Trastuzumab-Induced Cardiomyopathy: Incidence and Associated Risk Factors in an Inner-City Population

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ABSTRACT

Background: Although it is known that trastuzumab causes cardiotoxicity, its extent and reversibility are still in question. Earlier studies have not evaluated consecutive patients with reproducible nuclear ventriculography.

Objective: We sought to evaluate the baseline characteristics which predispose patients to increased risk of trastuzumab cardiotoxicity and to determine the natural history of the cardiotoxicity.

Methods and Results: Left ventricular ejection fraction (LVEF) was measured in 76 women aged 36−73 years who had been treated with trastuzumab at the University of Maryland Greenebaum Cancer Center. LVEF was determined at baseline and then 3, 6, 9, and 12 months after treatment initiation. Cardiotoxicity was defined as ≥16% decrease in LVEF or ≥10% decrease in LVEF to <50%. There were no differences in comorbidities, earlier treatment, or demographics between patients with and without trastuzumab-induced cardiomyopathy except that African Americans were more likely to develop decreased LVEF ($P < .05$). Twenty-one patients (28%) met criteria for cardiotoxicity. Four of those patients were continued on trastuzumab and 17 patients had therapy withheld at some point. Only 1 patient developed symptomatic heart failure requiring inpatient hospitalization. LVEF improved in most patients regardless of whether or not trastuzumab was continued.

Conclusions: Decreased LVEF while undergoing trastuzumab therapy occurs frequently and is usually reversible. African Americans had a higher risk of developing decreased LVEF. These findings raise clinically important questions as to whether it is necessary to discontinue trastuzumab for asymptomatic decrease in LVEF and whether African Americans are more predisposed to a decrease in LVEF while receiving trastuzumab. Further studies carefully assessing LVEF should address these hypotheses. (*J Cardiac Fail 2014;20:555−559*)

Key Words: Trastuzumab, heart failure, congestive, cardiomyopathy.

The use of trastuzumab is one of the most significant advances in the treatment of human epidermal growth factor receptor 2 (HER2)−positive breast cancer, improving overall patient survival and quality of life.[1,2] Although it is known that trastuzumab causes cardiotoxicity, the extent and reversibility of the cardiotoxicity is still in question. Some studies have shown that the trastuzumab-induced cardiotoxicity is reversible, with most patients recovering cardiac function anywhere from 1 to 6 months after discontinuation of treatment.[3,4] Conversely, other studies have shown that a significant proportion of patients have a sustained decrease in left ventricular ejection fraction (LVEF) for anywhere from 6 months to several years after cessation of treatment.[5,6]

The definition and evaluation of cardiotoxicity used even in recent studies have been variable. Some studies have used qualitative methods of defining cardiotoxicity based on clinical signs and symptoms of congestive heart failure (CHF) with the use of the New York Heart Association (NYHA) stratification, whereas others have assessed LVEF with the use of >1 modality in the same study. LVEF evaluation by transthoracic echocardiography (TTE) is subject to reader variability, inaccuracy, and imaging quality, because it requires visualization of endocardial borders, and either estimation of LVEF or calculations of left ventricular end diastolic and systolic volumes based

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on geometric assumptions.[7,8] Conversely, nuclear imaging with radionucleotide ventriculography reports a more precise and reproducible LVEF.[7,8] Earlier studies have not evaluated LVEF in unselected patients undergoing trastuzumab treatment solely with the use of radionucleotide ventriculography.

The focus of our study was to (1) evaluate the baseline characteristics that may predispose patients to increased risk of trastuzumab cardiotoxicity and (2) determine the natural history of trastuzumab cardiotoxicity and the effect of both continuation and cessation of therapy.

Methods

A retrospective review was performed of stage I−IV breast cancer patients who had been treated with trastuzumab at the University of Maryland Greenebaum Cancer Center from January 2000 to June 2011. To evaluate for potential cardiotoxicity associated with trastuzumab therapy, LVEF had been routinely measured with radionucleotide ventriculography with the use of standard technology. For each patient, except where noted, a baseline LVEF was established before initiation of trastuzumab therapy and then was routinely measured at 3, 6, 9, and 12 months (±6 weeks) after initiation of trastuzumab therapy. This protocol was approved by the University of Maryland Institutional Review Board.

Key inclusion criteria included patients who were HER2 positive and receiving trastuzumab, which was given at an 8 mg/kg loading dose followed by 6 mg/kg every 3 weeks for 16−17 doses or at a 4 mg/kg loading dose followed by 2 mg/kg weekly for 52 doses, according to provider preference. Patients with stage 4 (metastatic) breast cancer were routinely treated with trastuzumab as maintenance therapy, whereas other systemic therapies may have been changed as the disease progressed. As more data emerged about the 8 mg/kg loading regimen, more providers switched to that regimen; it was shown to be more convenient for patients and just as effective. Data were collected on patient baseline characteristics, including demographics, tumor features, earlier chemotherapy and radiation exposure, and preexisting cardiac and comorbid conditions.

Our definition of cardiotoxicity was a ≥16% absolute decrease in LVEF from baseline or a ≥10% absolute decrease in LVEF from baseline with LVEF below institutional limits of normal (50%). This definition is consistent with the criteria for discontinuation of trastuzumab from the prescriber manual.[9]

The data were analyzed with the use of SPSS software version 19. For the purpose of analysis the patient population was divided into 2 groups: those patients who did and those who did not meet the criteria for cardiotoxicity. Baseline characteristics were compared between the 2 groups with the use of the Fisher exact test. Analysis of variance (ANOVA) was used to look at the effect of time in all of the patients and each group. The 2 groups were compared with the use of 2-way ANOVA. Statistical significance was assumed with $P < .05$. Continuous variables are reported as mean ± SD.

There were 20 patients with radionucleotide ventriculograms at all 5 time points. Data were available for 60 patients at 3 months, 55 patients at 6 months, 47 patients at 9 months, and 36 patients at 12 months. Mean data for all time points reflect only patients with data at that time point. For the statistical ANOVA comparing time points, to include all patients, if a ventriculogram was missing for an individual time point, the last LVEF was carried forward.

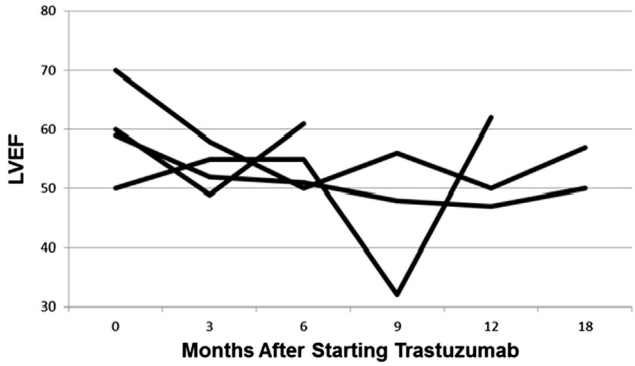

Fig. 1. Ejection fraction in decreased left ventricular ejection fraction (LVEF) group in whom trastuzumab was continued. LVEF frequently recovered despite continuation of therapy.

Data were unavailable for tumor type and estrogen receptor/progesterone receptor-positive status in 1 patient, earlier radiation exposure in 2 patients, and current or active smoking status in 3 patients. In 3 patients, the 1st radionucleotide ventriculogram was not obtained before initiation of therapy, and those data were excluded from statistical calculations. For 12 patients, LVEF data were available at 18 months; those data were only used to graph the natural history of LVEF during trastuzumab therapy (Figs. 1 and 2).

Results

There were 76 women aged 36−73 years with stage I−IV breast cancer (Table 1). Sixty-three percent of patients were African American, 33% were white, and 3% were of Hispanic or Asian origin. Overall, 44 patients (58%) had previously received anthracycline-based chemotherapy, 29 patients (38%) had received or were concurrently receiving nonanthracycline−based chemotherapy (taxotere and cyclophosphamide were concurrent), and 3

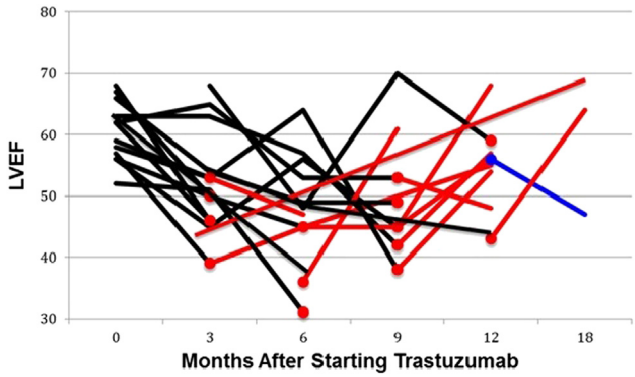

Fig. 2. Ejection fraction in decreased left ventricular ejection fraction (LVEF) group in whom trastuzumab was discontinued. Red lines indicate when not receiving trastuzumab, and blue line indicates reinitiation of trastuzumab.