

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 can-

cers. 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. Anthracyclines, 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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