CLINICAL CHALLENGES

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Chemotherapy-Induced Cardiomyopathy

Case Study

Mrs. H is 67 years old, obese, and hypertensive and has been diagnosed with infiltrating ductal carcinoma of the right breast. She had a modified radical mastectomy, and pathology revealed a poorly differentiated 2.8 cm tumor that was estrogen- and progesterone-receptor negative and HER2 positive. Two axillary lymph nodes were positive for malignant cells. A baseline blood pool multiple-gated acquisition scan (MUGA) obtained prior to commencing chemotherapy with doxorubicin and cyclophosphamide demonstrated a left ventricular ejection fraction (LVEF) of 67%. After completion of four cycles of chemotherapy, Mrs. H had a short, disease-free interval but subsequently developed metastatic disease. She will begin a course of paclitaxel (Taxol®, Bristol-Myers Squibb, Princeton, NJ) and trastuzumab (Herceptin®, Genentech, Inc., South San Francisco, CA). You are concerned about her risk for developing cardiomyopathy.

Clinical Problem Solving

Responding to this clinical challenge are Julia Smith, RN, MSN, APRN, AOCN®, former faculty member of the Yale University School of Nursing in the Adult Advanced Practice Nurse Program, Oncology Specialty Track, in New Haven, CT, and Jessica Shank Coviello, RN, MSN, APRN, a lecturer at the Yale University School of Nursing in the Adult Advanced Practice Nurse Program, Acute Care Track, and an adult nurse practitioner at the Connecticut Heart Group in New Haven.

What are the potential risk factors contributing to the development of cardiomyopathy?

Trastuzumab is an anti-HER2 monoclonal antibody that has demonstrated reduction in tumor size, delay in disease progression, and increased survival in women with the HER2 protein overexpressed in metastatic breast cancers. It is used with paclitaxel as a first-line therapy and as second-line treatment for metastatic breast cancer (Seidman et al., 2002). Cardiac dysfunction has been noted in 3%–5% of patients when trastuzumab was administered as a single agent and in up to 64% of patients receiving the drug in combination with anthracyclines during phase III clinical trials (Seidman et al.). The risk of cardiac dysfunction also exists when trastuzumab is administered to patients after anthracycline therapy. Anthracylines, particularly doxorubicin, are known to cause cumulative dose-related cardiomyopathy. The risk of cardiac dysfunction with an anthracycline and cyclophosphamide is 8% (Seidman et al.). The incidence of trastuzumab cardiotoxicity is 4% when used as monotherapy, 27% when combined with an anthracycline and cyclophosphamide, and 13% when combined with paclitaxel (Keefe, 2002). In 2002, the third arm of a phase III study that involved concurrent paclitaxel with trastuzumab for 12 weeks followed by trastuzumab for 40 weeks was halted temporarily because of concerns about a small number of patients in one arm of the trial who developed congestive heart failure after one week of treatment (Freidrich, 2002). The affected patients responded to treatment and recovered cardiac function.

The pathogenesis of trastuzumab cardiotoxicity is poorly understood, but HER2 is known to be involved in embryonic cardiogenesis and cardiac hypertrophy (Ewer, Gibbs, Swafford, & Benjamin, 1999). However, researchers have not determined whether trastuzumab exacerbates anthracycline-induced damage or acts independently on the cardiac myocyte (Seidman et al., 2002). In addition, Chien (2000) suggested that some patients may have an inherent genetic susceptibility to the mechanisms that influence the pathways to heart failure. Risk factors for developing trastuzumab cardiotoxicity are not clear, although age has been an associated factor (Seidman et al.). Obesity and hypertension are known risk factors for cardiac dysfunction.

What are the prevention and surveillance strategies?

Cardioprotective strategies and surveillance protocols should be developed for patients undergoing treatment with trastuzumab. Although cardiotoxic effects of cancer treatment occur infrequently, early detection of trastuzumab toxicity requires cardiac monitoring that is similar to that of anthracycline-treated patients. Unfortunately, no proven strategies are available and the approaches used in clinical trials are varied. Concurrent administration of trastuzumab and an anthracycline is not recommended because the highest rates of cardiac dysfunction are found with concomitant therapy (McKeage & Perry, 2002; Seidman et al., 2002). The use of liposome-encapsulated doxorubicin has been proposed as a means to minimize trastuzumab toxicity, but reduction in rates of cardiotoxicity have not been demonstrated.

In contrast to anthracyclines, trastuzumab toxicity does not appear to be dose related. For patients beginning trastuzumab therapy, a baseline assessment of cardiac function by physical examination and LVEF with MUGA is warranted. However, MUGA does not identify early evidence of cardiac dysfunction. Echocardiography is being compared to MUGA to determine whether it may be more sensitive (Seidman et al., 2002). Nuclear medicine scintigraphy and endomyocardial biopsy can identify early damage but are neither feasible nor economical. Clinical trials

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currently are under way exploring the use of troponins and other markers that may predict early and late cardiac damage associated with anthracyclines and trastuzumab (Sparano, Brown, & Wolff, 2002).

In clinical trials, among the patients who developed cardiac dysfunction, differences in clinical presentation were noted between patients who received trastuzumab with an anthracycline and cyclophosphamide versus trastuzumab with paclitaxel. The anthracycline and cyclophosphamide group presented with significant functional impairment in contrast to the trastuzumab with paclitaxel group (Seidman et al., 2002). Periodic LVEFs should be measured based on considerations of other risk factors (e.g., age, prior hypertension, prior anthracycline exposure). An asymptomatic reduction in LVEF warrants a clinical investigation. Any clinical presentation of symptoms, such as orthopnea, dyspnea on exertion, or paroxysmal nocturnal dyspnea, should be evaluated immediately.

What are some management strategies for trastuzumab-associated cardiotoxicity?

The majority of reported cardiac effects of trastuzumab have been mild to moderate and generally are considered manageable (Keefe,

Clinical Highlights: Heart Failure

Definition: The clinical syndrome of heart failure is the end result of myriad diseases that affect the heart. Heart failure is a complex blend of structural, functional, and biologic alterations that account for the progressive nature of the disease if left untreated. Symptoms are related to the inadequate profusion of tissue during exertion and often to the retention of fluid. Its primary cause is an impaired ability of the heart to empty (as in systolic failure) or fill (as in diastolic failure). The management of heart failure no longer is directed only at symptom relief. Management now is aimed at improvement in cardiac function by addressing this complex pathophysiologic syndrome (Jessup & Brozena, 2003).

Incidence: Nearly 5 million Americans have heart failure with the incidence approaching 10 per 1,000 among patients older than age 65. Heart failure accounts for at least 20% of all hospital admissions among those older than age 65. Since the early 1990s, the rate of hospitalizations for heart failure has increased by more than 159% (American Heart Association, 2000). Certain antineoplastic agents, notably anthracyclines and trastuzumab, have been shown to cause cardiomyopathy.

Pathophysiology: Limited data are available about the physiologic mechanisms responsible for anthracycline- and trastuzumab-induced cardiomyopathy and the subsequent symptoms of heart failure. Researchers have proposed that anthracyclines are absorbed by the cardiac myocyte. Histologic findings in anthracycline-induced cardiomyopathy include myofibrillar loss leading to the death of the myocyte or cardiac muscle cell. With anthracyclines, this cell death appears to be dose related, preceding a decrease in left ventricular function (i.e., a reduced ejection fraction) (Nousiainen et al., 2001). The irreversibility of doxorubicin-induced damage to the heart is believed to be related to the generation of free radicals that cause cellular injury, a concurrent decrease in endogenous antioxidants that results in oxidative stress, and subcellular changes that include loss of myocytes (Keefe, 2002).

The pathogenesis and histologic changes responsible for trastuzumab-associated cardiomyopathy are under investigation. Unlike anthracycline-induced toxicity, trastuzumab-associated toxicity usually responds to standard treatment or the discontinuation of the drug. With trastuzumab, no evidence exists to confirm that the toxicity is dose related.

Clinical findings of heart failure: Most reported trastuzumab-related cardiomyopathy is asymptomatic except for findings indicative of the loss of left ventricular function, as with a decrease in left ventricular ejection fraction (Keefe, 2002). When signs and symptoms appear, they are usually mild to moderate in nature and include tachycardia, palpitations, dyspnea, and occasional chest pain.

Tachycardia is an early sign of anthracycline-induced cardiotoxicity and is an early indicator of most patients with heart failure. Additional findings of heart failure include peripheral edema, weight gain, orthopnea, and paroxysmal nocturnal dyspnea. Other physical findings are congestion in the lung bases, jugular venous distention, third heart sound, and peripheral edema.

Differential diagnosis: Patients with heart failure usually can be identified in one of three ways: (a) They experience exercise intolerance, (b) they present with signs of fluid overload, or (c) they are asymptomatic but with incidentally discovered left ventricular dysfunction. Although the presence of any one symptom is sufficient to warrant consideration of heart failure as the underlying cause, orthopnea, paroxysmal nocturnal dyspnea, and dyspnea on exertion are the three classic symptoms of heart failure coupled with the physical findings of elevated jugular venous pressure, a third heart sound, and a laterally displaced apical impulse. Peripheral edema or pulmonary congestion alone is nonspecific when found in isolation from radiographic findings or other signs and symptoms.

Screening: Although heart failure is a major public health problem, until recently, no national screening efforts, such as those for breast and prostate cancers, have been undertaken to detect the disease at earlier stages. In the general public, heart failure is largely preventable and can be accomplished through control of blood pressure as well as evaluation and management of other vascular risk factors such as diabetes. In 2001, the American College of Cardiology and the American Heart Association developed a new approach to the classification of heart failure that emphasizes its evolution and progression (Hunt et al., 2001). This classification augments the New York Heart Association functional class categories devised by the Criteria Committee of the New York Heart Association (1994). The categories underscore the fact that established risk factors and structural abnormalities are necessary for the development of heart failure. They also demonstrate its progressive nature. The complete heart failure guidelines are available through the American Heart Association Web site at www.acc.org/clinical/guidelines/failure/hf_index.htm.

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Table 1. Proposed Guidelines for the Management of Patients Treated With Trastuzumab Based on Physical Status and Left Ventricular Ejection Fraction

Physical Status[a]	LVEF	Action		
		Trastuzumab	LVEF Monitoring	Management
Asymptomatic	↓ but normal	Continue	Repeat in 4 weeks	
	↓ > 10 points but normal	Continue	Repeat in 4 weeks	Consider beta blockers
	↓ 10–20 points and LVEF > 40%	Continue	Repeat in 2–4 weeks • Improved: monitor • Not improved: stop trastuzumab	Treat for CHF
	↓ > 20 points to < 40% or LVEF < 30%	Hold	Repeat in 2 weeks • Improved to > 45%: restart trastuzumab • Not improved: stop trastuzumab	Treat for CHF
Symptomatic	↓ < 10 points	Continue		Search for noncardiac pathology (e.g., anemia)
	↓ > 10 points and LVEF > 50%	Continue	Repeat in 2–4 weeks • Stable or improved: continue trastuzumab • Worsened: stop trastuzumab	Treat for CHF
	↓ < 30 points	Stop		Treat for CHF

[a] Heart rate and body weight should be monitored weekly. Asymptomatic is defined as changes in heart rate and/or weight but without symptoms of dyspnea on exertion. Symptomatic is defined as a new, spontaneous (i.e., unsolicited) report of symptoms of dyspnea on exertion, pulmonary vascular congestion, or edema.

CHF—congestive heart failure; LVEF—left ventricular ejection fraction

Note. From "Trastuzumab-Associated Cardiotoxicity" by D. Keefe, 2002, *Cancer, 95,* p. 1596. Copyright 2002 by the American Cancer Society. Reprinted with permission.

2002). Guidelines for the management of patients treated with trastuzumab are noted in Table 1. Patients who develop congestive heart failure can be treated according to the American College of Cardiology and the American Heart Association guidelines (Hunt et al., 2001). Generally, cardiac function improves with cessation of the drug, although some patients are managed successfully while continuing trastuzumab (Slamon et al., 2001; Smith, 2001). Because the prognosis associated with HER2-positive breast cancer is limited, the decision to discontinue trastuzumab therapy is a risk-benefit analysis that should be determined on an individual basis.

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