardial infarction</td>
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<td>Left ventricular dysfunction</td>
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<td>Venous thrombosis</td>
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<td></td>
<td>Stroke</td>
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<td></td>
<td>Heart failure</td>
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<td></td>
<td>Angina</td>
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<tr>
<td><strong>Anthracylines</strong></td>
<td>Atrial and ventricular arrhythmias</td>
<td>Progressive decrease in left ventricular function, often leading to overt heart failure</td>
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<tr>
<td></td>
<td>Pericarditis and myocarditis</td>
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<td>Reduced ejection fraction, cardiomyopathy, and death</td>
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<td><strong>Antimetabolites</strong></td>
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<td>5-fluourouracil and capecitabine</td>
<td>Heart failure</td>
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<td></td>
<td>Atrial or ventricular ectopy</td>
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<td>Myocardial ischemia and infarction</td>
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<td>Methotrexate</td>
<td>Arrhythmias</td>
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<td>Myocardial ischemia and infarction</td>
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<tr>
<td>Radiotherapy</td>
<td>Angina</td>
<td>Coronary artery disease</td>
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<td>Dyspnea</td>
<td>Pericardial constriction</td>
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<td>Heart failure</td>
<td>Atherosclerosis</td>
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<td>Diffuse intimal hyperplasia of coronary arteries and left main stenosis</td>
<td>Mediastinal fibrosis</td>
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<td></td>
<td>Pericardial effusion</td>
<td>Carotid lesions</td>
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<td>Sudden death</td>
<td>Thickening of the pericardium</td>
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<td><strong>Endocrine therapy</strong></td>
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<td>Tamoxifen</td>
<td>Venous thrombosis</td>
<td>–</td>
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<td>Aromatase inhibitors</td>
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<td>–</td>
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<td><strong>HER2-directed therapies</strong></td>
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<tr>
<td>— trastuzumab</td>
<td>Left ventricular dysfunction</td>
<td>–</td>
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<td></td>
<td>Heart failure</td>
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<td><strong>Microtubule-targeting drugs</strong></td>
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<td>— taxanes</td>
<td>Bradycardia and atroventricular block</td>
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<td></td>
<td>Atrial and ventricular arrhythmias</td>
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<td></td>
<td>Myocardial ischemia</td>
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* The time (early versus late effects) of cardiovascular risk associated with endocrine therapy, HER2-directed therapies, and angiogenesis inhibitors has not been established because of the relatively short period of time the agents have been used in the management of early breast cancer. However, a recent presentation of data from BCIRG 006, a large adjuvant trial, showed no increase in grade 3 or 4 congestive heart failure or cardiac death between the two-year and five-year follow-up in patients treated with trastuzumab, docetaxel, and carboplatin.


The irreversible, dose-related myocardial damage associated with anthracycline therapy has been referred to in the literature as type I chemotherapy-related CD (Ewer & Lippman, 2005). The condition occurs via oxidative stress, which is caused by the formation of free radicals that damage the cardiomyocyte ultrastructure (Doroshow, Locker, & Myers, 1980) (see Figure 1). It can occur acutely but usually occurs months or years after treatment (Barrett-Lee et al., 2009). The damage to cardiomyocytes generally is irreversible and can lead to later CD if the anthracycline-damaged heart is subjected to subsequent stresses, such as further treatment with a cardiotoxic agent or an infection (Ewer & O’Shaughnessy, 2007).

Trastuzumab is a humanized monoclonal antibody that targets the HER2 protein on HER2-positive breast tumor cells. In 20%–25% of patients with breast cancer, the HER2 gene is amplified or the HER2 protein is overexpressed (Owens, Horten, & Da Silva, 2004; Sjögren, Inganäs, Lindgren, Holmberg, & Bergh, 1998; Slamon et al., 1987), resulting in tumors that have an aggressive phenotype and are associated with poorer outcomes, including high rates of recurrence and shorter overall survival compared with HER2-negative tumors (Slamon et al., 1987).

The CD observed in some patients treated with trastuzumab is distinct from that with anthracyclines and is referred to in the literature as type II CRCD (Ewer & Lippman, 2005). Type II CRCD often is reversible, is not dose related, and does not appear to result in ultrastructural abnormalities. Furthermore, patients often recover from trastuzumab-related CD and rarely, if ever, experience sequential stress-related CD after treatment (Ewer & Lippman, 2005).

Preclinical studies gave no indication that trastuzumab might have adverse cardiac effects, and the exact mechanisms of trastuzumab-associated CD are not fully understood. Preclinical work demonstrated that the HER2 receptor is expressed in cardiomyocytes and is important for the normal development and function of the heart (Lee et al., 1995). HER2 signaling results in cell proliferation and survival (Force, Krause, & Van Etten, 2007) and enables
Cardiomyocytes to adapt to biomechanical stress (Chien, 2006). In some patients, trastuzumab is believed to block signaling via the HER2 receptor in cardiomyocytes, resulting in CD. This is supported by preclinical work, which showed that the absence of HER2 receptors in murine myocardial tissue led to dilated cardiomyopathy (Crone et al., 2002; Negro, Brar, & Lee, 2004).

When trastuzumab was studied in a large-scale phase III trial of patients with HER2-positive metastatic breast cancer (MBC), the risk of CD was increased significantly in patients who received concomitant treatment with anthracyclines (Slamon et al., 2001). HER2 signaling may be important for protecting cardiomyocytes from the stress caused by anthracyclines (Liu et al., 2005; Love & Steingart, 2007). The blockade of HER2 signaling in cardiomyocytes resulting from trastuzumab treatment may reduce this cardioprotective effect, thereby exacerbating the cardiotoxic effect of anthracyclines (Chien, 2006; Gianni, Salvatorelli, & Minotti, 2007).

This article discusses the incidence of trastuzumab-related CD in the context of chemotherapy-associated cardiotoxicity. It examines how healthcare professionals can minimize the risks of CD by adhering to guidelines for cardiac monitoring and looks at current and future monitoring and management strategies for patients receiving trastuzumab therapy.

**Cardiac Safety of Trastuzumab**

In general, trastuzumab has been well tolerated in all metastatic and adjuvant clinical trials; for example, trastuzumab has not been associated with side effects commonly experienced with cytotoxic chemotherapies (e.g., alopecia). However, some patients who received trastuzumab during clinical trials experienced CD (Cobleigh et al., 1999; Slamon et al., 2001). As a result, stringent cardiac monitoring procedures have been included in protocols for subsequent clinical trials.

**Trials in the Metastatic Setting**

The association between trastuzumab and the risk of CD was reported first in trials in the metastatic setting. In the phase III trial, Slamon et al. (2001) reported a 27% incidence of CD in patients who received an anthracycline plus cyclophosphamide (AC) concurrently with trastuzumab compared with 8% in patients who received AC alone. For patients who received paclitaxel and trastuzumab, the incidence of CD was 15% compared with 1% in patients who received paclitaxel as a single agent. The substantially lower incidence of CD associated with paclitaxel and trastuzumab led to the U.S. Food and Drug Administration's approval of that combination in the metastatic setting.

An independent cardiac review and evaluation committee was established to study the risk of CD with trastuzumab. It conducted a retrospective review of patient data from seven phase II and III trials in patients with HER2-positive metastatic disease (Seidman et al., 2002). The review confirmed an increased incidence of CD with trastuzumab, particularly when it was given concomitantly with AC. The review also found that when given standard treatment for heart failure (e.g., diuretics, angiotensin-converting enzyme [ACE] inhibitors), most patients with CD improved (Seidman et al., 2002).

Subsequent trastuzumab trials in MBC either have not involved anthracyclines given concomitantly with trastuzumab or have investigated a nonanthracycline-containing regimen. In addition, patients with preexisting cardiac disease have been excluded. As a result, the rate of CD reported since 2002 has been lower than that described by Seidman et al. (LV dysfunction, 0%–17%; CHF, 0%–2.3%) (Marty et al., 2005; O’Shaughnessy et al., 2002; Pegram et al., 2007; Seidman et al., 2008).

**Adjuvant Trials**

Four large-scale adjuvant trastuzumab trials have been conducted and reported cardiac safety data: National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31, North Central Cancer Treatment Group (NCCIT) N9831, Breast Cancer International Research Group (BCIRG) 006, and Herceptin Adjuvant (HERA). Table 2 and the text that follows describe data from the trials in detail.

In all four trials (N = 12,271), patients were required to have adequate cardiac function at baseline, and they received regular cardiac monitoring during the trial. The NSABP B-31 and NCCIT N9831 trials looked at AC followed by paclitaxel (the “gold standard” adjuvant chemotherapy regimen) with or without trastuzumab. Trastuzumab was administered for one year in both studies. A cardiac event safety cutoff was set at 4%, so if the difference in the rate of cardiac events between treatment arms had exceeded 4%, accrual would have been suspended (Perez, Suman, et al., 2008; Tan-Chiu et al., 2005). The researchers in both trials observed an increased rate of cardiac events in patients who received anthracycline therapy followed by trastuzumab, but the rate remained below the 4% safety cutoff.

In the NSABP B-31 trial, the greatest declines in mean left ventricular ejection fraction (LVEF) with the addition of trastuzumab to paclitaxel occurred at the six- and nine-month assessments. By month 18, the mean LVEF was above that observed at the six-month assessment. Significant risk factors for CHF in the trial were age of at least 50 years, requirement...
TREATMENT CARDIAC EVENT RATE

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>TREATMENT</th>
<th>DEFINITION OF CARDIAC EVENTS</th>
<th>At 65 months: 0.4% in the docetaxel and carboplatin arm, 2% in the AC followed by docetaxel and trastuzumab arm, 0.7% in the control arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCIRG 006 (Slamon et al., 2009)</td>
<td>Three arms: AC followed by docetaxel, with or without one year of trastuzumab; or docetaxel, carboplatin, and one year of trastuzumab</td>
<td>Cardiac death; grade 3 or 4 of the following: CHF, cardiac ischemia and infarction, or cardiac arrhythmia</td>
<td>3.64% in the one-year trastuzumab monotherapy arm versus 0.59% in the control arm</td>
</tr>
<tr>
<td>HERA (Picart-Gebhart et al., 2005; Smith et al., 2007; Suter et al., 2007)</td>
<td>Three arms: (neo)adjuvant therapy followed by trastuzumab monotherapy, for one or two years; or observation alone</td>
<td>Cardiac death; severe CHF, defined as NYHA class III or IV and LVEF lower than 50% with an absolute decrease 10% or more below baseline</td>
<td>At three years: 2.8% in the sequential arm, 3.3% in the concurrent arm, and 0.3% in the control arm</td>
</tr>
<tr>
<td>NCCTG N9831 (Perez, Suman, et al., 2008)</td>
<td>Three arms; arm A: AC followed by paclitaxel (12 weeks); arm B: AC followed by paclitaxel (12 weeks) and sequential trastuzumab (52 weeks); arm C: AC followed by paclitaxel with concurrent trastuzumab (12 weeks) then an additional 40 weeks of trastuzumab monotherapy</td>
<td>Cardiac death; heart failure, defined as NYHA class II or III symptoms with either an absolute drop in LVEF of more than 10% from baseline to less than 55%, or a decline in LVEF of more than 5% to less than LLN</td>
<td>At five years: 3.8% in the trastuzumab arm versus 0.9% in the control arm</td>
</tr>
<tr>
<td>NSABP B-31 (Tan-Chiu et al., 2005; Rastogi et al., 2007)</td>
<td>Two arms: AC followed by paclitaxel, with or without one year of trastuzumab</td>
<td>Cardiac death; heart failure, defined as NYHA class II or III symptoms with either an absolute drop in LVEF of more than 10% from baseline to less than 55%, or a decline in LVEF of more than 5% to less than LLN</td>
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</table>

**Table 2. Cardiac Safety in Adjuvant Trastuzumab Trials**

AC—anthracycline and cyclophosphamide; BCIRG—Breast Cancer International Research Group; CHF—congestive heart failure; HERA—Herceptin adjuvant trial; LLN—lower limit of normal; LVEF—left ventricular ejection fraction; NCCTG—North Central Cancer Treatment Group; NSABP—National Surgical Adjuvant Breast and Bowel Project; NYHA—New York Heart Association

for hypertensive medications, and baseline LVEF of 50%–54% (Rastogi et al., 2007).

In BCIRG 006, patients received AC followed by docetaxel; AC followed by docetaxel and trastuzumab; or docetaxel, carboplatin, and trastuzumab (Slamon et al., 2009). Each trastuzumab-containing study arm received trastuzumab for one year. The cardiac event criteria in this trial differed from those in NSABP B-31 and NCCTG N9831; therefore, direct comparisons between the trials are difficult. At the 65-month follow-up, the incidence of symptomatic CHF was 0.7% in the AC followed by docetaxel control arm and 2% in the AC followed by docetaxel and trastuzumab arm. The incidence in the docetaxel, carboplatin, and trastuzumab arm was 0.4% (Slamon et al., 2009). The efficacy and cardiac safety data from the BCIRG 006 trial prompted the National Comprehensive Cancer Network (NCCN) to recommend this nonanthracycline-containing regimen for the treatment of HER2-positive tumors of larger than 1 cm, particularly for patients who have cardiac risk factors (NCCN, 2009).

The HERA trial compared trastuzumab monotherapy for one or two years after neoadjuvant or adjuvant therapy with observation only (Smith et al., 2007). The incidence of any type of cardiac event was 3.64% for patients who received trastuzumab for one year compared with 0.6% in the control arm.

**Reversibility of Trastuzumab-Associated Cardiac Dysfunction**

The adverse cardiac effects experienced by patients receiving treatment with trastuzumab may be reversible. Ewer et al. (2005) published results from their study of 38 patients with HER2-positive breast cancer who had been referred to them for suspected trastuzumab-related CD. All patients had decreased LVEF, and 20 had symptomatic CHF. Trastuzumab was discontinued in 37 patients. Standard treatment for CD (i.e., ACE inhibitors and beta blockers) was administered to 31 of the patients, and 6 were simply observed. After a mean time to recovery of 1.5 months, the mean LVEF increased from 43% ± 16% after trastuzumab therapy to 56% ± 11% (p < 0.001); the increases in LVEF were observed in all 37 patients.

Trastuzumab treatment was reintroduced to 25 patients who had initially responded to therapy. During rechallenge, the patients received concomitant ACE inhibitors and beta blockers. No further LV dysfunction occurred in 22 of them. For the remaining 3 patients, LV dysfunction and/or CHF occurred again; as a result, trastuzumab therapy was discontinued (Ewer et al., 2005).

**Monitoring Cardiac Function**

**Adjuvant Trastuzumab**

The prescribing information provides a recommended schedule for monitoring cardiac function in patients receiving adjuvant trastuzumab (Genentech, Inc., 2009). The schedule is based on the cardiac monitoring schedule used in the four large-scale adjuvant trastuzumab trials.

Before initiating treatment, healthcare providers should conduct a thorough cardiac assessment, including a complete
medical and family history, physical examination (with an emphasis on cardiac history and signs and symptoms of cardiac disease), review of prior and current medications, electrocardiogram, and measurement of LVEF by either echocardiography (ECHO) or multiple gated acquisition (MUGA) scan. The baseline result “sets the bar” for all other evaluations. Healthcare providers generally compare subsequent scans with the baseline assessment when calculating the degree of dysfunction.

Trastuzumab should be measured immediately prior to initiation of trastuzumab and then every three months during and upon completion of trastuzumab. If trastuzumab is withheld for significant LV dysfunction, LVEF measurements should be repeated at four-week intervals. After completion of therapy, LVEF should be measured every six months for at least two years (see Figure 2). The prescribing information also provides an algorithm for withholding treatment in the event of decreased LVEF (see Table 3). It recommends that trastuzumab be withheld in the event of a 16% or higher absolute decrease in LVEF from pretreatment values or an LVEF value below institutional lower limit of normal and at least 10% absolute decrease in LVEF from pretreatment values (Genentech, Inc., 2009).

At the author’s institution, patients with a history of hypertension who are 65 years or older and present with low normal LVEF are considered at highest risk for cardiotoxicity. Such patients undergo a baseline assessment as described earlier, followed by a symptom review and physical assessment at the start of each cycle. If a patient is receiving adjuvant anthracycline-based therapy, the healthcare team repeats the MUGA or ECHO scan at the end of four cycles, earlier if any new symptoms or clinical findings are found. If the LVEF is within normal limits at the end of AC therapy, the 12 weekly cycles of taxane and trastuzumab may be initiated, followed by another MUGA or ECHO scan during the subsequent 28 weeks of therapy.

Trastuzumab for Metastatic Breast Cancer

The cardiac monitoring schedule detailed in the trastuzumab prescribing information is based on the schedule followed in the large-scale adjuvant trastuzumab clinical trials. However, the prescribing information recommends cardiac monitoring for all patients receiving trastuzumab treatment. In addition to the algorithm described in the prescribing information, Memorial Sloan-Kettering Cancer Center established a practice guideline (Keefe, 2002). Before receiving trastuzumab, patients undergo physical examination, LVEF measurement, and detailed medical history. Any patient who is symptomatic for heart failure or has an abnormal baseline LVEF does not receive trastuzumab. For patients who are able to receive treatment, weekly monitoring of heart rate and body weight can detect changes indicative of CHF (i.e., increase in heart rate of 10–20 beats per minute with or without an increase in body weight of 2 kg or more in one week). Patients undergo an LVEF assessment if either of those changes is observed or if they report having any other symptoms associated with CHF. Standard treatment for CHF (i.e., ACE inhibitors and beta blockers) is initiated if a reduction in LVEF is confirmed (Keefe, 2002).

Echocardiography and Multiple Gated Acquisition Scan

ECHO is an ultrasound technique used to determine the size of the heart and how the chambers are functioning. In the context of CD, it can be used to assess LVEF and diagnose defects such as ventricular hypertrophy, valvular defects, and pericardial effusion (Viale & Yamamoto, 2008). A MUGA scan involves the administration of an IV radioactive tracer, which is measured with a gamma counter, and provides the operator with images and measurements of LV function. MUGA scanning often is used to monitor cardiac function in patients receiving chemotherapy (Viale & Yamamoto, 2008). Both methods are associated with advantages and disadvantages; therefore, neither is considered to be superior to the other. ECHO can provide additional information such as diastolic function, which may be useful for diagnosing asymptomatic or early cardiotoxicity. Furthermore, ECHO is superior at detecting arrhythmias (Becze, 2007), although intra-observer variation may create a bias in diagnosis. Conversely, MUGA is considered to be a more reliable way of measuring LV function (Becze, 2007). The most important consideration for cardiac monitoring in patients receiving cancer therapy is consistency (i.e., the same methodology should be used each time for measuring cardiac function for an individual patient). An ejection fraction consistent with each institution’s determined level of normal is the mainstay.

Managing Chemotherapy-Induced Cardiac Dysfunction

General Guidance

No specific evidence-based guidelines exist for the management of chemotherapy-induced CD; instead, healthcare providers generally use the guidelines for the management of CHF. The Heart Failure Society of America’s (2006) practice
guidelines state that before treatment, interventions should be employed to control the following cardiovascular risk factors: body weight, hypertension, hyperglycemia, smoking, and alcohol consumption. ACE inhibitors and beta blockers are central to the treatment of CD, and the guidelines recommend that hypertension be treated with one of those rather than other agents because they may have a cardioprotective benefit. Those therapies also should be used to treat patients with demonstrated diastolic or systolic dysfunction.

In clinical practice, some patients present with an increased risk of CD at baseline. In such cases, the oncologist may consult with the cardiologist to decide whether to proceed with trastuzumab treatment if the benefit to the individual patient outweighs the risk of developing heart failure. Discussion with the patient also would be prudent.

**Guidance for Managing Congestive Heart Failure**

The Heart Failure Society of America practice guidelines emphasize that patients who are asymptomatic but have reduced LVEF are at high risk of developing CHF without treatment. This is important because patients who experience CRCD often have no symptoms. Clinical studies have demonstrated the benefit of ACE inhibitors and beta blockers in patients with chemotherapy-induced CD (Lenihan et al., 2003; Newsome et al., 2002). As understanding of chemotherapy-induced CD improves, other treatment options may further improve patient outcomes. For example, prophylactic therapy with statins may be introduced to the therapeutic regimen if initially promising results are supported by larger-scale studies. In a retrospective study, older adult patients with newly diagnosed CHF but without cancer were treated with statin therapy, resulting in a reduction in the risk of death (Ray, Gong, Sykora, & Tu, 2005).

**Guidance for Managing Trastuzumab-Associated Cardiac Dysfunction**

The trastuzumab prescribing information describes management guidelines for cardiomyopathy that occurs during treatment (Genentech, Inc., 2009). In addition, the Cardiac Guidelines Consensus Committee proposed cardiac safety guidelines for the use of trastuzumab in the adjuvant setting (Ewer et al., 2007) (see Figure 3). They are based on the monitoring schedules and data from the four large-scale adjuvant trastuzumab trials. They were developed to help healthcare professionals identify patients who would derive optimal benefit from adjuvant trastuzumab based on their cardiac function. Two management algorithms detail the recommended management strategy for asymptomatic and symptomatic decreases in LVEF. In both cases, consultation between the oncologist and cardiologist is advised with respect to cardiac support, monitoring of cardiac function, and feasibility of restarting trastuzumab therapy.

Although the trastuzumab prescribing information recommends cardiac monitoring for all patients, the guidelines are based on studies in the adjuvant setting. Keefe (2002) outlined guidelines for managing cardiac function in the metastatic setting (see Figure 4). Patients with HER2-positive MBC and asymptomatic heart failure can continue trastuzumab unless (a) LVEF has declined more than 20% to less than 40%, or (b) LVEF is less than 30%. For such patients, trastuzumab should be withheld and standard treatment for CHF should be administered. Trastuzumab can be restarted after LVEF has increased to more than 45%. For patients with symptomatic CHF, trastuzumab therapy can continue unless LVEF is less than 30%. In such cases, trastuzumab should be discontinued permanently and standard treatment for CHF should be given.

**Nursing Implications**

**Risk Factors and Risk Reduction**

Many factors can increase the risk of cardiac toxicity in patients receiving cancer therapy, and nurses should be aware of them. In the NSABP B-31 and NCCTG N9831 adjuvant trastuzumab trials, older age, requirement for antihypertensive medications, and reduced baseline LVEF were significantly associated with increased risk of cardiac events (Perez, Suman, et al., 2008; Rastogi et al., 2007). In the HERA trial, reduced baseline LVEF and high body mass index were associated with increased cardiac risk, but hypertension was not (Suter et al., 2007). Cardiac risk factor data have not been published for the BCIRG 006 trial.

Rigorous assessment of patients before treatment and careful monitoring during and after treatment can help to minimize risk and identify early signs of CD. Examples of preexisting conditions associated with increased risk of CD include...
hypertension, hyperglycemia, coronary artery disease, prior CHF, and decreased LVEF. Lifestyle factors also can affect the degree of risk for cardiac toxicity, including smoking, lack of physical activity, recreational drug use, and heavy consumption of alcohol (Shenoy, Chapman, Nawaz, & Sweitzer, 2006). Nurses can help to minimize these risk factors by educating patients about the importance of quitting smoking, increasing physical activity, and limiting alcohol intake.

Nurses also can minimize the risk of cardiac toxicity by understanding the types and doses of chemotherapy or targeted therapy that patients have received previously, and whether patients have received radiation therapy to the chest (Viale & Yamamoto, 2008). Knowledge about patients’ previous exposure to chemotherapy could help nurses alleviate potential risks associated with treatment administered in the metastatic setting.

**Identifying Trastuzumab-Related Cardiac Dysfunction**

Oncology nurses should familiarize themselves with the cardiac safety profile of trastuzumab so they can identify any signs and symptoms of CD if they occur (e.g., dyspnea, fatigue, insomnia, rapid weight gain over a short period of time). Nurses can educate their patients about the symptoms, which may lead to the early reporting, detection, and treatment of CD. The increased risk of CD associated with patients receiving trastuzumab also means that nurses should ensure that they maintain certification in cardiopulmonary resuscitation techniques (Frankel, 2000).

More often than not, however, trastuzumab-associated CD is asymptomatic and can be diagnosed only through monitoring of cardiac function with MUGA or ECHO. Nurses who are aware of this can educate patients about the importance of regular monitoring of cardiac function during treatment with trastuzumab.
cardiac monitoring during and after trastuzumab treatment, as well as methods to assess their cardiac function (Moss, Starbuck, Mayer, Harwood, & Glotzer, 2009).

Future Directions in Adjuvant Therapy

The small-molecule, dual tyrosine kinase inhibitor lapatinib targets HER1 and HER2 receptors (GlaxoSmithKline, 2009). Lapatinib is indicated for use in combination with capecitabine for the treatment of patients with advanced or MBC whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab (GlaxoSmithKline, 2009). In the phase III clinical trial supporting this indication, the addition of lapatinib to capecitabine improved the risk of disease progression by 51% (95% confidence interval, 0.34–0.71; p < 0.001) (Geyer et al., 2006). In a pooled analysis of cardiac safety data from 3,689 patients who had received lapatinib therapy (Perez, Koehler, et al., 2008), 60 patients (1.6%) had a decrease in LVEF and no cardiac deaths occurred. The CD rate reported in the analysis is lower than that associated with trastuzumab in the metastatic setting. However, a number of important differences existed between the patients in the lapatinib pooled analysis and those in the phase III trial of trastuzumab in MBC. For example, in the lapatinib trials, all patients were screened before enrollment, and patients with preexisting CD were excluded (Perez, Koehler, et al., 2008). In addition, many patients (27%) in the lapatinib trials reviewed already had received treatment with trastuzumab; therefore, they already had passed the trastuzumab “stress test.” In addition, not all of the patients in the pooled analysis had breast cancer (2.27% of 3,689 patients did). Trials of lapatinib in the adjuvant setting are ongoing, such as the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization Trial; whether

Baseline LVEF measurement (MUGA or ECHO) plus physical examination

Normal baseline ejection fraction and no signs and symptoms of CHF

Patient may receive trastuzumab treatment.

Monitor heart rate and body weight weekly.

Heart rate does not increase, and body weight remains stable.

10–20 bpm increase in heart rate and/or > 2 kg increase in body weight and/or CHF symptoms

Continue trastuzumab treatment.

Assess LVEF.

Patient has asymptomatic drops in LVEF. Continue trastuzumab treatment with caution.

Patient has symptomatic CHF: Administer standard treatment (i.e., ACE inhibitors and beta blockers with or without digoxin and diuretics).

Continuation and reinitiation of trastuzumab treatment should be based on clinical examination and LVEF. Risks and benefits of reinitiation of trastuzumab treatment after discontinuation for CHF should be discussed with the patient.

Abnormal baseline ejection fraction and/or signs or symptoms of CHF

Patient is excluded from receiving trastuzumab treatment.

Figure 4. Algorithm Based on Memorial Sloan-Kettering Cancer Center Guidelines for Monitoring Cardiac Function Before and During Treatment in Patients Receiving Trastuzumab in the Metastatic Setting

Note. Based on information from Keefe, 2002.

Exercise caution when treating patients with a history of hypertension, coronary artery disease, or significant valvular disease.

For example, new fatigue or impaired exercise tolerance

Use the same method as that used at baseline, then repeat studies using an alternate method to confirm abnormalities.

ACE—angiotensin-converting enzyme; bpm—beats per minute; CHF—congestive heart failure; ECHO—echocardiograph; LVEF—left ventricular ejection fraction; MUGA—multiple gated acquisition scan
lapatinib's cardiac safety profile in that setting will be superior to that of trastuzumab remains to be seen, when results from that and other trials become available.

Other novel combinations for the adjuvant treatment of patients with HER2-positive breast cancer are being assessed in clinical trials, and the cardiac safety of those regimens will be investigated.

Conclusion

In suitable patients with early or metastatic HER2-positive breast cancer, trastuzumab is the standard of care. In large-scale clinical trials, trastuzumab improved the overall survival of patients with metastatic disease and improved disease-free and overall survival in the adjuvant setting. Yet trastuzumab can be associated with CD; the risk is increased when trastuzumab is used concomitantly with anthracyclines. However, the pathophysiology of trastuzumab-associated CD is significantly different than that of anthracyclines because it is not dose related, does not appear to cause changes to the cardiac ultrastructure, and appears to be largely reversible.

Trastuzumab-associated CD presents clinically as either asymptomatic decreases in LVEF or symptomatic CHF. To optimize the cardiac safety of trastuzumab, healthcare professionals should perform thorough evaluation of cardiac risk factors before treatment. The risk factors include preexisting conditions such as hypertension, hyperglycemia, prior CHF, and decreased LVEF. In addition, the healthcare team should monitor cardiac function closely with either ECHO or MUGA scanning to measure LVEF. The measurements should be taken at baseline and then at regular intervals thereafter, and the same methodology (i.e., either ECHO or MUGA) should be used throughout.

If a patient presents at baseline with cardiac risk factors, trastuzumab therapy is not necessarily precluded; the risk-benefit ratio for trastuzumab treatment should be considered on an individual basis. If trastuzumab is initiated in patients with cardiac risk factors, monitoring of cardiac function should be rigorous throughout the treatment period. Trastuzumab can be used as part of a low-risk regimen (i.e., in combination with docetaxel and carboplatin); that regimen is preferred by NCCN for use in such patients (NCCN, 2009). If trastuzumab-related CD does occur, treatment should be stopped and the patient’s condition managed with ACE inhibitors and beta blockers. In patients for whom the benefits of receiving trastuzumab therapy outweigh the cardiac risks, trastuzumab may be restarted once cardiac function has stabilized.

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