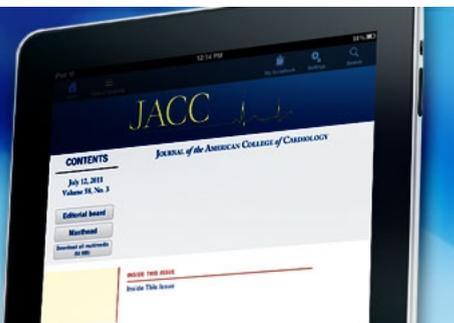


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Early Identification of Left Ventricular Dysfunction Induced by Trastuzumab

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trastuzumab. The authors might consider providing a baseline image before chemotherapy for comparison. The paper describes baseline CMR, including T2-weighted imaging, in the Methods section, but does not report results. Our own experience with CMR imaging after trastuzumab therapy instead points to reversibly impaired LV function without LGE lesions, corresponding to previous findings in echocardiography (5). So far, the authors are the first to report LGE lesions after trastuzumab; therefore, confirmatory studies by other groups are required. CMR might have the potential to visualize tissue changes after chemotherapy independent from changes in LV function and thereby guiding patient management.

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Clinical Risk Stratification of Chemotherapy-Induced Cardiac Dysfunction

I read with great interest the recent publication by Fallah-Rad et al. (1) on chemotherapy-induced cardiac dysfunction. I applaud the authors for this integrated research in cardio-oncology utilizing a multi-imaging modality, including cardiovascular magnetic resonance as I advocated in a previous publication (2).

Despite the valuable insights into early diagnosis of chemotherapy-induced cardiac dysfunction provided by this study, there remain a few unanswered clinical questions. First, among the cohort with trastuzumab-associated cardiac dysfunction, what was the contri-

bution from coronary artery disease (CAD) or ischemic heart disease? CAD has been identified as a risk factor for chemotherapy (3); additionally, antimetabolite chemotherapy agents, such as 5-fluorouracil, may be associated with ischemic heart disease (4). Second, what was the impact of antiplatelet therapy on the results? Aspirin therapy, part of the primary cardiovascular prevention armamentarium, may also be beneficial in cancer patients, including those with thrombocytopenia (5). Third, what was the statin utilization rate among this cohort of cancer patients and its impact on study outcome? In an animal model, statin pretreatment with fluvastatin attenuated doxorubicin-induced cardiotoxicity (6).

This study demonstrates the promise of combined biomarker and multi-imaging tools for early diagnosis of chemotherapy-induced cardiac dysfunction; however, clinical cardiovascular risk stratification of the cancer patients and survivors on chemotherapy remains to be fully elucidated.

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Early Identification of Left Ventricular Dysfunction Induced by Trastuzumab

Cardiac monitoring and managing of patients receiving antineoplastic therapy is an actual issue. We agree with the interesting article by Fallah-Rad et al. (1): new, sensitive indexes of cardiac function are needed to predict cardiac dysfunction before ejection fraction (EF) is compromised. Normal hearts have enormous recruitable contractile capacity, and to show a decrease in EF, the

myocardium must have undergone enough damage to exceed its ability to compensate. The authors conclude that both tissue velocity and strain imaging could detect pre-clinical changes in cardiac function, before EF decreases, in patients receiving adjuvant trastuzumab. Notably, they found no change in plasma biomarkers (troponin T, C-reactive protein, and brain natriuretic peptide); troponin I (TnI) was not evaluated.

Recently, Cardinale et al. (2) identified a subgroup of trastuzumab-treated patients who exhibited elevations in serum TnI, and who were more likely to develop cardiotoxicity and less likely to recover, even when treated for cardiac dysfunction: prior use of anthracyclines was a significant risk factor; cumulative anthracycline dose was significantly higher. Elevation of TnI, observed exclusively in patients with prior anthracycline exposure, was also found in 7 patients prior to trastuzumab therapy, despite normal EF, suggesting ongoing anthracycline-mediated myocyte damage that would have otherwise gone unrecognized (3). Thus, it appeared that TnI leak was not a “pure” marker of trastuzumab cardiotoxicity. Rather, trastuzumab exerted a modulating effect on the vulnerable myocyte, previously damaged by anthracyclines.

Also, in line with our preliminary data on speckle tracking detection of early left ventricular (LV) dysfunction in mice treated with anti-ErbB2 agents, with increased cardiac fibrosis evidenced by histology (4,5), Fallah-Rad et al. (1) show evidence of subepicardial linear delayed enhancement in the lateral wall of the LV in trastuzumab cardiomyopathy, with a progressive decline in LVEF, despite discontinuation of trastuzumab and initiation of heart failure therapy, suggesting that the paradigm of reversibility of trastuzumab-induced cardiomyopathy needs to be re-evaluated.

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Reply

Breast cancer and cardiovascular disease are major public health concerns worldwide. The 2 diseases are intricately linked as treatment with established chemotherapeutic agents and monoclonal antibodies, including doxorubicin and trastuzumab, may lead to breast cancer remission, but alternatively, may also lead to significant cardiotoxicity. In the emerging field of cardio-oncology, early indices of left ventricular (LV) systolic dysfunction would be useful for addressing the cardiac safety profile of trastuzumab, potentially avoiding the detrimental effects of heart failure.

We recently evaluated the utility of cardiac biomarkers, tissue Doppler imaging (TDI), and cardiac magnetic resonance imaging (CMR) for predicting early LV systolic dysfunction in HER-2-positive breast cancer patients treated with trastuzumab in the adjuvant setting (1). Of the 10 (25%) women who developed trastuzumab-induced cardiotoxicity (TIC), cardiac biomarkers including troponin (Tn)T, C-reactive protein, and brain natriuretic peptide did not predict early LV systolic dysfunction (1). As suggested by Tocchetti et al. (2), our findings contrast with a previous study in which troponin I was able to identify a subset of women at high risk of doxorubicin- and trastuzumab-mediated cardiac dysfunction prior to a decrease in left ventricular ejection fraction (LVEF). One potential explanation for the difference is the frequent sampling of TnI, both before and after each trastuzumab cycle, as in the study by Cardinale et al. (3), which provides a more accurate assessment of biomarker levels in this patient population.

As compared with cardiac biomarkers, echocardiography using TDI was sensitive in detecting pre-clinical changes in LV systolic dysfunction. We agree with Dr. Tocchetti and colleagues that a number of both basic science and clinical studies have recently confirmed the utility of TDI for the early identification of LV systolic dysfunction in breast cancer patients receiving doxorubicin and trastuzumab (2,4–7). Although both TDI and strain imaging were able to detect pre-clinical changes in LV systolic dysfunction in breast cancer patients, the decision to either continue or withhold trastuzumab therapy requires further study.

CMR using delayed enhancement (DE) is the gold standard for the noninvasive assessment of cardiac volumes, systolic function, and degree of fibrosis. To address the comments by Drs. Wassmuth and Schulz-Menger, all 10 women in our study had normal CMR studies at baseline, with no evidence of DE of the LV myocardium, prior to initiation of doxorubicin and trastuzumab. At 1-year follow-up, there was mid-myocardial DE of the lateral wall of the LV in each of the 10 women with TIC, with no evidence of myocardial edema on T2 imaging (1). We agree with Drs. Wassmuth and Schulz-Menger that confirmatory studies by other groups are required and likely forthcoming. As there was no evidence of subendocardial DE in our patient population, one can assume that there was no significant obstructive coronary artery disease as questioned by Dr. Ntim. Finally, in response to Ntim, there was no use of antiplatelet or statin therapy in our patient cohort. The identification of DE of the LV myocardium in breast cancer patients challenges the paradigm of whether trastuzumab-mediated cardiac dysfunction is truly reversible in all cases.

The anticipated goal of cardio-oncologists should be to continue to improve overall morbidity and mortality in breast cancer patients

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