Can serial changes of diastolic dysfunction signal incremental risk of chemotherapy-induced heart failure missed by the timing of declining LV ejection fraction?

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Cardiologists and oncologists are challenged to optimize safety and effectiveness of chemotherapy. The quest for therapeutic cancer cure is hampered by the risk of cardiotoxicity including potentially fatal clinical heart failure.[1] Management of chemotherapy administration concordant with strategic baseline EF guideline recommendations for cumulative doxorubicin dose-related timing of accurate and precise radionuclide LVEF measurements, and recommendations for termination of therapy have been demonstrated in high-risk patients to change the natural history of heart failure associated with anthracycline cardiotoxicity.[1–4] Personalizing cardio-oncologic care with specific chemotherapy regimens requires use of techniques and monitoring guidelines which have been proven effective by study of long term outcomes in high-risk patients who have abnormal baseline LVEF or those whose residual cancer risk requires consideration of ongoing chemotherapy.[4] However, evidence of safe and effective management for timing and termination of chemotherapy by serial EF determinations without use of strategic baseline EF guidelines, use of other techniques such as echocardiographic EF and strain imaging, LV and RV volume indices, MIBG, biomarkers, and other novel markers remains undefined by prospective trials in high-risk patients receiving anthracycline and other types of chemotherapy.[4] A potentially important set of novel risk markers of chemotherapy-induced heart failure includes measures of diastolic LV dysfunction which can precede systolic dysfunction in anthracycline and perhaps other chemotherapies and provide a more sensitive and specific predictor of long-term chemotherapy-induced heart failure.

The importance of diastolic dysfunction and its progression to diastolic heart failure, now called ''HFpEF'' or ''heart failure with preserved ejection fraction'' in clinical cardiology, have been recognized for decades. Early studies identified a role for the negative inotropic and chronotropic therapies including the calcium channel blocker verapamil and beta blockers in the management of diastolic heart failure in hypertension or hypertrophic cardiomyopathy.[5–7] Radionuclide ventriculography identified a reduction in the diastolic peak filling rate and prolongation of the time to peak filling associated with HFpEF, and improvements in these dynamic filling characteristics and clinical heart failure with calcium and beta blockade therapy have been demonstrated.[5–7]

Diastolic dysfunction was identified by Lee et al. with serial radionuclide angiography as an early marker of doxorubicin cardiotoxicity prior to reduction of LVEF in patients receiving doxorubicin.[8] This observation was soon followed by reports of early diastolic dysfunction using Doppler echocardiography of LV filling dynamics during doxorubicin treatment.[9] These observations suggested nearly three decades ago the potential to enhance the diagnostic and prognostic assessment of heart failure risk associated with progressive myocytolysis defined by serial endomyocardial biopsy during anthracycline

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treatment[10–12] prior to the predictive decline of radionuclide LVEF. Recent findings of TOPCAT demonstrating reduced HF admissions and regional variation in the Western but not the Eastern hemispheric countries, despite a negative finding of the primary composite endpoint suggest the potential value of spironolactone as an additional therapy for treatment of chemotherapy-induced HFpEF.[13]

Thus, it would be reasonable to expect serial monitoring of diastolic dysfunction by MUGA parameters of peak filling rate and time to peak filling rate might enhance the sensitivity for detecting cardiotoxicity and lead to recommendations to discontinue therapy earlier than the signal of declining LVEF, enhance the precision of personalized prescription of therapy, and lead to effective treatment of HFpEF with verapamil, beta blockers, and spironolactone. However, evaluation of this enticing hypothesis has eluded our literature and guidelines for decades.

In the current issue of the Journal of Nuclear Cardiology, Reuvekamp and Bulten et al. report a study evaluating diastolic dysfunction as a more sensitive marker of trastuzumab (Herceptin) cardiotoxicity.[14] Trastuzumab is a humanized monoclonal antibody which targets human epidermal growth factor receptor type 2 (HER2) and has shown to be effective at reducing breast cancer progression, recurrence, mortality, and prolong survival in patients with metastatic breast cancer and in the curative adjuvant setting.[15–19] Trastuzumab has also been shown to increase risk of cardiotoxicity and LV systolic dysfunction. Trastuzamab differs from anthracyclines in the timing of more rapid onset and substantial reversibility of LV systolic dysfunction within a few months of terminating therapy.[20] Indeed, the investigators of the current study observed trastzumab-induced systolic and diastolic dysfunction by serial MUGA. Importantly, an impairment of MUGA-derived parameters of diastolic dysfunction was not observed prior to systolic dysfunction. The authors conclude serial MUGA measurements of diastolic dysfunction cannot be used as earlier predictors of trastuzumab cardiotoxicity.

Both study limitations and differences in the toxicity of trastuzumab compared to anthracyclines might influence the findings of this study. As always, the methods of patient selection can potentially influence results. Calculation of EF, peaking filling rate (PFR), and time to PFR are key metrics of cardiac function in this study. Of concern, the authors offer no data on the reproducibility of these measurements in their laboratory, although historically high accuracy and reproducibility have characterized radionuclide ventriculographic measurements of LV systolic and diastolic function. Potentially confounding influences of anemia and tachycardia common in cancer patients might have influenced results. A very high proportion of patients (63/77) in this study received anthracyclines, which might have altered the functional response of the LV to trastuzumab. Nevertheless, most patients receiving trastuzumab also receive anthracyclines, so the use of both agents in this study reflects common practice and the need for monitoring this population with advanced breast cancer.

Beyond the potential limitations of this study, what differences in anthracyclines and trastuzumab might account for the absence of diastolic dysfunction preceding systolic dysfunction with trastuzumab cardiotoxicity? Anthracyclines impair cardiac function in a dose-dependent and cumulative manner. Characteristic pathologic features include vacuole formation, myofibrillar disarray, and eventual myocyte necrosis.[10–12] These changes are likely mediated by free radical formation and associated oxidative stress.[21] In contrast to Type I anthracycline cardiotoxicity with progressive cardiac dysfunction associated with progressive myonecrosis, trastuzumab is now considered to be the prototype agent which produces Type II chemotherapy-related cardiotoxicity which is characterized by reversible cardiac dysfunction not associated with irreversible myocytolysis.[20] Trastuzumab Type II cardiotoxicity is not dose related, does not occur predictably in all patients, and is reversible within a few months after discontinuation of therapy, and the clinical spectrum of heart failure severity is variable and long-term tolerability is favorable.[20,22]

The mechanism by which trastuzumab exerts its cardiotoxic effects is not clearly understood. HER2 receptors (also known as ErbB2) are expressed by cardiac myocytes and exert cardioprotective effects when neuregulin-1 binds to ErbB3 or ErbB4 causing heterodimerization with ErbB2. Subsequent effects are accomplished via the ERK1/2 and Pl3K/AKT signaling pathways.[23,24] Animal models have demonstrated that ErbB2 signaling is essential for normal embryonic development.[23] Furthermore, mice with ventricular restricted ErbB2 deletion developed findings of dilated cardiomyopathy and isolates of cardiac myocytes in affected mice were more susceptible to anthracycline toxicity.[24,25] Thus, trastuzumab toxicity is believed to be mediated by loss of ErbB2 cardiac repair and survival pathways which normally mitigate the effects of cardiac stress signals, including anthracycline toxicity.[26,27]

The optimal method of monitoring for trastuzumab cardiotoxicity has not yet been clearly identified. The United Kingdom National Cancer Research Institute issued revised recommendations to guide cardiologists and oncologists in monitoring the cardiotoxic effects of trastuzumab.[28] These guidelines were developed in

accordance with the cardiac monitoring algorithm in the Herceptin Adjuvant Trial[29] with additional modifications based on growing clinical experience and understanding of the pathophysiology and natural history of trastuzumab cardiotoxicity.[28] Prior cardiac disease and anthracycline exposure may potentiate the short-term cardiotoxic effects of trastuzumab, and in the absence of large prospective clinical trials, alternative algorithms for management varying recommendations for close monitoring of these patients have been proposed.[4,30–32] These algorithms continue to focus on serial assessment of LVEF which remains a relatively late marker of cardiotoxicity.

Despite the negative outcome of the trastuzumab trial, Reuvekamp and Bulten must be credited with a broader important question to grace the field: Can serial changes in diastolic dysfunction signal the risk of chemotherapy-induced heart failure missed by the timing of declining LV ejection fraction? If not observed during trastuzumab therapy, can abnormalities of diastolic peak filling rate and time to peak filling defined routinely by planar and SPECT blood pool ventriculography help refine the published guidelines of quantitative radionuclide LVEF which has improved the natural history of anthracycline-induced heart failure? For trastuzumab, it may be the tolerability and survival of its reversible Type II functional cardiotoxicity rests on the accurate identification of the baseline vulnerability of the left ventricle by virtue of systolic or diastolic LV dysfunction and / or LV dilation prior to administration of trastuzumab. In the prior published evaluation of high-risk patients with reduced baseline LVEF prior to or within 100 mg/m^2 doxorubin, a substantial percentage of these patients had no clinically identifiable etiology of the baseline LV systolic dysfunction observed; nevertheless with strategic guideline-based monitoring these patients with baseline LV dysfunction safely received substantial and clinically effective cumulative doses of doxorubicin.[3,33] Future research in cardio-oncology would likely do well to follow the evidence-based lead of accurate, reproducible, and prognostically validated radionuclide blood pool ventriculography[2–4,33,34] by identifying the patient with cardiac baseline systolic or diastolic functional vulnerability of the left ventricle who may have reduced tolerance of the substantial, potentially reversible, and unpredictable insult of highly effective trastuzumab in patients with advanced cancer whose cure depends on its safe and timely administration.

Good science leads to many new questions that advance knowledge in the field. The field is indebted to Reuvekamp and Bulten for reminding us radionuclide measures of diastolic dysfunction we have known about for decades may yet have a critical role to play in the assessment of heart failure risk of therapeutic radiation and chemotherapy.

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