Prechemotherapy Cardiac Assessment

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The topic for this article arose from a question submitted by Doris Cowell, RN, BSN, OCN®, from the University Medical Center of Southern Nevada in Las Vegas, asking about a nurse's liability if the physician does not want to have a standard prechemotherapy test completed (e.g., multigated radionuclide acquisition [MUGA]) for doxorubicin in a patient diagnosed with early-stage breast cancer. This column will discuss clinical and legal issues related to pretreatment cardiac assessment.

Case Study

M.G. was a 39-year-old woman diagnosed with stage I, 1.5 cm, grade 3, hormone receptor-positive, HER2-negative invasive ductal carcinoma in the upper inner quadrant of her left breast. She underwent a lumpectomy and sentinel node biopsy that confirmed no spread to the lymph nodes. M.G. consulted a medical oncologist who recommended systemic chemotherapy consisting of four cycles of doxorubicin and cyclophosphamide (AC) followed by radiation therapy and hormonal therapy. M.G. was in excellent health, took no prescription medications, and had no personal or family history of heart disease. She was physically active and worked out daily. Her blood pressure was normal at 110/62 during her examination. A note in M.G.'s medical record stated that, "Patient is in excellent health without history or signs of cardiac dysfunction. Okay to give AC without MUGA." The nurse clinician in the ambulatory infusion center noted the physician's comment and was concerned about not having pretreatment MUGA results before M.G.'s chemotherapy.

Definition of Cardiac Failure

Cardiac failure is defined as inadequate contractile force of the left ventricle to eject the required amount of blood for perfusion (Hunt et al., 2005), and an absolute decrease in left ventricular ejection fraction (LVEF) greater than 10% from baseline and is associated with a decline below the institutional lower limit of normal, generally accepted to be 50% (Rosenthal & Braunwald, 2001). Anthracycline-induced cardiotoxicity (AIC) may include cardiomyopathy (enlargement of the cardiac muscle).

Risk Factors

The most obvious risk factor for AIC is exposure to anthracycline chemotherapeutic agents. M.G. had a left-sided breast cancer, raising the question about increased risk if radiation therapy involves the left mediastinum region. Giordano et al. (2005) examined cancer registry datasets (N = 27,283) to evaluate the risk of cardiac-related mortality in patients with breast cancer following adjuvant radiation therapy, specifically evaluating differences in mortality for left- versus right-sided radiation therapy. For women diagnosed from 1973–1979, a statistically significant difference exists in 15-year cardiac-related mortality between patients with left-sided (13.1%) and those with right-sided (10.2%) breast cancer. No difference was found for women diagnosed from 1980–1984 (9.4% versus 8.7%, respectively) or from 1985–1989 (5.8% versus 5.2%, respectively). The investigators concluded that risk of cardiac-related mortality associated with left-sided radiation therapy has decreased substantially over time (Giordano et al.). Additional risk factors are found in Figure 1.

Pathophysiology

Injury to the myocardium can be caused by a number of chemotherapy and biologic agents. For the purposes of this article, the focus is on AIC (see Table 1). Anthracycline antitumor antibiotics include doxorubicin, epirubicin, daunorubicin, and idarubicin. Cardiac muscle is composed of cells called myocytes that contain myofibrils (cells that cause the cardiac muscle to contract). The mechanism for AIC remains poorly understood but is thought to be caused by free radical-induced oxidative stress and elevated levels of intracellular calcium (Safra, 2007; Shan, Lincoff, & Young, 1996).

Incidence

The incidence of AIC is about 3% in patients receiving a lifetime cumulative dose of 400 mg/m^2 of doxorubicin, rising to 7% at 550 mg/m^2, and 18% at 700 mg/m^2 (Youssef & Links, 2005). When combined with taxanes, the incidence of AIC is reported to be 11% (Gianni, Salvatorelli, & Minotti, 2007). Taxanes were not found to increase AIC in a European Cooperative Trial in operable breast cancer study when lower cumulative doses of doxorubicin (240 mg/m^2) were given (Gianni et al., 2005).

Prechemotherapy Cardiac Evaluation

MUGA or echocardiography assess systolic cardiac function through measurement of LVEF and are the most common methods of monitoring cardiac function during cancer treatment. However,

- Cumulative dose more than 450 mg/m^2
- Concurrent administration of paclitaxel or docetaxel
- Concurrent administration of trastuzumab
- Administration schedule (shorter infusion equals higher risk of toxicity)
- Radiation therapy to mediastinum
- Preexisting cardiac disease including poorly controlled hypertension
- Increased age
- Smoking

Figure 1. Risk Factors for Anthracycline-Associated Cardiotoxicity in Early Breast Cancer Treatment

Note. Based on information from Gianni et al., 2007; Giordano et al., 2005; Kaszyk, 1986; Loerzel & Dow, 2003; Von Hoff et al., 1979.

Table 1. Classification of Anthracycline-Induced Cardiotoxicity

Type	Time of Onset	Clinical Presentation
Early onset (type I)	During or immediately after anthracycline exposure	Stable, asymptomatic changes in left ventricular ejection fraction Electrocardiogram changes Dose related
Late onset (type II)	One year or more following completion of anthracycline therapy	Progressive left ventricular dysfunction More common than early onset May be chronic, nonreversible

Note. Based on information from Ganz et al., 2008; Gianni et al., 2007.

LVEF can underestimate actual cardiac damage because the compensatory reserve of the myocardium enables adequate LVEF output even in the presence of dysfunctional myocytes (Altena, Perik, van Veldhuisen, de Vries, & Gietema, 2009). MUGA is highly reproducible and able to detect a decline in LVEF in patients treated with anthracyclines, but cumulative radiation exposure may limit the applicability of MUGA for frequent monitoring. Echocardiography is used regularly to monitor LVEF but is considered more prone to operator-dependent variability (Hershman & Shao, 2009). Doxorubicin prescribing information states that prechemotherapy assessment of LVEF should be performed, but does not stratify assessment recommendations based on patient age. In addition, the prescribing information does not specify how often LVEF assessments after chemotherapy should be done (Pfizer, Inc., 2006) (see Figure 2).

As with many clinical conundrums, opposing views on prechemotherapy cardiac assessment have been published. Sabel et al. (2001) reported a retrospective chart review of 296 patients, of which 59 of 95 (62%) patients receiving doxorubicin-based regimens and 3 of 39 (7%) receiving nondoxorubicin regimens had pretreatment MUGA scans. LVEF was normal in 58 patients and low-normal in 4 patients. No cardiac complications occurred in the 59 women who received doxorubicin-based therapy. The authors suggested that routine use of MUGA prior to doxorubicin for adjuvant breast cancer therapy may not be necessary and the recommendations for pretreatment MUGA assessment should be reconsidered.

Mitani, Jain, Joska, Burtness, and Zaret (2003) performed a retrospective analysis of 265 patients ($\bar{X}$ age = 53, range = 39–67, 76% were women) treated with doxorubicin who had serial LVEF assessments during treatment. Changes in LVEF were associated with chronic heart failure up to three years after treatment. Patients were identified as being at-risk (decrease in LVEF of more than 10% to less than 50%) or at low risk of cardiotoxicity. Mitani et al. concluded that 15 cases of chronic heart failure were prevented by stopping cancer treatment when patients met the criteria for being at risk and that monitoring cardiac function to identify those patients who are at risk was effective in preventing progression to chronic heart failure.

Recommendations for Cardiac Assessment

The American Heart Association (AHA) recommended close monitoring of cardiac function during anthracycline treatment but does not specify how often or by which means (Hunt et al., 2005). The National Comprehensive Cancer Network ([NCCN], 2009) guideline for breast cancer does not address pretreatment cardiac assessment or serial monitoring except when the treatment regimen will include trastuzumab. Shelton (2009) has published nursing guidelines endorsed by the Oncology Nursing Society and recommended pretreatment and serial evaluation of LVEF for patients undergoing anthracycline-based chemotherapy. The absence of data on routine monitoring to prevent cardiac disease in asymptomatic adult cancer survivors was emphasized in a recent American Society of Clinical Oncology clinical evidence review (Carver et al., 2007). Published guidelines are not consistent in their recommendations and seem to be based on less than robust evidence. In addition, none of the guidelines define an approach to long-term follow-up of cardiac function in adult cancer survivors, although cardiac morbidity can become apparent up to several years after treatment (Altena et al., 2009).

Implications for Nursing Practice and Nurse Liability

Nursing is a knowledge-based profession. The body of knowledge includes nursing science; the biomedical, physical, economic, behavioral, and social sciences; and ethics. A nurse's ability to be a critical thinker and use this knowledge in the delivery of nursing care is essential to the protection of the health and safety of patients (American Nurses Association, 2005). Failure to order pretreatment evaluation of LVEF is a deviation from the standard of care, which is defined as the community standard, and what reasonable healthcare providers would do in the same or similar circumstance. One might argue that the physician's order releases the nurse from liability because he or she is following doctor's orders. Nurses are independently licensed and accountable for their actions and the nurse could be held accountable for knowingly deviating from the standard of care and not following the drug manufacturer's recommendations (Schulmeister, 2009). Documentation in

- The risk of serious cardiac impairment may be decreased through regular monitoring of left ventricular ejection fraction (LVEF) during the course of treatment with prompt discontinuation of doxorubicin at the first sign of impaired function.
- The preferred method for assessment of cardiac function is evaluation of LVEF measured by multigated radionuclide angiography (MUGA) or echocardiography (ECHO). An electrocardiogram also may be done.
- A baseline cardiac evaluation with a MUGA scan or an ECHO is recommended, particularly in patients with risk factors for increased cardiac toxicity.
- Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses.
- The technique used for assessment should be consistent through follow up.
- For inpatients with cardiac risk factors, particularly prior anthracycline use, monitoring of cardiac function must be particularly strict, and the risk-benefit of continuing treatment with doxorubicin in patients with impaired cardiac function must be carefully evaluated.

Figure 2. Doxorubicin Prescribing Information Regarding Pretreatment Assessment

Note. Based on information from Pfizer, Inc., 2006.

the medical record serves to meet legal and professional standards and is valuable in demonstrating that the oncology nurse has applied nursing knowledge, skills, and judgment according to professional standards (Teytelman, 2002). The documentation does not protect the nurse but, rather, serves as evidence that the nurse was not passive in the situation.

When the standard of care appears to be in jeopardy, open communication between the nurse and physician is crucial. The dialogue may be opened by asking, "I'd like to learn more about why you don't want to have a MUGA done" to determine the reason the physician does not want the procedure performed (Schulmeister, 2009). Nurses have a duty to advocate for the patient through the organizational hierarchy when the nurse believes the physician is unresponsive to concerns about the patient's condition or is making inappropriate patient care decisions (Hall & Hall, 2001).

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Clinical Highlights: Prechemotherapy Cardiac Assessment

Definition

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Pathophysiology

Anthracycline antitumor antibiotics, which include doxorubicin, epirubicin, daunorubicin, and idarubicin, can cause AIC. The cardiac muscle is composed of cells called myocytes that contain myofibrils (cells that cause the cardiac muscle to contract). The mechanism for AIC remains poorly understood but is thought to be caused by free radical-induced oxidative stress and elevated levels of intracellular calcium (Safra, 2007; Shan, Lincoff, & Young, 1996). AIC can be classified as early-onset (type I), occurring during or within 12 months of anthracycline exposure, or late-onset (type II), which occurs a year or more following anthracycline therapy. Late onset is more common (Ganz et al., 2008; Gianni, Salvatorelli, & Minotti, 2007).

Incidence

The incidence of AIC is about 3% in patients receiving a lifetime cumulative dose of 400 mg/m^2 of doxorubicin, rising to 7% at 550 mg/m^2, and 18% at 700 mg/m^2 (Youssef & Links, 2005). When combined with taxanes, the incidence of AIC is reported to be 11% (Gianni et al., 2007).

Diagnostic Evaluation

Measurement of LVEF with multigated acquisition (MUGA) scan or echocardiography assesses systolic cardiac function and is the most common method of monitoring cardiac function during cancer treatment. LVEF can underestimate actual cardiac damage because of the compensatory reserve of the myocardium that enables adequate LVEF output even in the presence of dysfunctional myocytes (Altena, Perik, van Veldhuisen, de Vries, & Gietema, 2009). MUGA is highly reproducible and able to detect a decline in LVEF in patients treated with anthracycline, but cumulative radiation exposure may limit the applicability of this technique for frequent monitoring. Echocardiography is used regularly to monitor LVEF and is more widely available than MUGA but is considered more prone to operator-dependent variability (Hershman & Shao, 2009).

Nursing Implications

Nursing is a knowledge-based profession using a body of knowledge that includes nursing science; the biomedical, physical, economic, behavioral, and social sciences; and ethics. A nurse's ability to be a critical thinker and use this knowledge in the delivery of nursing care is essential to the protection of the health and safety of patients (American Nurses Association, 2005). Failure to order pretreatment evaluation of LVEF is a deviation from the standard of care, which is defined as the community standard, and what reasonable healthcare providers would do in the same or similar circumstance. Nurses are independently licensed and accountable for their actions regardless of physician's orders. When the standard of care appears to be in jeopardy, open communication between the nurse and physician is crucial. Nurses have a duty to advocate for the patient through the organizational hierarchy when the nurse believes the physician is unresponsive to concerns about the patient's condition or is making inappropriate patient care decisions (Hall & Hall, 2001).

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