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EDITORIAL COMMENT

Left Ventricular Ejection Fraction Monitoring Adherence Rates

Why So Low?*

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Over the past 2 decades, trastuzumab has revolutionized the treatment of (human epidermal growth factor receptor 2 (HER2)-positive breast cancer in both the metastatic and early breast cancer settings (1-4). More than a decade of follow-up results show patients continue to benefit from the addition of trastuzumab to standard treatment compared to chemotherapy alone. The initial enthusiasm of oncologists to prescribe trastuzumab was attenuated to some degree by the potential increased risk of patients who experienced a cardiac event, notably heart failure (HF). Long-term follow-up studies (10 years) of trastuzumab, however, have shown no increased risk of late cardiac events, namely symptomatic HF and/or probable cardiac death (3-7).Was this due to arbitrary rules implemented in these trials in which patients were required to undergo routine cardiac surveillance (i.e., left ventricular ejection fraction [LVEF] monitoring every 3 months) with strict stopping rules for asymptomatic drops in LVEF (≥16% from baseline or 10% to 15% lower limit of normal)? In those who had appropriate recovery, was the temporary cessation of trastuzumab a plausible explanation for recovery of LVEF, considering the half-life of this antibody would be approximately 3 weeks?

The U.S. Food and Drug Administration currently recommends LVEF monitoring every 3 months while the patient is taking adjuvant trastuzumab therapy, based on protocols in the clinical trials (8). These recommendations have been adopted by several co-operative groups and embedded in clinical practice guidelines (9-10). Despite current recommendations, over the past few years there have been reports that rates of adherence to these guidelines have been low in clinical practice (11). One such recent report was by Henry et al. (12), in this issue of *iJACC*, who performed a database search using Truven MarketScan (IBM Watson Health, Cambridge, Massachusetts) and identified 16,456 patients who received systemic treatment within 6 months of diagnosis for early breast cancer

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from 2009 to 2014. Henry et al. (12) aimed, first, to identify the rates of cardiotoxicity defined as HF with 1 claim as inpatient or 2 claims as outpatient 30 days apart and, second, to assess adherence to LVEF monitoring among patients treated with trastuzumab-based therapy. Guideline adherence was defined as LVEF monitoring at baseline and every 4 months during treatment, with echocardiograms or multi-gated acquisition scans. Variables analyzed were age, year of diagnosis, Deyo score, hypertension, coronary artery disease, valve disorder, diabetes, insurance, region, and exposure to trastuzumab, anthracycline, taxane, or radiation. The median age of patients was 56 years. Overall, HF occurred in 4.2% in this group; it was 8.3% exposed to trastuzumab and 2.7% in the group not exposed to trastuzumab. Young patients, that is, <35 and 36 to 49 years of age had fewer events

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than those >65 years old. Risk factors for events were higher Deyo scores, trastuzumab exposure, anthracycline use, hypertension, coronary artery disease, and valve disorder. In the 4,325 patients who were treated with trastuzumab, adherence to LVEF monitoring was 46.2% (40.2% and 47.6% in patients who were <35 and those 36 to 49 years of age, respectively). Overall, guideline-adherent monitoring was associated with anthracycline, taxane, and radiation exposure. The adherence rate of approximately 46% in this study was slightly higher than the rate of 36% reported in a previous study in older patients but still not high, nevertheless (11). Thus, why was adherence low in the overall study? Authors offered 1 explanation, which was the possibility that the need for routine monitoring was perceived as low by clinicians. However, one must ask if there are sufficient data to demonstrate that adherence to cardiovascular monitoring guidelines is associated with better outcomes and if these guidelines are still relevant today. Here we discuss the utility of stringent LVEF monitoring guidelines, knowledge gaps, and a potential pathway forward.

UTILITY OF STRINGENT LVEF MONITORING AND KNOWLEDGE GAPS

To date it remains unclear whether detection of asymptomatic LVEF decline predicts for the subsequent risk of overt HF in patients with early stage breast cancer treated with trastuzumab-based therapy. In the pivotal adjuvant trials, the rates of significant LVEF decline were as high as 18.6%, which led to temporary or permanent cessation of trastuzumab therapy (13–16). However, with a decade of follow-up, there remain no increased rates of symptomatic HF, and thus, evidence is still lacking that asymptomatic LVEF decline during active therapy is associated with acute or late HF events (3–7). We do recognize that these rates of HF are lower than those reported from large retrospective nonclinical trial reports (17–19). This could be due to an inclusion of older, less healthy subjects or to an overestimation of the true cardiotoxicity risk reported in claims-based data abstraction.

How do we prevent HF events? Primary prevention trials, evaluating the potential role of cardioprotective medication in “all” breast cancer patients treated with potentially cardiotoxic drugs, have not clearly demonstrated clinically meaningful results, namely the MANTICORE 101 (Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research) and PRADA (Prevention of Cardiac Dysfunction during Adjuvant Breast Cancer Therapy) trials (20,21). MANTICORE 101 demonstrated that LVEF decline occurred in only 3% and 1% of patients treated with an angiotensin-converting enzyme inhibitor and beta-blocker, respectively, versus 5% with placebo, but the study failed to meet its primary endpoint, which was the prevention of cardiac remodeling. One possible reason for the negative result in the MANTICORE study was that the majority of patients (76%) received nonanthracycline-based treatments with trastuzumab. There are ample data demonstrating that rate of symptomatic HF was very low in this group, at least in the clinical trial setting, on the order of 0.4% to 0.5% (4,22–24). Similar to MANTICORE, PRADA demonstrated that LVEF decline was attenuated with an angiotensin receptor blocker but not with a beta-blocker, compared with placebo. Notably, in these studies, most patients did not have cardiovascular risk factors, and both studies were too small and underpowered to determine whether the abrogation of LVEF led to lower rates of HF events. Finally, a third trial, led by the University of South Florida, showed that prophylactic treatment with lisinopril and carvedilol did appear to be effective at preventing LVEF decline versus placebo in patients on trastuzumab therapy after an anthracycline, but not in those on a non-anthracycline based treatment; thus, we eagerly await the final publication (25). If the preventive implementation of HF medications in “all” patients is over-treatment, then what tools can we use to identify the “high-risk” patients to initiate HF medications and/or hold curative therapy? Are cardiac biomarkers predictive of early detection of cardiotoxicity? To date, there is a lack of consistent data for the utility of biomarkers (troponin I and T, brain natriuretic peptide, and others) to definitively recommend standard use of these markers in routine practice (26–28). Echocardiograms with strain imaging is currently being explored as a tool to detect early LV dysfunction, but its utility in standard practice is still unclear, pertaining to its impact on the decision to hold curative therapy or not (29,30).

What about risk prediction models? The National Surgical Adjuvant Breast and Bowel Group B-31 developed a cardiac risk score which could identify patients at highest risk for HF, based on age and baseline LVEF (5). Ezaz et al. (31) developed a 7-factor clinical risk score (CRS) based on age, adjuvant chemotherapy, coronary artery disease, atrial fibrillation or flutter, diabetes mellitus, hypertension, and renal failure. They were able to stratify older patients into low, moderate, and high risk of developing HF or