

Heart Failure in a Breast Cancer Survivor

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A 64-year-old woman named J.G. was diagnosed with a right side, node-negative, HER2-positive, hormone-negative (stage I) breast cancer about eight years ago. Following lumpectomy and sentinel node biopsy, she was referred to a medical oncologist at a National Cancer Institute–designated comprehensive cancer center for consultation on the need for adjuvant chemotherapy. The oncologist recommended four cycles of doxorubicin plus cyclophosphamide. Final trials for trastuzumab in the adjuvant setting had not been completed at the time of the consultation. And, because of the small size of the primary tumor (0.8 cm), the oncologist did not recommend trastuzumab, citing evolving concerns about cardiotoxicity related to long-term use of the drug. J.G. had a positive family history of cardiac events: Both of her parents died from sudden myocardial infarctions in their 60s and her older brother had congestive heart failure (CHF). J.G. had a personal history of hypertension (for which she declined antihypertensive treatment), was obese (body mass index of 38.4), and was sedentary. She agreed with the treatment plan as discussed with her oncologist. A prechemotherapy cardiac assessment of an electrocardiogram and multigated acquisition (MUGA) scan showed no cardiac problems. The MUGA scan's result for left ventricular ejection fraction (LVEF) was 61% (normal is 50% or greater). J.G. proceeded with treatment, which she tolerated well. Following chemotherapy, she underwent six weeks of external beam radiation to her right breast with a boost to the tumor site.

After completing adjuvant therapy, J.G. was seen regularly during a five-year period by her surgeon and medical oncologist. Two months ago, however, J.G. noted a sudden increase in fatigue. She had a persistent dry cough and was gaining weight without an increase in

food intake. She dismissed the cough and fatigue as symptoms of a viral infection. Within weeks, however, she had rapidly increasing orthopnea. And, in the space of two weeks, she had progressed from sleeping on two pillows to having to sit upright in a chair day and night.

J.G.'s assumption was that her breast cancer had recurred in her lungs. She had an annual follow-up appointment already scheduled with her oncologist within a week and, as a teacher, she wanted to wait for the assumed "bad news" until after the close of the school year. Two days before that appointment, however, her feet suddenly began to swell and she experienced mild nausea, difficulty fitting into her clothing and shoes, and a dull ache in her abdomen. When she presented in the oncology clinic, she had 3+ pitting edema in her bilateral lower extremities, her blood pressure was 110/62, pulse was 122, and respiration was 30. Evidence was noted of significant jugular vein distension, pulmonary rales, and an S3 gallop heart sound.

The oncologist ordered a chest x-ray, echocardiogram, complete blood count, chemistry panel, B-type natriuretic peptide (BNP)—a marker of heart failure—and liver enzymes. The chest x-ray showed cardiomegaly (enlargement of the heart); the complete blood count, chemistry panel, and liver enzymes all were within normal limits. The BNP was markedly elevated at 1,542 pg/ml (normal is less than 100 pg/ml). The echocardiogram result of 10% LVEF confirmed the most likely differential diagnosis: cardiomyopathy and acute presentation of CHF. Diagnostic criteria for CHF are shown in Figure 1. J.G.'s LVEF had declined by 51% over her prechemotherapy baseline. In addition, a BNP value greater than 900 pg/ml is indicative of severe heart failure (Hunt et al., 2009).

J.G. was advised to go to the medical center's emergency department, where she was aggressively diuresed and admitted to a telemetry unit. During her inpatient stay, J.G. was seen by a heart failure team, including a board-certified cardiologist specializing in heart failure and a cardiology nurse practitioner. Additional workup during her stay

Major Criteria

- Acute pulmonary edema
- Hepatojugular reflux
- Increased central venous pressure (more than 16 cm H₂O at right atrium)
- Neck vein distention
- Paroxysmal nocturnal dyspnea
- Radiographic cardiomegaly (increasing heart size on chest radiography)
- Rales
- S3 gallop
- Weight loss of more than 4.5 kg in five days in response to treatment

Minor Criteria

- Bilateral ankle edema
- Decrease in vital capacity by one-third from maximum recorded
- Dyspnea on ordinary exertion
- Hepatomegaly
- Nocturnal cough
- Pleural effusion
- Tachycardia (heart rate more than 120 beats per minute)

Note. Minor criteria are acceptable only if they cannot be attributed to another medical condition (e.g., pulmonary hypertension, chronic lung disease, cirrhosis, ascites, nephrotic syndrome). The Framingham Heart Study criteria are 100% sensitive and 78% specific for identifying individuals with definite congestive heart failure (CHF). Diagnosis of CHF requires the simultaneous presence of at least two major criteria or one major criterion in conjunction with two minor criteria.

Figure 1. Framingham Criteria for Congestive Heart Failure

Note. Based on information from McKee et al., 1971.

Table 1. Heart Failure Drug Protocol

Classification	Exemplar	Initial Dose	Target Dose
ACE inhibitor	Lisinopril	2.5 mg daily	40 mg daily
Beta blocker	Carvedilol	3.125 mg BID	25 mg BID
Loop diuretic	Bumetanide	1–2 mg BID	2 mg BID
Potassium-sparing diuretic	Spirinolactone	12.5–25 mg BID	25 mg BID

ACE—angiotensin-converting enzyme

Note. Frequent monitoring of potassium levels is necessary to prevent hyperkalemia because of interactions between the potassium-sparing diuretic and ACE inhibitor.

Note. Based on information from Hunt et al., 2009.

included an angiogram and endocardial biopsy on day 2 of her stay. The angiogram showed clear arteries with no need for intervention.

Pathophysiology

The etiology of anthracycline-induced cardiotoxicity is not well understood. Myocardial changes following anthracycline treatment include myocardial cell loss by necrosis or apoptosis, myofibrillar loss, distention of the sarcoplasmic reticulum, and mitochondrial swelling (Hershman & Shao, 2009). The leading mechanistic hypothesis for doxorubicin-induced cardiotoxicity is that doxorubicin differentially increases reactive oxygen species (ROS) within cardiac myocyte mitochondria as compared to other tissue (Hershman & Shao, 2009). Anthracyclines can induce the generation of oxygen-derived free radicals through two main pathways: a nonenzymatic pathway that uses iron and an enzymatic mechanism using the mitochondrial respiratory chain. Free radicals are highly toxic and can cause direct damage to proteins, lipids, and DNA. Myocytes are terminally differentiated and cannot sufficiently replace cells damaged during treatment. Administering doxorubicin in humans results in an elevation of tissue ROS and products of lipid peroxidation as well as a decrease in plasma and tissue antioxidant levels. The level of doxorubicin-induced oxidative stress may be 10 times greater in the heart than in the liver, kidney, and spleen (Hershman & Shao, 2009).

Heart Failure Treatment

When hospitalized, J.G. was started on an evidence-based heart failure drug protocol of an angiotensin-converting enzyme (ACE)-inhibitor, a beta blocker,

diuretics, and a lifestyle protocol of a heart-healthy diet with a daily 2,000 mg sodium restriction and a 1,500 ml fluid restriction. During her hospitalization, J.G. lost 17 pounds (7.7 kg). She was discharged on day 4 with instructions to see the cardiology nurse practitioner in clinic in 10 days and to continue her medications at home. The plan was to increase the ACE-inhibitor and beta blocker to the target doses within the next two to three months (see Table 1). Results of the endocardial biopsy were available about three weeks after J.G.'s hospitalization. The pathology report showed evidence of mild to moderate anthracycline toxicity, but no other contributory results.

Patients with heart failure should be encouraged to discontinue cigarette smoking and alcohol use and maintain an optimal blood pressure and weight while eating a heart-healthy (low sodium, low fat) diet. Patients with New York Heart Association (NYHA) func-

tional class I–III heart failure (see Table 2) should be encouraged to participate in regular physical activities such as walking. A treadmill stress test should be completed before beginning an exercise program. Formal cardiac rehabilitation should be considered for patients who are dyspneic at rest (Viale & Yamamoto, 2008).

Case Resolution

Three months after the initial diagnosis of acute heart failure syndrome, J.G. is dealing with CHF that will necessitate ongoing lifestyle changes. She monitors her weight, blood pressure, and pulse daily, keeping a log for her clinic visits. In total, she has lost about 40 pounds since her hospital admission. She continues with her medications and is at the target dose of the beta blocker. The ACE-inhibitor still is being titrated. She is losing weight gradually and is increasing her activity as tolerated. A repeat echocardiogram after two months of drug therapy showed an increase in her LVEF to 20%. A repeat BNP level at the same time was 849 pg/ml, a decrease of about 50% from baseline. BNP levels decrease in most patients who are receiving effective therapy for heart failure (Hunt et al., 2009). J.G.'s NYHA functional classification is III. She returned to work and is hopeful that diligent monitoring of her cardiac function will allow her to complete the school year in good health and eventually improve her NYHA functional classification to II. If her progress is compromised, an

Table 2. New York Heart Association Functional Classification

Classification	Severity	Patient Symptoms
I	Mild	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
II	Mild	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
III	Moderate	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Severe	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Note. Based on information from Criteria Committee of the New York Heart Association, 1994; Hunt et al., 2009.

Clinical Highlights: Heart Failure in a Breast Cancer Survivor

Definition of Heart Failure

Heart failure is defined as inadequate contractile force of the left ventricle to eject the required amount of blood for perfusion. An absolute decrease in left ventricular ejection fraction (LVEF) greater than 10% from baseline is associated with a LVEF decline below the institutional lower limit of normal, generally accepted to be 50%. Anthracycline-induced cardiotoxicity may include cardiomyopathy (enlargement of the cardiac muscle) (Hunt et al., 2009).

Pathophysiology

The etiology of anthracycline-induced cardiotoxicity is not well understood. The leading hypothesis for doxorubicin-induced cardiotoxicity is that doxorubicin differentially increases reactive oxygen species (ROS) within cardiac myocyte mitochondria, as compared to other tissue. Anthracyclines can induce the generation of oxygen-derived free radicals through two main pathways: a nonenzymatic pathway that uses iron and an enzymatic mechanism using the mitochondrial respiratory chain. Free radicals are highly toxic and can cause direct damage to proteins, lipids, and DNA. Myocytes are terminally differentiated and cannot sufficiently replace cells damaged during treatment. Administering doxorubicin in humans results in an elevation of tissue ROS and products of lipid peroxidation and a decrease in plasma and tissue antioxidant levels. The level of doxorubicin-induced oxidative stress is as much as 10 times greater in the heart than in the liver, kidney, and spleen (Hershman & Shao, 2009).

Risk Factors

General risk factors for congestive heart failure (CHF) include being older than age 50, hypertension, and a history of coronary artery disease, cardiac dysrhythmias, diabetes, sleep apnea, and obesity. Lifestyle risk factors include excessive alcohol consumption, smoking, and long-term use of anabolic steroids (Hunt et al., 2009). Specific risk factors for anthracycline-induced cardiotoxicity include exposure to an-

thracycline chemotherapy. The length of time since exposure does not affect risk; cardiotoxicity has been known to occur as many as 20 years after exposure (Hershman & Shao, 2009).

Prevention

A cumulative lifetime maximum dose of doxorubicin of 450 mg/m² is recommended to prevent cardiotoxicity; however, doses greater than 300 mg/m² can potentiate cardiotoxicity, particularly in the presence of other cardiac risk factors (Hershman & Shao, 2009). Although adjuvant therapy for breast cancer rarely exceeds the recommended maximum cumulative dose, monitoring the cumulative dose for each patient is essential. Even with doxorubicin doses less than the recognized maximum, cardiotoxicity may still occur.

Incidence

Heart failure is a major and growing public health issue in the United States. About five million patients have heart failure, and more than 550,000 patients are diagnosed with heart failure for the first time each year (American Heart Association, 2011). The exact number of breast cancer survivors who develop CHF is unknown, primarily because the condition may be diagnosed many years after treatment when breast cancer survivors are older and CHF may be attributed to other causes. Reported incidence ranges from 0.45% (Russell et al., 2010) to 4% (Nadeem et al., 2011).

Differential Diagnoses

CHF is diagnosed based on presenting symptoms. Patients with a history of breast cancer who have developed symptoms of CHF also should be evaluated for disease recurrence, primary lung cancer, viral infection, chronic obstructive pulmonary disease, and liver disease.

Diagnostic Evaluation

Measurement of LVEF with multigated acquisition (MUGA) scan or echocardiography assesses cardiac function and can be used for surveillance or diagnostic workup (Hersh-

man & Shao, 2009; Hunt et al., 2009). Symptomatic patients should have a complete blood count, chemistry panel, B-type natriuretic peptide, chest x-ray, and electrocardiogram pending further evaluation by a cardiologist (Hunt et al., 2009).

Implications for Practice

Oncology nurses must be familiar with cancer therapies associated with cardiotoxicity, which, in the treatment of breast cancer, include anthracyclines, trastuzumab, and lapatinib. Prior to initiation of potentially cardiotoxic chemotherapy, patients should be assessed for underlying risk factors for cardiotoxicity and review of symptoms, as well as undergo baseline testing by echocardiogram or MUGA scan. Any abnormal findings or lifestyle risk should be stringently addressed. Patients with a borderline LVEF should be evaluated by a cardiologist and considered for heart failure drug therapy prior to starting chemotherapy.

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implanted pacemaker-defibrillator or implanted left ventricular assistive device may be considered. In patients with refractory and progressive heart failure, a heart transplantation might be required (Hunt et al., 2009).

Implications for Nursing Practice

Oncology nurses must be familiar with cancer therapies associated with cardiotoxicity, which, in the treatment of breast cancer, include anthracyclines, trastuzumab, and lapatinib. Prior to initiation of potentially cardiotoxic chemotherapy, patients should be assessed for underlying risk factors for cardiotoxicity and review of symptoms, as well as undergo baseline LVEF testing by echocardiogram or MUGA scan (Moore, 2009). Any abnormal findings or lifestyle risk should be stringently addressed. Patients with a borderline LVEF should be evaluated by a cardiologist and considered for heart failure drug therapy, including ACE-inhibitors and beta blockers, prior to starting chemotherapy.

Breast cancer survivors who have been exposed to cardiotoxic agents should be regularly assessed for symptoms of heart failure. Unfortunately, many survivors and oncology nurses view patient symptoms through the lens of cancer, assuming that symptoms

such as dyspnea, fatigue, and cough are indicative of disease recurrence. Adopting a more holistic view of the care of survivors might allow oncology nurses to evaluate the full spectrum of differential diagnoses rather than assuming the symptoms are cancer related. Educating survivors about which symptoms to report sooner rather than later can help improve patient outcomes by discovering the underlying cause and initiating supportive treatment or referrals to specialists in a timely manner.

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