Cardiac Surveillance Guidelines for Trastuzumab-Containing Therapy in Early-Stage Breast Cancer: Getting to the Heart of the Matter

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Trastuzumab-containing regimens for breast cancer have significantly improved survival both in the early-stage and metastatic settings.¹⁻⁸ Nevertheless, given the early signals of cardiotoxicity, a prevailing concern exists regarding the risk of cardiotoxicity, defined as a decline in left ventricular ejection fraction (LVEF) both asymptomatic and symptomatic. This concern that LVEF decline would be an early and actionable surrogate for subsequent development of congestive heart failure (CHF) led to the design and implementation of specific eligibility criteria and LVEF surveillance guidelines for the pivotal randomized adjuvant trials. These guidelines were subsequently adopted as the standard of care. However, it is increasingly unclear whether these specific recommendations are justified for all patients. Resolution of this matter is critical for our community because adherence to these guidelines was recently proposed as a quality metric.⁹ This issue raises the general question of the level of evidence needed to accept a toxicity screening schedule as a quality indicator. If following these guidelines is not associated with improved outcomes, then adherence to them as a quality metric should be challenged. Cardiotoxicity screening can serve to illuminate this issue. Here, we review the historical events that led to the development of the current guidelines and highlight critical knowledge gaps with regard to the benefits of screening and intervention.

Trastuzumab-Associated Cardiotoxicity and Current Surveillance Guidelines

Trastuzumab-associated cardiotoxicity was first recognized as an unanticipated adverse effect in the late 1990s during the early trials in metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer, as reported by the independent Cardiac Review and Evaluation Committee.¹⁰ In seven studies, the Cardiac Review and Evaluation Committee independently reviewed and adjudicated cases of asymptomatic and symptomatic LVEF decline. One of these studies was the pivotal phase III trial demonstrating that 27% of the patients receiving concurrent anthracycline-trastuzumab-based therapy developed symptomatic or asymptomatic left ventricular (LV) dysfunction. Among them, 16% experienced New York Heart Association (NYHA) class III or IV heart failure.^{6,10} However, much lower rates were seen in studies

involving trastuzumab alone or combined with other chemotherapy agents.¹⁰

The findings from the metastatic trials guided the design of subsequent adjuvant trials.¹⁻³ The pivotal adjuvant studies mainly included patients with high-risk, node-positive breast cancer. Therefore, the typical chemotherapy regimen included an anthracycline followed by a taxane. Because of concerns that heart failure could be a significant risk, and given the unknown efficacy of adjuvant trastuzumab, the following study mandates were implemented with the overall goal of minimizing cardiotoxicity: (1) administration of trastuzumab sequentially after completion of anthracycline-containing chemotherapy; (2) LVEF monitoring at baseline and the arbitrarily designated 3-month interval during trastuzumab treatment; (3) exclusion of patients with a significant cardiovascular history such as recent myocardial infarction, CHF, angina, significant arrhythmias or conduction system disease, uncontrolled hypertension, LV hypertrophy, or significant valvular heart disease; and (4) implementation of strict criteria for initiation and/or continuation of trastuzumab on the basis of the LVEF results. In most trials, significant asymptomatic LVEF decline was defined as an absolute decrease in LVEF of $\geq 10\%$ to below the lower limit of normal or $\geq 16\%$ from baseline value.^{1-3,11} Trastuzumab was stopped temporarily or permanently as indicated on the basis of adequate or insufficient recovery, respectively. In these four large trials, the incidence of significant LVEF decline ranged from 7.1% to 18.6%, whereas the rate of NYHA class III or IV heart failure ranged from 0.4% to 4.1%.^{1-3,11} Given the overall study results, the US Food and Drug Administration approved the adjuvant use of trastuzumab in November 2006 and recommended assessment of LVEF at baseline and every 3 months during therapy. These recommendations were endorsed by the National Comprehensive Cancer Network and were widely accepted as a standard of care.^{12,13} However, over the past decade, research in the area of cardio-oncology, particularly in the assessments for cardiotoxicity in HER2-positive early-stage breast cancer, has expanded our understanding of this entity and provided the opportunity to ask whether the initial guidelines are useful for the majority of patients or whether they should be reconsidered.

Utility of Cardiac Surveillance Guidelines: Too Much, Too Little, or Just Right?

The clinical utility of routine testing should be determined on the basis of whether it can be used to detect an actionable end point that improves outcomes for the tested population. With regard to serial LVEF monitoring, one can ask whether the detection of asymptomatic LVEF decline by means of serial LVEF monitoring is predictive of the subsequent risk of overt heart failure in patients with early-stage breast cancer and, more importantly, whether early intervention in asymptomatic patients—including cessation of anti-HER2 therapies or initiation of cardioprotective drugs—prevents progression to symptomatic heart failure. One must also consider the potential harm and cost of testing, including those related to additional interventions and compromised delivery of curative care. To clarify these issues, we ask the three questions that follow.

Is asymptomatic LVEF decline a predictor of heart failure in early-stage breast cancer? Serial cardiac surveillance has been performed under the simple assumption that detection of a subclinical decline in LVEF is predictive of future clinical events, in this case heart failure, and that treatment will reduce the risk of heart failure. In an unselected population without cancer, asymptomatic LVEF decline was predictive of heart failure and death.¹⁴ Yet, a notable 62% of patients with asymptomatic LVEF decline who developed CHF had a history of baseline or interval myocardial infarction.¹⁴ However, in the oncology setting, the association between asymptomatic LVEF decline and CHF is unclear with 7 to 9 years of follow-up from two large, adjuvant trastuzumab trials that included the anthracyclines.^{15,16} In the National Surgical Adjuvant Breast and Bowel Project (NSABP), B-31 trial, the incidence rates of NYHA class III or IV heart failure and of cardiac death were 4.1% and 4.0% with a median follow-up of 2 and 7 years, respectively.^{11,15} Similarly, in the North Central Cancer Treatment Group (NCCTG) N9831 study of patients who received trastuzumab sequentially versus concurrently with paclitaxel, the incidence rates were 2.8% versus 3.3%, respectively, after 3.75 years of follow-up and remained static at 2.8% versus 3.4%, respectively, after 9.2 years of follow-up.¹⁶ Therefore, it remains unclear if asymptomatic LVEF decline is predictive of acute or late-onset heart failure in this population with almost 10 years of follow-up.

However, claims-based reports showed higher rates of heart failure and/or cardiomyopathy.¹⁷⁻¹⁹ In the older population with a mean age of at least 60 years, the 3-year incidence rates of heart failure and/or cardiomyopathy were 32.1% for trastuzumab and 41.9% for trastuzumab with an anthracycline in one study, and the 5-year rates were 12.1% for trastuzumab and 20.1% for trastuzumab with an anthracycline in another study.^{17,18} The higher rates in these retrospective studies, when compared with those of well-designed prospective trials, could be due to the fact that patients in the trials were healthier and younger as a result of selection and/or they could simply reflect an overestimation of the true risk of cardiotoxicity in claims-based studies in which rigorous adjudication of events was lacking.

Does intervention for asymptomatic patients with early-stage breast cancer prevent subsequent heart failure? To date, we are not aware of any published data from well-designed trials to

show whether early intervention prevents symptomatic heart failure in patients who undergo treatment with trastuzumab-containing regimens in the adjuvant setting. A few trials have been conducted to assess whether early intervention reduces trastuzumab-associated cardiotoxicity, as measured on the basis of changes in the LV. The Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research (MANTICORE) 101 study found that the small drop (5%) of LVEF from baseline seen with placebo was reduced to 3% by using an angiotensin-converting enzyme inhibitor and to 1% by using a beta blocker. Nevertheless, the study failed to reach its primary end point, which was to demonstrate prevention of LV remodeling.²⁰ Similar to the MANTICORE study, the Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy (PRADA) study also demonstrated that an angiotensin-receptor blocker (but not a beta blocker) prevented LVEF decline when compared with placebo, with LVEF decrement of 0.8% versus 2.6%, respectively, from baseline. However, neither study reported that their interventions led to any difference in CHF outcomes, albeit that neither may have had sufficient statistical power in this regard.²¹ The National Cancer Institute–sponsored NCT01009918 (Lisinopril or Coreg CR in Reducing Side Effects in Women With Breast Cancer Receiving Trastuzumab) study also has a similar design, and we eagerly await the results of these trials.²²

Is there potential harm and cost in overscreening? Finally, an issue of harm and cost exists. A low but real error rate is observed with echocardiographically based measurements such that LVEF decline may reflect temporal or interobserver variability.²³ The harm is the time and effort required to confirm a false-positive finding and the risk that some patients will be wrongly identified as having cardiotoxicity, a situation that compromises delivery of curative therapy. The cost may be fiscal, especially in overscreening of those populations that may not derive any benefit.

Does Adherence to Current Guidelines Improve Outcomes?

If sequential, regimented screening is useful, then adherence to the current guidelines becomes important both for patients' cardiac outcomes and for opportunities for continuous quality improvement. However, routine LVEF monitoring may not be justified with the current evidence, which indicates that rates of symptomatic and asymptomatic LVEF decline are strikingly low, specifically in patients who receive trastuzumab-based therapy without previous anthracycline exposure.^{3,24,25} For instance, in a study of 406 patients with node-negative HER2-positive breast cancer who were treated with paclitaxel and trastuzumab, Tolaney et al²⁴ reported asymptomatic LVEF decline and heart failure in 3.2% and 0.5% of patients, respectively. In this study, an exploratory analysis was done to assess the relationship between baseline characteristics and cardiac outcomes, and there seemed to be a correlation between a low baseline LVEF of $\leq 55\%$ and an increased incidence of significant asymptomatic LVEF decline or symptomatic heart failure (risk ratio, 0.30; 95% CI, 0.10 to 0.90; $P = .05$).²⁶ Another phase II study of a nonanthracycline chemotherapy consisting of docetaxel and cyclophosphamide plus trastuzumab in 498 patients revealed that only 5.6% of patients

developed an LVEF less than 50%, with 0.4% developing heart failure.²⁵ In the randomized Breast Cancer International Research Group (BCIRG) 006 study, 9.4% and 0.4% of patients receiving a docetaxel, carboplatin, and trastuzumab regimen developed asymptomatic LVEF decline and symptomatic heart failure, respectively.³ Of note, a similar low cardiotoxicity profile has also been observed in the metastatic setting with a nonanthracycline-based therapy using single and dual anti-HER2 treatment consisting of trastuzumab and pertuzumab.^{8,27-29} On this basis, it is unclear whether the current guidelines for serial LVEF monitoring are appropriate for all patients receiving trastuzumab-based therapy in the adjuvant setting, especially without an anthracycline.

The Need for Evidence-Based Guidelines

Important knowledge gaps in cardio-oncology force us to question the utility of existing one-size-fits-all cardiotoxicity screening. First, the identification of a subset of patients truly at a high risk for cardiotoxicity is needed. Previous studies have revealed several predictors of cardiotoxicity that include age $\geq$ 50 years, low baseline LVEF (eg, 50% to 54%), hypertension, and previous anthracycline chemotherapy exposure.³⁰ However, these risk factors must be validated. Second, to directly inform optimal monitoring schedules, randomized trials or larger, unbiased prospective registries are required that not only describe the outcomes after surveillance but also demonstrate the utility of intervention. For example, in terms of trials, for those patients who are receiving trastuzumab-containing therapy without an anthracycline and without cardiotoxicity risk factors, random assignment to serial monitoring versus less testing may be considered. For patients given trastuzumab-containing therapy with an anthracycline, serial monitoring can be implemented, and random assignment could be considered in the following situations: (1) interruption of trastuzumab-based therapy for significant LVEF decline versus (2) continuation despite the development of significant asymptomatic LVEF decline, with cardiac medications recommended per the standard of care. The SAFE-HEART (A Pilot Study Assessing the Cardiac Safety of HER2 Targeted Therapy in Patients With HER2 Positive Breast Cancer and Reduced Left Ventricular Function) study is an ongoing single-arm trial to evaluate the safety of continuing anti-HER2 therapy in patients with significant asymptomatic LVEF decline to 40% to 49%. We eagerly await the results of this important trial. Patients can receive long-term follow-up for cardiac outcomes. Given the lack of well-designed studies, it remains difficult to know whether screening or intervention should be performed in most patients and whether it matters.

Summary

With about a decade of follow-up involving patients treated in the adjuvant setting with trastuzumab-containing regimens, the available evidence does not definitively support a specific schedule of screening nor does it demonstrate improved outcomes for the screened patients. Currently, the American Society of Clinical Oncology and American College of Cardiology are collaborating to develop guidelines for patients undergoing trastuzumab-based therapies, and this effort may provide some clarity. Ideally, guidelines should be evidence based, informed by well-conducted

and adequately powered trials. Lacking that, we should attempt to conduct informative studies before establishing arbitrary metrics and labeling them quality indicators. This principle should be considered broadly as increasing emphasis and attention is focused on the development of surrogate markers and endpoints for quality across oncology and all of medicine.

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