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Early Increases in Multiple Biomarkers Predict Subsequent Cardiotoxicity in Patients With Breast Cancer Treated With Doxorubicin, Taxanes, and Trastuzumab

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Objectives The aim of this study was to determine if individual or multiple biomarkers are associated with cardiotoxicity in patients with breast cancer undergoing cancer therapy.

Background Current methods to identify patients at risk for cardiotoxicity from cancer therapy are inadequate.

Methods We measured 8 biomarkers in a multicenter cohort of 78 patients with breast cancer undergoing doxorubicin and trastuzumab therapy: ultrasensitive troponin I (TnI), high-sensitivity C-reactive protein (CRP), N-terminal pro–B-type natriuretic peptide (NT-proBNP), growth differentiation factor (GDF)-15, myeloperoxidase (MPO), placental growth factor (PlGF), soluble fms-like tyrosine kinase receptor (sFlt)-1, and galectin (gal)-3. Cardiotoxicity, defined by the Cardiac Review and Evaluation Committee criteria, was assessed every 3 months for up to 15 months. Hazard ratios (HRs) of cardiotoxicity risk were assessed for each biomarker at baseline, at visit 2 (3 months), and as a function of the difference between visit 2 and baseline. Joint models were assessed for the most promising biomarkers.

Results TnI, CRP, GDF-15, MPO, PlGF, and sFlt-1 levels increased from baseline to visit 2 ($p < 0.05$). A greater risk of cardiotoxicity was associated with interval changes in TnI (HR: 1.38 per SD; 95% confidence interval: 1.05 to 1.81; $p = 0.02$) and MPO (HR: 1.34 per SD; 95% confidence interval: 1.00 to 1.80; $p = 0.048$) and in models combining both markers ($p = 0.007$ and $p = 0.03$, respectively). The risk of cardiotoxicity was 46.5% in patients with the largest changes in both markers (ΔTnI >121.8 ng/l; ΔMPO >422.6 pmol/l).

Conclusions Early increases in TnI and MPO levels offer additive information about the risk of cardiotoxicity in patients undergoing doxorubicin and trastuzumab therapy. Independent validation of these findings is necessary before application to clinical practice. (J Am Coll Cardiol 2014;63:809–16) © 2014 by the American College of Cardiology Foundation

Highly-effective cancer drugs such as doxorubicin and trastuzumab (Herceptin Genentech, San Francisco, California) are used widely in the treatment of patients with HER2-positive breast cancer and have led to important gains in survival. However, these agents carry a significant risk of cardiovascular morbidity. Clinical trial data suggest that, when used in combination, treatment with doxorubicin and trastuzumab

See page 817

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Abbreviations and Acronyms

CI = confidence interval
CRP = C-reactive protein
gal = galectin
GDF = growth differentiation factor
HF = heart failure
HR = hazard ratio
LVEF = left ventricular ejection fraction
MPO = myeloperoxidase
NT-proBNP = N-terminal pro–B-type natriuretic peptide
PlGF = placental growth factor
sFlt = soluble fms-like tyrosine kinase receptor
TnI = troponin I

results in an incidence of cardiac dysfunction on the order of 18%, with 2% to 4% developing severe symptomatic heart failure (HF) (1–3). Retrospective analyses suggest a greater risk of dysfunction in the nonclinical trial population. Data from the Cancer Research Network showed that the use of anthracyclines and trastuzumab in combination was associated with a >7-fold increased risk of HF or cardiomyopathy (4).

As such, there remains a fundamental need to identify patients with cancer undergoing treatment with these agents who are at high risk for cardiac complications. Early identification of subclinical cardiac dysfunction could enable the institution of cardioprotective strategies, prevent the interruption or discontinuation of necessary cancer therapy, and reduce early and late cardiovascular and oncological morbidity and mortality.

The methods currently used to identify patients at risk for cardiotoxicity are inadequate. Screening of patients before treatment and monitoring of cardiac function during therapy have relied traditionally on left ventricular ejection fraction (LVEF) (5). However, assessment of LVEF lacks the sensitivity to detect early subclinical changes or predict subsequent declines in function with treatment (6,7). Newer metrics are needed to identify vulnerable patients during the pre-clinical stage of cardiotoxicity; in other cardiovascular diseases, the assessment of multiple biomarkers has been shown to be of incremental utility in identifying patients at increased risk for adverse outcomes (8–10).

The overall objective of this study was to determine the potential utility of biomarkers for the early identification of patients with breast cancer at risk for cardiac dysfunction. We evaluated the associations between 8 biomarkers and the risk of subsequent cardiotoxicity in a multicenter cohort of 78 patients with breast cancer undergoing therapy with doxorubicin and trastuzumab. We hypothesized that the following cardiovascular biomarkers could be mechanistically relevant to cardiotoxicity with cancer therapy: ultrasensitive troponin I (TnI) (cardiomyocyte injury), high-sensitivity C-reactive protein (CRP) (inflammation), N-terminal pro–B-type natriuretic peptide (NT-proBNP) (neurohormonal activation), growth differentiation factor (GDF)-15 (inflammation and oxidative stress), myeloperoxidase (MPO) (oxidative stress), placental growth factor (PlGF) (angiogenesis), soluble fms-like tyrosine kinase receptor (sFlt)-1 (vascular remodeling), and galectin (gal)-3 (fibrosis). Our objectives were to determine whether individual biomarker levels, early changes in biomarker levels, or a combination of biomarkers could predict subsequent cardiotoxicity in patients treated with doxorubicin and trastuzumab.

Methods

Study population. The study population consisted of outpatients with HER2-positive breast cancer recruited across 4 centers as previously reported (11,12). Patients with HER2-positive breast cancer who were scheduled to undergo adjuvant therapy with an anthracycline-containing regimen followed by taxanes and trastuzumab were included. This regimen typically consisted of doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 3 weeks for 4 cycles. At 3 months, paclitaxel (80 mg/m^2) was administered concurrently with trastuzumab every week for 12 weeks; trastuzumab was then continued every 3 weeks to complete 1 year of therapy. Patients with an LVEF <50% before chemotherapy or those who were unwilling or unable to provide informed consent were excluded. This study consisted of participants with biomarker data who completed the protocol.

Participants were studied before chemotherapy and at standardized intervals every 3 months during anthracycline, paclitaxel, and trastuzumab therapy using serial questionnaires and echocardiograms for a total of 6 study visits per participant (Fig. 1). Transthoracic echocardiograms were acquired using Vivid 7 or E9 (GE Healthcare, Milwaukee, Wisconsin) at these time intervals. Blood samples were obtained at baseline, 3 months, and 6 months, processed, and stored at −80°C until the time of assay. The primary endpoint of cardiotoxicity was the Cardiac Review and Evaluation Committee definition of trastuzumab-associated cardiotoxicity, that is, a reduction in LVEF of ≥5% to <55% with symptoms of HF or an asymptomatic reduction of LVEF of ≥10% to <55% (1).

All participants provided written informed consent, and the protocol was approved by the institutional review boards of the participating institutions.

Echocardiography. Digital echocardiograms were analyzed on the EchoPAC workstation (GE Healthcare). Left ventricular end-diastolic and -systolic volumes were obtained using

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