Utility of Prechemotherapy Evaluation of Left Ventricular Function for Patients With Lymphoma

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Abstract

We reviewed the records of patients with lymphoma to determine whether a prechemotherapy evaluation of left ventricular function led to a change in patient management. We determined that testing rarely alters the choice of chemotherapy and that testing is a poor predictor of subsequent cardiac damage. Guidelines that recommend a cardiac evaluation for all patients with lymphoma who receive anthracyclines should be reexamined.

Background: Published guidelines recommend baseline cardiac function testing before initiating anthracycline-based chemotherapy. These recommendations are based largely on consensus, and there is little information regarding how often testing leads to alterations in therapy or whether testing is able to predict subsequent cardiac toxicity. **Patients and Methods:** We performed a retrospective analysis of patients with Hodgkin lymphoma and non-Hodgkin lymphoma to determine whether there was a prechemotherapy evaluation of left ventricular function and whether findings from the evaluation led to alterations in therapy. Records also were reviewed to evaluate subsequent test results of cardiac function. **Results:** We identified 309 patients with lymphoma between 2004 and 2012 with a planned anthracycline- or anthracenedione-based regimen. Of this total, 232 patients (75%) had a pretreatment cardiac evaluation. There were 201 patients (87%) in this group with no history of cardiac disease. Although 22 of these patients (11%) had abnormal echocardiograms, none had a change in therapy and no subsequent cases of cardiomyopathy were identified. Five of the remaining 179 patients with a normal cardiac evaluation developed a cardiomyopathy. Thirty-one patients had a history of cardiac disease, and only 4 patients had a change in therapy. There were 77 patients (25%) who did not have a prechemotherapy cardiac evaluation. No subsequent cases of cardiomyopathy were identified in this group. **Conclusions:** Pretreatment evaluation rarely leads to a change in management and is not helpful in predicting subsequent cardiomyopathy. Guidelines that recommend evaluation of left ventricular function in all patients before anthracycline-based chemotherapy should be reexamined.

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Introduction

Doxorubicin-based chemotherapy is widely used in a variety of regimens for Hodgkin lymphoma and non-Hodgkin lymphoma. Unfortunately, administration of this agent is associated with cardiotoxicity. Acute toxicity occurs during or immediately after infusion and usually consists of supraventricular or ventricular arrhythmias, heart block, pericarditis, or myocarditis. Chronic or late toxicity is characterized by a cardiomyopathy leading to subclinical or overt left ventricular dysfunction and congestive heart failure that may be seen within a year or several years after finishing chemotherapy.

A variety of mechanisms may be responsible for the development of anthracycline-induced cardiotoxicity.[1-3] The most frequently proposed mechanism is thought to be related to the formation of reactive oxygen species generated by the interaction of doxorubicin with iron. This results in subsequent damage to myocytes, causing myofibrillar loss, cytoplasmic vacuolization, and apoptosis.

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A number of risk factors have been associated with the development of anthracycline-induced cardiomyopathy, including age, coronary artery disease, valvular heart disease, hypertension, combination treatment with other chemotherapy agents, and the use of radiation therapy. There is also evidence that single nucleotide polymorphisms may alter susceptibility to cardiomyopathy from these agents.[4] However, the most important risk factor for toxicity is the cumulative dose of anthracycline.[5,6]

Because of the risk of cardiotoxicity, the package insert for doxorubicin recommends that treatment should be preceded by a careful baseline assessment of cardiac function as measured by left ventricular ejection fraction.[7] Current National Comprehensive Cancer Network (NCCN) guidelines state that it is essential for patients with diffuse large B-cell lymphoma, mantle cell lymphoma, lymphoblastic lymphoma, Burkitt lymphoma, and chronic lymphocytic leukemia/small lymphocytic lymphoma to have a multiple gated acquisition (MUGA) scan or echocardiogram to evaluate left ventricular function if therapy with an anthracycline- or anthracenedione-containing regimen is indicated.[8] The NCCN has identical recommendations for patients with Hodgkin lymphoma who receive anthracycline-containing chemotherapy regimens.[9] In addition to the NCCN, the European Society for Medical Oncology guidelines for management of diffuse large B-cell lymphoma state that left ventricular ejection fraction should be assessed before treatment.[10] Hodgkin lymphoma guidelines from the European Society for Medical Oncology also state that cardiac function tests are mandatory before treatment.[11] In addition, baseline evaluation of left ventricle function by echocardiography for patients receiving cardiotoxic chemotherapy was given a class I recommendation in updated guidelines from the American College of Cardiology and American Heart Association.[12] Guidelines that also include the American Society for Nuclear Cardiology state that ejection fraction should be measured in all patients before receiving doxorubicin.[13] Finally, recommendations from the cardiology committee of the Children's Cancer Study Group state that all patients expected to receive doxorubicin or daunorubicin should have baseline cardiac evaluation with electrocardiography, echocardiography, and, when available, radionuclide angiocardiography.[14]

The recommendations to evaluate left ventricular function before initiating therapy with anthracyclines are based primarily on consensus. Echocardiography and radionuclide angiography are insensitive measures of cardiac damage, and a decline in left ventricular ejection fraction may not occur until long after the completion of chemotherapy. There is limited literature about the ability of a single baseline test of left ventricle function to estimate the probability of developing anthracycline-related cardiotoxcity.[15] In addition, there is little information on whether routine testing of left ventricular function before initiating chemotherapy influences the outcome of patients with lymphoma. Because of this, we performed a retrospective analysis in an attempt to determine the value of measuring left ventricular function before initiating anthracycline-based therapy for lymphoma.

Patients and Methods

A list of patients with Hodgkin lymphoma or non-Hodgkin lymphoma treated with anthracycline- or anthracenedione-based chemotherapy at the University of Nebraska Medical Center between August 2004 and May 2012 was obtained from the Nebraska Lymphoma Study Group database.

Baseline characteristics were collected, including age, histology, gender, and history of cardiac diagnosis. Prior cardiac diagnoses consisted of a history of atrial fibrillation/flutter, supraventricular tachycardia, heart block requiring pacemaker implantation, coronary artery disease, valvular disease, pulmonary hypertension, or cardiomyopathy.

Charts were reviewed to determine whether there was a prechemotherapy evaluation of left ventricular function and the method of evaluation (echocardiogram, MUGA, or magnetic resonance imaging [MRI]). In addition, records of post-treatment evaluation of cardiac function were evaluated for any change in cardiac function. Inpatient and outpatient records were reviewed to determine whether the findings from the cardiac evaluation influenced the selection of the initial chemotherapy regimen.

A left ventricular ejection fraction less than 50% was considered abnormal. Echocardiogram findings of moderate to severe valvular disease, diastolic dysfunction (grade 1-3), and moderate or severe pulmonary hypertension (moderate = pulmonary artery systolic pressure 45-60 mm Hg, severe = pulmonary artery systolic pressure $>$ 60 mm Hg) also were collected.

Characteristics of patients were summarized using descriptive statistics. Comparisons of patient characteristics were analyzed using the Wilcoxon test or chi-square test for continuous or categoric variables, respectively.

Results

We identified 309 patients with lymphoma who started chemotherapy with an anthracycline- or anthracenedione-based regimen during the study period. Of these, 232 (75%) had an evaluation of left ventricular function performed before therapy. The majority of patients in this group (94%) were evaluated with echocardiograms, whereas the remaining 13 patients (6%) were evaluated with MUGA scans (n = 9) or MRI (n = 4). The characteristics of the patients who had a baseline prechemotherapy evaluation of left ventricular function and those who were not evaluated are shown in Table 1. Patients who received a pretreatment cardiac evaluation were more likely to be older (median age, 56 vs. 42 years; $P < .001$). Patients who had pretreatment cardiac evaluations also were more likely to have a history of cardiac disease (14% vs. 4%, $P = .01$). Otherwise, the groups were similar with respect to patient-, disease-, and treatment-related characteristics.

The outcomes of patients are shown in Figure 1. Among the 232 patients who had pretreatment evaluation of left ventricular function, 201 (87%) had no history of cardiac disease. No patients evaluated with MUGA scans or MRI had left ventricular function abnormalities. Twenty-two patients (9%) had prechemotherapy echocardiograms that demonstrated 1 or more of the following abnormalities: moderate-severe valvular disease (n = 4), diastolic dysfunction (n = 14), moderate-severe pulmonary hypertension (n = 3), patent foramen ovale (n = 1), or left ventricular ejection fraction $<$ 50% (n = 1). However, none of these findings led to a change in the choice of chemotherapy regimen or a change in dose for these patients. Thirty-one (13%) of the patients with a prechemotherapy evaluation had a history of cardiac disease, as described earlier. Only 4 of these patients had an alteration of