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Trastuzumab-Induced Cardiotoxicity

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Purpose/Objectives: To review trastuzumab-related cardiotoxic effects in the breast cancer adjuvant setting, present a system for pretreatment screening for cardiovascular risk factors, describe monitoring recommendations, provide a tool to facilitate adherence to monitoring guidelines, and discuss implications for patient education.

Data Sources: Literature regarding cardiotoxicity and trastuzumab in breast cancer.

Data Synthesis: Trastuzumab was approved in 2006 for use in the adjuvant setting. A small percentage of women (~ 4%) developed heart failure during or after treatment. However, the trials excluded women with cardiac disease. Current screening for cardiotoxicity relies on sequential left ventricular function measurements with either echocardiography or multigated acquisition scanning at baseline and every three months. Treatment modifications are recommended if changes from baseline are detected. Long-term and late effects have yet to be determined.

Conclusions: Although a small number of women experienced cardiotoxicity in the adjuvant setting, an increase may be seen because women with preexisting heart disease receive this treatment. Guidelines and tools will be helpful for appropriate and consistent screening of cardiac risk factors and disease prior to initiation of trastuzumab and for monitoring during and after administration.

Implications for Nursing: Nurses are instrumental in assessing, monitoring, and treating women receiving trastuzumab. Implementing guidelines to promote adherence to recommended monitoring is important in the early detection of cardiotoxicity in this population. Educating women about their treatment and side effects is an important aspect of care.

Breast cancer is the most common cancer diagnosis for women in the United States, excluding skin cancer; it is the second leading cause of cancer death among women in the United States (American Cancer Society [ACS], 2009). In 2009, an estimated 192,370 new cases of invasive breast cancer will be diagnosed in women and about 40,610 men and women will succumb to the disease (ACS). Many treatment options are available, including surgery, radiation, and systemic therapies such as endocrine therapy, chemotherapy, and biologic treatments (National Cancer Institute [NCI], 2008). Tremendous progress has been made in the treatment of breast cancer, but not without cost in terms of short- and long-term toxicities, one of which is cardiotoxicity from anthracyclines, taxanes, radiation, hormonal therapy, tyrosine kinase–targeting drugs, and trastuzumab (Bird & Swain, 2008; Menna, Salvatorelli, & Minotti, 2008; Viale & Yamamoto, 2008).

Trastuzumab (Herceptin®, Genentech, Inc.) is a biologic treatment originally approved by the U.S. Food and Drug Administration (FDA) in 1998 for treatment of metastatic breast cancer (FDA, 2006). Clinical trials have demonstrated a disease-free and overall survival benefit for women receiving trastuzumab in an adjuvant setting, leading to FDA approval for that indication in 2006. One of the major risks of trastuzumab is cardiotoxicity, including left ventricular (LV) cardiac dysfunction, dysrhythmias, hypertension, cardiac failure, cardiomyopathy, and death (Genentech, Inc., 2009b). The clinical challenge is to treat women to prevent or delay recurrence while sparing them the cardiotoxic effects.

Adjuvant clinical trials of trastuzumab excluded women with a history of cardiac symptoms, abnormal electrocardiographs, abnormal radiologic films, or abnormal LV ejection fraction (LVEF), as well as uncontrolled hypertension. The incidence of cardiotoxicity in such women if they are treated with trastuzumab is not known. Current recommendations for patient selection and cardiac monitoring are stated in the package insert (Genentech, Inc., 2009b) and were developed based on

women without preexisting heart disease. Therefore, the purpose of this article is to discuss cardiotoxic effects related to the use of trastuzumab in the adjuvant setting; review guidelines for pretreatment screening to evaluate cardiovascular risk factors, monitoring, and management during and after treatment for women with preexisting cardiovascular risk factors or disease; provide a tool to facilitate adherence to monitoring guidelines; and discuss implications for patient education. An additional purpose is to make recommendations for future research that will afford women the opportunity of curative treatment while sparing or decreasing the risk for cardiovascular complications that can lead to compromised quality of life.

The MEDLINE® and *CINAHL®* databases were searched for the terms *trastuzumab* and *cardiotoxicity* or *trastuzumab-induced cardiotoxicity*. English-language-only journals were searched, but the search was not limited to humans. The results were reviewed and used if clinical trial information in the adjuvant setting or cardiotoxic effects of trastuzumab were discussed. Articles with cardiotoxicity information prior to 2001 were excluded to provide the most current knowledge, and articles discussing the effects of trastuzumab use prior to 2005 were excluded because it was not used in the adjuvant setting until 2006. The final review included 22 articles. In addition, the authors reviewed patient education information from the ACS, American Heart Association (AHA), Cleveland Clinic Cancer Center, FDA, and Genentech, Inc., Web sites. The sites were selected based on credibility of information provided and because oncology providers frequently use them for patient education.

Trastuzumab Use in Breast Cancer

Treatment decisions for women with breast cancer are based on stage of disease and other important tumor-related factors, including estrogen and progesterone status and HER2 expression. HER2 is a human epidermal growth factor receptor contributing to cell division and growth (Pugatsch, Abedat, Lotan, & Beeri, 2006). HER2 status is diagnosed by two methods: immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) (Hudis, 2007). FISH testing determines the number of HER2 genes; if two or more are found for each normal gene, the tumor is considered HER2 positive (Gonzalez-Angulo, Hortobagyi, & Esteva, 2006). IHC testing on a scale of 0–3+ looks at the surface of the cancer cell and determines how much HER2 protein is present. A tumor with a score of 3+ is considered HER2 positive. Women with HER2-positive breast cancer have an overexpression of HER2 and a decreased response to traditional chemotherapy as a result of increased growth of malignant cells (Ewer et al., 2005). The changes result in shorter periods of disease-free and overall survival and a higher incidence of brain metastasis.

Research has shown improved three-year overall survival benefit of 2.7%–6.3% and disease-free survival of 6.4%–12% in women with HER2-positive breast cancer when they are treated with trastuzumab in combination with or sequentially after chemotherapy versus those who are not treated with trastuzumab in the adjuvant setting (Popat & Smith, 2008).

Women who participated in trastuzumab clinical trials were different from the population of women who develop breast cancer in a number of ways: Selection criteria were for women with no preexisting cardiac disease; they also were younger, with an average age of 50 years (Telli, Hunt, Carlson, & Guardino, 2007). In comparison, the median age of women at the time of diagnosis is 61, and 65.2% are older than 55; many can be expected to have underlying heart disease (Horner et al., 2009). Whether the cardiotoxicity findings from the adjuvant trials will apply to the general population of women receiving adjuvant trastuzumab remains to be seen.

Systemic therapy is used to kill any undetected tumor cells that may have migrated to parts of the body other than the breast, with the goal of preventing or delaying any recurrence of disease (ACS, 2009a). Factors taken into consideration when determining who receives systemic treatment include tumor size, histology, and spread to lymph nodes (ACS, 2009a). Approximately 15%–20% of breast cancers overproduce a protein known as HER2/neu, which renders them eligible for treatment with trastuzumab (ACS, 2009a). Considering the number of new invasive breast cancers that will be diagnosed in women in 2009, an estimated 28,855–57,711 women will be candidates for treatment with trastuzumab, if systemic treatment is clinically indicated. Based on the adjuvant clinical trials leading to FDA approval of trastuzumab, approximately 4% of women (estimated to range from 339–678 per year) will develop cardiotoxicity. Although small, those numbers probably will be higher when women with preexisting cardiovascular risk factors or heart disease are treated and longer-term follow-up is conducted. Data projections based on adjuvant trials indicate that 1 in every 30 women treated with trastuzumab may develop class III or IV heart failure or cardiac death, and 20% may develop some type of cardiac dysfunction requiring treatment cessation (Telli et al., 2007). Considering initial short-term data from the adjuvant trials, the risk of cardiac dysfunction associated with the use of trastuzumab may be as high as 16% (Ewer et al., 2005). Currently, no data predict the cumulative 10-year risk of cardiac events (Telli et al.). Therefore, the benefit of treatment should be balanced with the risks of cardiotoxicity.

Pharmacology of Trastuzumab

Trastuzumab (see Figure 1) is a monoclonal antibody to ErbB2, a member of the epidermal growth factor family of tyrosine (Grazette et al., 2004) that inhibits

Current use: biologic therapy for breast cancer tumors that are HER2 positive. Trastuzumab is a monoclonal antibody that recognizes proteins on specific cells and signals the body's immune system to destroy them. The agent is a more targeted form of therapy than chemotherapy. It may be used in adjuvant or metastatic settings.

Pathophysiology: attaches to HER2+ cancer cells and tells the defense system to target them, stopping growth and division

Dosage: based on patient body weight. Initial loading dose is 4 mg/kg with weekly subsequent doses of 2 mg/kg.

Pharmacokinetics: Mean half-life and clearance are decreased with increasing dose levels. The average half-life was 1.7 and 12 days at the 10 mg and 500 mg dose levels. With a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/kg, a mean half-life of 5.8 days was observed. Mean serum trough concentrations when administered with paclitaxel were elevated 1.5-fold in comparison to its use with doxorubicin and cyclophosphamide. Its use with paclitaxel resulted in a reduction of trastuzumab clearance.

Administration: IV or infusion port access. Initial dose is given over 90 minutes with subsequent doses administered over 30 minutes.

Exclusion criteria: history of active cardiac disease, abnormal electrocardiography, abnormal chest x-ray, decreased left ventricular function, or uncontrolled hypertension

Monitoring: cardiac status via multigated acquisition scanning or echocardiography before initiation of doxorubicin, after doxorubicin, and before trastuzumab, 3 months after initiation, again at 6 months, and again at 15 months. Treatment modifications occur with signs and symptoms of heart failure or more than 10% decrease in left ventricular function.

Side effects: at first dose, chills, fever, nausea, vomiting, pain, headache, dizziness, shortness of breath, low blood pressure, rash, and weakness (usually mild to moderate). Allergic reactions include swelling, lung problems, inflammation, and severe shortness of breath. Worsening of low white blood cell counts can occur, which could lead to sepsis. Severe side effects include significant hypotension, shortness of breath requiring oxygen therapy, or, rarely, death. Treatment can result in reduced heart function and heart failure that could lead to mural thrombosis and stroke or even death.

Figure 1. Trastuzumab Prescribing Information

Note. Based on information from Genentech, Inc., 2009b.

proliferation of tumor cells that overexpress HER2. Trastuzumab is a humanized IgG1 kappa monoclonal antibody that works by selectively binding to extracellular human epidermal growth factor receptor 2 protein. Trastuzumab is administered as a weight-based IV infusion on a weekly or every-three-week schedule (Genentech, Inc., 2009b). The most common side effects (i.e., occurring more than 30% of the time) include fever or chills during infusion, arthralgias, weakness, and nausea (Genentech, Inc., 2009b). A small number of patients receiving trastuzumab (2.6%–4.5%) also developed cardiotoxicity, which was found to be the most debilitating of the side effects. Cardiotoxicity presented as a decline in LV function (Gonzalez-Angulo et al., 2006). The incidence increased to 27% when trastuzumab was combined with anthracycline chemotherapy, also known to cause cardiotoxicity, to treat metastatic disease.

Pathophysiology of Cardiotoxicity

Growth factors are found in all tissues of the body and regulate cell division by stimulating either positive or negative proliferation (Guntinas-Lichius & Wittekindt, 2003). Cardiomyocyte survival and growth require ErbB2. Although the actual mechanism is unknown, interruption of this pathway with trastuzumab may cause damage to the myocyte itself and may contribute to decline in LV function (Grazette et al., 2004; Pugatsch et al., 2006). Mouse model studies have found ErbB2 to be important in development of the fetal heart muscle and valves, with death occurring if the ErbB2 gene is deleted (Bird & Swain, 2008; Telli et al., 2007). A study of rat cardiomyocytes by Pugatsch et al. found that blocking the ErbB2 pathway influences the cell cycle involved in heart function, impairing the heart's response to stress. Telli et al. found that all mutant mice lacking the ErbB2 gene developed cardiac toxicity with LV dysfunction. Hearts lacking ErbB2 are suspected to be more at risk for cardiotoxic stress, resulting in cardiac myocyte damage that causes reversible LV dysfunction leading to heart failure (Telli et al.). This type of cardiac damage differs from that found with anthracyclines and appears to cause dysfunction rather than cell death, is not cumulative-dose-related, and appears to be reversible with partial or full recovery when trastuzumab is discontinued (Ewer & Ewer, 2008; Guglin, Cutro, & Mishkin, 2008; Menna et al., 2008; Montemurro et al., 2008).

Heart failure is a condition in which the left ventricle is unable to pump enough blood to organs because of decreased ejection, causing backflow into the lungs, which results in congestion of tissues (Hunt et al., 2005). Dyspnea, fatigue, edema, and rales are classic signs and symptoms of heart failure. The AHA uses the New York Heart Association (NYHA) classification system as the standard to classify heart failure, and that system was used in the clinical trials that led to the approval of trastuzumab in the adjuvant setting. Four stages are used to describe heart failure (see Table 1). Trastuzumab clinical trials defined cardiotoxicity as NYHA class III or IV (Baselga, Perez, Pienkowski, & Bell, 2006). The percentage of women experiencing class I or II cardiotoxicity was not reported because treatment adjustment or termination was only required for class III and IV cardiotoxicity. A decrease in LVEF from baseline occurred in 71% of clinical trial patients during treatment, ranging from 25%–69% (normal 55%–70%) (Telli et al., 2007). The changes persisted in some of the patients six months after cardiotoxicity was diagnosed, despite treatment. Patients who develop heart failure are treated with standard therapy such as angiotensin-converting enzyme (ACE) inhibitors and beta blockers (Popat & Smith, 2008).

Table 1. New York Heart Association Classification System for Heart Failure

Class	Symptoms
I	No symptoms and no limitation in ordinary physical activity
II	Mild symptoms and slight limitation during ordinary activity; patient comfortable at rest
III	Marked limitation in activity because of symptoms, even during less than ordinary activity; patient comfortable only at rest
IV	Severe limitations; symptoms even while patient is at rest

Note. Based on information from Criteria Committee of the New York Heart Association, 1994.

In summary, trastuzumab causes cardiotoxicity, specifically a decline in LV function, in some patients during and after treatment, even in women without cardiovascular risk factors or disease. Determining the long-term and late effects of trastuzumab is important, as are ongoing studies examining incidence and identifying populations at high risk for cardiac issues.

Monitoring and Management Strategies

Cardiac Risk Assessment and Monitoring

Trastuzumab was used to treat metastatic disease before it was approved for use in the adjuvant setting. Recommendations for use in advanced disease included a careful risk-versus-benefit assessment in patients with symptomatic heart failure, hypertension, or coronary artery disease. Overall, trastuzumab had a favorable risk-versus-benefit ratio in patients with metastatic disease and was believed to be safe to administer with appropriate cardiac monitoring (Cook-Bruns, 2001). Although that approach worked in the metastatic setting, a careful cardiac evaluation and more thorough discussion may be needed in the adjuvant setting, where women's prognoses are better and life expectancies are greater.

Baseline cardiac function assessment is done with an electrocardiogram (ECG) and echocardiography (ECHO) or multigated acquisition (MUGA) scanning. ECHO evaluates heart structure and motion by creating ultrasound images of the heart chambers and walls, whereas MUGA scanning uses radioactive isotopes to show LV function and, if damage from a previous infarct is present, view it by radiographic images (Hunt et al., 2005). A normal LVEF is 55%–70%. Clinical signs and symptoms of heart failure include dyspnea, increased cough, paroxysmal nocturnal dyspnea, peripheral edema, and S3 gallop (Telli et al., 2007). Other causes of heart failure also should be evaluated and ruled out (Viale & Yamamoto, 2008).

LV function should be assessed prior to initiation of trastuzumab therapy, during therapy, and after treatment (Genentech, Inc., 2009b). Based on adjuvant studies, the manufacturer developed cardiac monitoring guidelines as well as recommendations for holding and discontinuing therapy (see Figure 2 and Table 2). Although the manufacturer recommends more frequent monitoring in patients with preexisting cardiac dysfunction, it did not make specific recommendations for the appropriate interval of testing, leaving the frequency up to the healthcare provider. Sengupta, Northfelt, Gentile, Zamorano, and Khandheria (2008) recommended weekly monitoring if treatment for heart failure is initiated and then every eight weeks if symptoms reverse and LV function stabilizes.

A careful history and physical assessment include risk factors for LV dysfunction, including a history of myocardial infarction, angina, heart failure, valvular disease, pacemaker or intracardiac device, hypertension, hyperlipidemia, tobacco use, and diabetes, as well as family history (Fleisher et al., 2007). Physical examination should include vital signs, pulses, bruits, and assessment for jugular venous distention, lung and heart auscultation, and presence of edema in extremities, all of which could be used for baseline comparison after therapy is initiated (Fleisher et al.). An assessment of functional capacity and NYHA classification prior to initiation of trastuzumab should be documented. Changes in status during treatment also should be noted. Assessment should include questions regarding activities of daily living and instrumental activities of daily living (e.g., dressing, showering, doing housework, walking, climbing stairs).

To help determine risk of cardiac events, the American College of Cardiology (ACC) and the AHA developed an algorithm for patients undergoing noncardiac surgery based on clinical risk factors to provide a cardiac risk assessment in a surgical setting (Fleisher et al., 2007). A similar model could be developed and tested related to trastuzumab. For example, the benefit of trastuzumab may be greater than the risk if a patient has good functional capacity and no risk factors. In the presence of one or two risk factors (e.g., hypertension),

- Baseline left ventricular ejection fraction prior to initiation of therapy
- Every three months during treatment and after completion
- Every six months for two years after treatment

Figure 2. Recommendations for Cardiac Monitoring Via Multigated Acquisition Scanning or Echocardiography

Note. Based on information from Genentech, Inc., 2009b.

Table 2. Recommended Treatment Modifications for Symptomatic Decrease in Left Ventricular Ejection Fraction (LVEF)

Ejection Fraction	Absolute Decrease From Baseline: < 10%	Absolute Decrease From Baseline: 10%–15%	Absolute Decrease From Baseline: ≥ 16%
Within normal limits	Continue treatment.	Continue treatment.	Hold for four weeks.
Below lower limit of normal	Continue treatment.	Hold for four weeks.	Hold for four weeks.

Note. When trastuzumab is held, it may be resumed within four to eight weeks if LVEF returns to normal limits and the absolute decrease from baseline is equal to 15%. Permanent discontinuation should occur if LVEF decline lasts more than eight weeks or dosing has to be held on more than three occasions related to cardiomyopathy. Trastuzumab should be discontinued in any patients who experience symptomatic congestive heart failure.

Note. Based on information from Genentech, Inc., 2009b.

trastuzumab may be administered if the risk factors are treated prior to trastuzumab initiation. In the presence of three or more risk factors, a careful benefit-versus-risk ratio should be calculated; if healthcare professionals and patients decide to proceed, heart function and functional capacity should be monitored more frequently than every three months (Fleisher et al.). Again, such a practice model would need to be tested.

Based on the ACC/AHA 2007 guidelines (Fleisher et al., 2007), a risk assessment tool prototype has been developed for possible use before and during trastuzumab administration (see Figure 3). Three medical oncologists, two nurse practitioners, and seven oncology nurses reviewed the tool for clarity and clinical usefulness. It currently is being pilot tested in clinical practice. However, research will be necessary to determine the efficacy of such a tool in increasing adherence to monitoring recommendations and the impact it may have on patient outcomes.

Based on ACC/AHA guidelines (Fleisher et al., 2007), all patients with or without cardiac symptoms should undergo baseline screening of LV function prior to initiation of trastuzumab therapy. An ECG is recommended in all patients with at least one risk factor and is reasonable in those with no risk factors (Fleisher et al., 2007). The presence of Q waves or significant ST segment elevation or depression could be indicative of coronary artery disease, and the presence of left ventricular hypertrophy could indicate uncontrolled hypertension. Both abnormalities need further assessment prior to trastuzumab therapy because underlying cardiac strain could exist. If patients are found to have coronary artery disease prior to administration of trastuzumab, revascularization could be recommended in patients with angina or recent myocardial infarction. Beta blockers should be continued in patients who were taking them prior to initiation of trastuzumab or initiated in those at high cardiac risk, unless contraindicated for bradycardia or heart block. Statin therapy for hyperlipidemia should be continued for patients currently taking such drugs. In patients who are diabetic, blood glucose should be well controlled prior to initiation of trastuzumab because of their high risk for cardiac disease. In cases of severe hypertension (systolic blood pressure greater than or equal to 180 mmHg), the potential benefits of delaying treatment to optimize effects of antihypertensive medications should be weighed against the risk of delay (Fleisher et al.). Further studies may find that treatment should not be withheld because of risk factors as long as they are managed according to recommended guidelines by the AHA or, if newly diagnosed, treated prior to initiation of therapy according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (National Heart Lung and Blood Institute, 2003).

In women identified as having additional risk factors (including but not limited to obesity, hypertension, smoking, and other comorbidities, such as diabetes and hyperlipidemia), healthcare providers can determine testing intervals based on the number and severity of risk factors. At a minimum, testing should be as frequent as for those without problems. With proper monitoring, the benefits of treatment with trastuzumab may be realized without the devastating effects of severe cardiac dysfunction in women who might otherwise be cured of their breast cancer. In women with no preexisting cardiac conditions, the recommendations provided by the manufacturer should be followed until other evidence-based guidelines become available.

Nurses also can play a vital role in monitoring patients. Nurses customarily monitor laboratory values prior to the initiation of chemotherapy; with the appropriate tools and guidelines, they can help ensure that proper cardiac monitoring is performed with trastuzumab treatment.

Treatment of Cardiotoxicity

Treatment guidelines for heart failure from the AHA include the use of ACE inhibitors and beta blockers, which have been shown to improve outcomes related to the progression of LV dysfunction, as standard therapy for

Name: _____
Date of birth: _____

Diagnosis: _____
Chemotherapy: _____

Cardiotoxicity Risk Factors[a]
- ❑ Current or prior adriamycin
- ❑ Radiation to left chest
- ❑ Hypertension (controlled or uncontrolled[b])
- ❑ Diabetes (controlled or uncontrolled[b])
- ❑ Hyperlipidemia (medical therapy or diet therapy)
- ❑ Prior coronary artery disease
- ❑ Tobacco use (current or former)
- ❑ Overweight (circle one: body mass index > 25 or > 30)
- ❑ Prior heart failure (Caution advised. If proceeding with trastuzumab, patient should be well controlled on angiotensin-converting enzyme inhibitors or beta blockers and have regular monitoring. Educate about signs and symptoms to report: shortness of breath, dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, edema, weight gain of two pounds per day or five pounds per week.)

Cardiac Status
- ❑ Abnormal electrocardiogram (ECG) indicative of left ventricular hypertrophy[c]
- ❑ Abnormal ECG indicative of coronary artery disease[c]
- ❑ Ejection fraction prior to chemotherapy
- ❑ Ejection fraction after chemotherapy[d]

Review of Systems (Check all that apply.)
- ❑ Shortness of breath at rest
- ❑ Dyspnea on exertion
- ❑ Paroxysmal nocturnal dyspnea
- ❑ Edema in lower extremities or abdomen
- ❑ Orthopnea
- ❑ Fatigue
- ❑ Chest pain

Note. If any symptoms are checked, patient may already have a decline in left ventricular function and may be at greater risk for developing cardiotoxicity.

Current Functional Status
Eastern Cooperative Oncology Group functional status: _____
Karnofsky Performance Scale status: _____
Other performance status: _____
Scale used: _____

Echocardiography (ECHO)/Multigated Acquisition Scanning History
- ❑ Ejection fraction prior to chemotherapy
- ❑ Ejection fraction postchemotherapy/pretrastuzumab[e]

Use chart below for ongoing assessment.

Testing Date	Ejection Fraction (EF)	EF Change From Trastuzumab Baseline	Action (Check one.)	Comments
3 months after initiation Date:			❑ Continue treatment. ❑ Hold treatment for four weeks. Repeat ECHO. ❑ Discontinue treatment.	
6 months after initiation Date:			❑ Continue treatment. ❑ Hold treatment for four weeks. Repeat ECHO. ❑ Discontinue treatment.	
9 months after initiation Date:			❑ Continue treatment. ❑ Hold treatment for four weeks. Repeat ECHO. ❑ Discontinue treatment.	
12 months after initiation Date:			❑ Continue treatment. ❑ Hold treatment for four weeks. Repeat ECHO. ❑ Discontinue treatment.	
15 months after initiation Date:			❑ Continue treatment. ❑ Hold treatment for four weeks. Repeat ECHO. ❑ Discontinue treatment.	
Repeat results Date:			❑ Continue treatment. ❑ Hold treatment for four weeks. Repeat ECHO. ❑ Discontinue treatment.	
Repeat results Date:			❑ Continue treatment. ❑ Hold treatment for four weeks. Repeat ECHO. ❑ Discontinue treatment.	
Repeat results Date:			❑ Continue treatment. ❑ Hold treatment for four weeks. Repeat ECHO. ❑ Discontinue treatment.	

[a] If any are checked, conduct a careful risk-versus-benefit assessment, and cardiology evaluation should be considered before trastuzumab initiation. [b] If uncontrolled hypertension or diabetes is noted, consider holding trastuzumab initiation until appropriate therapy has been instituted and improvement noticed (goal is blood pressure less than 140/90 and less than 130/80 if diabetic, hemoglobin A1c less than 7%). [c] If checked, patient needs cardiac evaluation and treatment prior to initiation of therapy and more frequent monitoring during trastuzumab therapy may be indicated. Discuss risk with patient. [d] If decline in ejection fraction is higher than 10% or less than 45%, patient is at increased risk and an appropriate risk-versus-benefit analysis should be determined. If patient is symptomatic with heart failure, therapy should be held until symptoms improve with medical management (e.g., angiotensin-converting enzyme inhibitors, beta blockers) or ejection fraction improves. [e] Should be at or above radiology facility's lower limit of normal and no more than 15 points below baseline (i.e., prior doxorubicin ejection fraction) to initiate trastuzumab

Figure 3. Trastuzumab Cardiac Risk Assessment and Monitoring Tool

heart failure, and they should be used for trastuzumab-induced cardiotoxicity (Hunt et al., 2005; Sengupta et al., 2008). The addition of ACE inhibitors and beta blockers as well as treatment modifications have been shown to reduce further decline in LV function and possibly reverse damage (Telli et al., 2007). Reporting cardiac symptoms and noting a decline in LV function in a timely manner are important in triggering trastuzumab adjustments and initiating appropriate cardiac medications.

The National Surgical Adjuvant Breast and Bowel Project reported complications in the B-31 trial; 28 of 31 patients developed cardiotoxic effects while undergoing adjuvant treatment, and 3 patients developed a cardiac event after completing therapy for a full year (Telli et al., 2007). Of those with cardiotoxic effects or decline in LV function, two-thirds continued to receive cardiac medication after trastuzumab despite being clinically asymptomatic (Baselga et al., 2006). At last follow-up, 27 of the 34 patients were asymptomatic and 18 remained on medication.

Many patients treated with trastuzumab also may develop asymptomatic LV dysfunction potentially progressing to heart failure in the years following treatment. Telli et al. (2007) found the one-year mortality in this population to be 11.4% for class IV heart failure despite standard medical therapy. Using cardioprotective agents such as ACE inhibitors and beta blockers may be beneficial in women at high risk if they are not contraindicated; however, further studies are needed to determine whether they are really beneficial. Whether the addition of such medications during trastuzumab treatment will decrease the development of heart failure in asymptomatic patients is unknown (Telli et al.). ACE inhibitors have been shown in preliminary reports to prevent cardiotoxicity in patients receiving chemotherapy (Telli et al.), and future studies may show that they reverse LV dysfunction. ACC practice guidelines recommend ACE inhibitors and beta blockers in patients who are asymptomatic but show decreases in LV function by ECHO or MUGA (Smith, 2007), and this practice could be explored with trastuzumab-induced cardiotoxicity as well.

When decline in LV function has been identified, trastuzumab has been discontinued, and appropriate medical management has been implemented, many patients experience improvement in LV function (Telli et al., 2007). In addition to ACE inhibitors and beta blocker therapy, other risk factors for further heart disease need attention (Hunt et al., 2005), including hypertension, diabetes, elevated lipids, and thyroid disorders.

Patient Education

Patient education is a critical component of any intervention or treatment, particularly one that has the potential to compromise quality of life. A review of print and Web-based trastuzumab educational materials showed that the risk of heart failure was listed as "uncommon" or "rare." However, the materials did not indicate that women with preexisting heart conditions were omitted from clinical trials and that women in the studies were younger than average. Another key factor omitted was the definition of heart failure in adjuvant trials: NYHA class III or IV. Patients should know that the statistics did not include women who developed class II heart failure, which is defined as mild symptoms and slight limitations during ordinary activity (Hunt et al., 2005). Given the overall prognosis in women with early-stage disease, this may matter much more than in women with metastatic disease.

Manufacturer literature acknowledges an increased risk of heart failure in patients who previously received anthracycline chemotherapy but does not include other risk factors. Cleveland Clinic Cancer Center (2005) provides patient education that includes an increased incidence of heart problems, specifically heart failure, in patients with a prior history of heart disease, those who have received radiation to the chest, those of advanced age, and individuals who have received treatment with other medications associated with cardiotoxicity, such as doxorubicin and cyclophosphamide. Other cardiac risk factors, such as obesity, smoking, hypertension, high cholesterol, and diabetes, which are believed to increase the risk of heart failure in the general population, were not included in the educational literature. Giving patients information about the importance of managing or decreasing cardiac risk factors will provide knowledge so that they can make other treatment decisions, including but not limited to regular appointments with primary care providers, smoking cessation, healthful diet, increased physical activity, and weight reduction, all of which can decrease the potential for heart failure. While receiving trastuzumab, patients should be counseled on appropriate diet, tobacco cessation, limited alcohol consumption, and other risk behaviors (Smith, 2007).

Current educational materials inform patients of the importance of early reporting of symptoms that could be indicative of heart failure, including swelling, rapid heartbeat, difficulty breathing, and excessive coughing. The ACS provides patient education on its Web site. The MEDLINE Web site provides information on how patients can report serious reactions to the FDA (National Institutes of Health, 2009).

Patient education related to side effects of trastuzumab must include the potential for cardiac damage as well as signs and symptoms to report to healthcare providers. Current education sheets for trastuzumab identify the potential for interference with the pumping action of the heart and indicate that it is a serious but uncommon side effect, stating that heart function may be checked prior to therapy and monitored closely during

treatment (Cleveland Clinic Cancer Center, 2005). Patient education materials prepared by the manufacturer state that trastuzumab treatment "can result in heart problems, including those without symptoms (reduced heart function) and those with symptoms (congestive heart failure)" (Genentech, Inc., 2009a). A Web site for patients (www.herceptin.com) describes breast cancer in general and the definition of adjuvant treatment. The site also offers trastuzumab-specific information such as a description of the drug, how HER2 testing is done, benefits of treatment, treatment duration, cardiac monitoring, potential side effects, and questions to address with healthcare providers.

A final component of the patient education process that is important for early detection of heart failure is adherence to monitoring recommendations. Currently, patient education materials explain the reason for cardiac monitoring, which tests are used for monitoring, and the potential for increased monitoring in patients with a history of heart problems, but the recommended monitoring schedule usually is not provided. When patients have this information, they can become another safeguard in the appropriate timing of ECHO or MUGA scanning.

Recommending strategies to reduce the risk of heart failure and stressing the importance of early detection of symptoms may decrease the severity of heart failure caused by trastuzumab. Reportable signs and symptoms and monitoring requirements are important components to consider in patient teaching. With appropriate written and verbal education, patients can be afforded the opportunity to make informed treatment decisions and to make lifestyle changes that may decrease the risk of heart failure. With early reporting of symptoms and appropriate cardiac monitoring, early detection of heart failure may decrease severity of symptoms and, hopefully, minimize the risk of further cardiotoxicity.

Implications for Research and Practice

Longer-term follow-up of patients who have received trastuzumab may reveal more heart failure and higher mortality than reported in initial adjuvant trials. In previous trastuzumab trials, follow-up periods were short, and long-term effects were not studied. Retrospective analysis of patients whose treatments were discontinued because of cardiotoxicity is needed. Identification of risk factors for trastuzumab-related cardiac dysfunction could better predict which patients are at increased risk and, therefore, may not be considered for treatment.

Based on the increased survival and improved prognosis for the subset of women with HER2+ breast cancers, trastuzumab will continue to be recommended in the adjuvant setting as the standard of care in the foreseeable future. Clinical guidelines are necessary to appropriately and consistently screen for cardiac risk factors and disease prior to initiation of trastuzumab and during and after administration.

Clinical trials have proven the benefit of adding trastuzumab to the treatment plan for women with HER+ disease, but many questions remain unanswered with regard to long-term safety and implications for monitoring in the adjuvant setting. Not enough time has passed since approval in the adjuvant setting to adequately allow for assessment of long-term cardiotoxicity. Many oncologists contend that the risk of cardiotoxicity is low compared to the benefit trastuzumab offers, whereas others believe that the risk of cardiotoxicity could increase with longer follow-up after administration. Long-term follow-up studies are needed to adequately determine late cardiotoxicities in this population.

The question remains whether the risk of cardiotoxicity is higher in women who have some underlying cardiac issues. More studies are needed to assess the risk of cardiotoxicity in women with preexisting cardiac disease. Information from such trials will give women more knowledge, thus affording them the opportunity to make more informed decisions related to their care.

Optimal treatment duration of trastuzumab has yet to be defined. In the Finnish Herceptin trial, similar survival results were found with nine weeks of treatment with trastuzumab compared to adjuvant trials that included one year of trastuzumab (Hudis, 2007). In fact, Finnish Herceptin trial results demonstrated 89% disease-free survival compared with 85% in the combined National Surgical Adjuvant Breast and Bowel Project B-31 and North Central Cancer Treatment Group N-9831 trials. Not only should length of treatment be evaluated, but dosing and schedules also should be studied. Currently, dosing is weight-based, but schedules can include weekly dosing versus every-three-week dosing schedules. Future studies should address the issue of what is the lowest dose possible, for the shortest amount of time, as well as optimal frequency to demonstrate the lowest cardiotoxicities while maintaining efficacy.

Based on the adjuvant trial information, one in five women will require discontinuation of treatment related to cardiac dysfunction (Telli et al., 2007). However, if providers are not monitoring cardiac function at appropriate intervals, the question remains how many women will continue to receive treatment after cardiac dysfunction begins and how severe the cardiac dysfunction will become before it is recognized and the drug discontinued. Current monitoring for cardiotoxicity related to trastuzumab relies on sequential measurements of LV function with either MUGA scanning or ECHO (Ewer et al., 2005). Early detection of abnormalities is not always possible with those methods because of physiologic compensation for cardiac damage (Ewer et al.). Both

MUGA scanning and ECHO can vary in results depending on loading conditions of the left ventricle. Future studies should use other screening tests to determine whether trastuzumab cardiotoxicity could be discovered earlier. Cardiac troponin I is a protein in muscle tissue that measures cardiac contractility and can be released as early as one hour after chemotherapy. Studies have shown that troponin levels are abnormal in patients who eventually develop LV systolic dysfunction (Ewer et al.). B-type natriuretic peptide, a blood test that can provide immediate feedback related to the risk of LV dysfunction and heart failure because the heart leaks this enzyme in the presence of cardiac insufficiency, also could prove to be advantageous (Ewer et al.). The possibility also exists to add ACE inhibitors or beta blockers to the treatment plan prophylactically to provide cardioprotection to patients at high risk. Clearly, this is an area that requires collaborative interdisciplinary clinical care and research.

Cancer survivors face many risks: disease recurrence and progression, second primaries, and other comorbidities, such as cardiovascular disease and diabetes (Demark-Wahnefried, Aziz, Rowland, & Pinto, 2005). Given the fact that 70% of breast cancer survivors are classified as overweight or obese, and obesity can lead to problems such as cardiovascular disease, the question remains whether health-promotion efforts could decrease cardiovascular complications. Education on health promotion should include maintaining a healthy weight, consuming a diet low in saturated fat with appropriate amounts of fruits and vegetables, and participating in moderate physical activity. As cancer becomes increasingly classified as a chronic disease, oncology healthcare providers will find themselves responsible for educating patients not only about acute cancer care, but also about how to manage their long-term health (Demark-Wahnefried et al.).

Summary and Recommendations

When determining the most advantageous treatment regimens for patients, healthcare professionals must remember that long-term cardiac safety of trastuzumab has yet to be defined. Decisions to add trastuzumab to surgery, chemotherapy, or radiation should be based on tumor size, node involvement, tumor biology, and cardiac risk factors. Using a trastuzumab cardiac risk assessment and monitoring tool in the treatment setting might help to decrease the impact of cardiotoxicity. Further research needs to be done to elucidate who is at high risk for developing cardiotoxic events and how best to prevent or treat them.

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