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Anthracycline and Trastuzumab-Based Therapy in Early Stage Breast Cancer: Do the Data Justify Cardiac Surveillance?

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Introduction

Anthracycline-based and trastuzumab-containing regimens make a significant impact on reducing the risk of distant metastases and improving cause-specific and overall survival in early stage breast cancer. However, these regimens may cause cardiomyopathy during and after treatment. Despite anthracyclines being in use for nearly fifty years, there are no evidence-based guidelines for cardiac surveillance in asymptomatic breast cancer survivors. In fact, the current guidelines for cardiac monitoring while on trastuzumab therapy were from clinical trials, with empiricism and not data informing the recommendations for cardiac monitoring.

Surveillance recommendations vary depending on which guidelines one reads. The American Society of Clinical Oncology (ASCO) recommends no further cardiac imaging in asymptomatic women with early breast cancer who received cumulative doses (called for purposes of this review "limited doses") of doxorubicin of less than 250 mg/m^2 (or epirubicin 300 mg/m^2)[1,2].

The National Comprehensive Cancer Network (NCCN) recommends a baseline echocardiogram (ECHO) and repeat ECHO in one year for those women with one or more risk cardiac risk factors, including age over 65 years, diabetes, hypertension, hyperlipidemia, family history of cardiomyopathy, atrial fibrillation, coronary artery disease, or structural heart disease[3]. In contrast, the European Society for Medical Oncology[4], the Canadian Cardiovascular Society[5], Italian Society of Cardiology and Working Group of Drug Cardiotoxicity and Cardioprotection[6], the American Society of Echocardiography and European Association of Cardiovascular Imaging[7], and others[8,9] recommend routine cardiac surveillance alone or the use of biomarkers plus cardiac imaging for surveillance to detect early declines in left ventricular function. Furthermore, in some instances, some guidelines endorse the initiation of cardiac medications in asymptomatic women.

Conflicting guideline recommendations leave clinicians and women with early breast cancer unsure about what surveillance recommendations are best in asymptomatic women who received limited doses of anthracycline and trastuzumab-based regimens. Reviewed in this commentary is the lack of evidence to support cardiac surveillance in asymptomatic women with breast cancer receiving limited-dose exposure to anthracyclines.

Type I and Type II Cardiotoxicity

It is essential to distinguish between anthracycline-induced myocardial damage (Type I) and trastuzumab-induced cardiac dysfunction (Type II). Type I myocardial injury causes direct myocyte death as confirmed by endomyocardial biopsy studies and is irreversible[10]. The frequency of Type I is related to the total cumulative dose of anthracycline; the route of administration with intravenous bolus dosing causing higher rates of cardiomyopathy than weekly lower doses or continuous infusions; underlying cardiac disease; aging (over age 65 years); or a history of mediastinal radiation. In contrast, there are no risk factors for Type II, and it does not cause myocardial cell death[10]. Other features that distinguish Type II from Type I are that it is not dose-dependent, and holding trastuzumab for a period of four to six weeks and repeating cardiac imaging often results in left ventricular ejection function (LVEF) recovery with or without cardiac medications. When LVEF recovers, retreatment with trastuzumab-based regimens is possible in more than fifty percent of women[11]. Thus, Type I and Type II are very different regarding their pathogeneses, and clinical implications and outcomes.

Lack of a Standard Definition of Cardiotoxicity by LVEF Declines

Whereas the development of congestive heart failure (CHF) or cardiac death are easy to define endpoints, there is no standard definition of cardiotoxicity based on the LVEF declining. Generally, the definitions involve an asymptomatic decreases LVEF within the normal range and asymptomatic or symptomatic decreases in LVEF below the normal range. Varying studies define cardiotoxicity as either a fall in LVEF to less than 50%, an asymptomatic reduction in LVEF of more than 10% to LVEF to less than 55%, LVEF decrease more than 20% from baseline or an asymptomatic fall in LVEF of 10-15% within the normal range or some combination of these[12,13]. These varying definitions unduly complicate cross-trial comparisons and impede the link between decreases in LVEF as a surrogate endpoint on the clinically meaningful endpoints of CHF or cardiac deaths.

The Scope of the Problem: Limited Doses of Anthracyclines and the Incidence of Clinically Meaningful Cardiac End Points

Table 1 describes the rates of CHF and cardiac deaths in

Table 1: The scope of the problem: Meaningful Cardiac Events with Limited Doses of Anthracyclines Alone or Anthracyclines followed by Trastuzumab

Trial	N	Follow-up (yr)	Total Median Doxorubicin (mg/m²)	Δ LVEF (%)	CHF (%)	Anthracyclines HR or OR* (95% CI)	No Anthracyclines HR or OR* (95% CI)	Cardiac Deaths (%)
Anthracyclines only								
Prospective randomized trials								
Shulman 2012 (14)	1107	5.3	240	NA	0.2	NA	NA	0.1
	766	5.3	360	NA	0.7	NA	NA	0.1
Advani 2016 (15)	664	6	240	-3	0.6	NA	NA	0.3
Case-Control								
Thavendiranathan 2016 (17)	10,160	3	NA	NA	3.0	0.97 (0.73 to 1.27)	0.94 (0.41 to 2.20)	0.5
SEER Registry								
Doyle 2005[&] (19)	5,571	5	NA	NA	3.0	1.38 (1.25 to 1.52)	1.13[λ] (1.03 to 1.23)	NA
Pinder 2007[&] (20)	8,083	10	NA	NA	3.0	1.26 (1.12 to 1.42)	0.90[π] (0.86 to 0.99)	NA
Anthracyclines followed Trastuzumab								
Prospective randomized trials								
Advani 2016 (15)	710	6	240	-3	2.8[Y]	NA	NA	0.1
	570	6	240	-3	3.5[f]	NA	NA	0.2
Cameron 2017 (21)	1697	11	NA	NA	1.0[♣]	NA	NA	NA
	1702	11	NA	NA	0.1[♣]	NA	NA	NA
Case-Control								
Thavendiranathan 2016 (17)	3,250	3	NA	NA	4.2	3.96 (3.01 to 5.22)	0.81 (0.25 to 2.66)	1.0

Abbreviations: years (yr); left ventricular ejection fraction (LVEF); congestive heart failure (CHF); hazard ratio (HR); odds ratio (OR); not available (NA). *Adjusted hazard or odds ratio. [λ]Women with early-stage breast cancer who received adjuvant non-anthracycline containing chemotherapy.[π]Women with early-stage breast cancer who received no adjuvant chemotherapy. [Y]Sequentially or [f]concurrently administered paclitaxel and trastuzumab. [♣]Major cardiac events in sequentially administered trastuzumab (1%) and controls (0.1%).

recent randomized trials. The crude rates of CHF and cardiac deaths with anthracyclines alone are dose-dependent and vary from 0.2% to 0.7% and 0.1% to 0.3%, respectively[14,15]. However, these are women who participated in randomized prospective trials, a group that is considered healthier than the general population[16].

An extensive retrospective case-control study from Ontario Canada compared over 10,000 women with breast cancer who received anthracyclines to over 92,000 heathy women without breast cancer[17]. The median age of anthracycline-treated women was 52 years, 31% had hypertension, 11% had diabetes, and the median Charleston co-morbidity index was 2[18]. The cumulative dose of doxorubicin was unknown. With a median follow-up of just over three years, in the cohort that received anthracyclines the rates of CHF that required hospitalization and cardiac deaths were 3% and 0.5%, respectively. In the controls the corresponding rates of major cardiac event were 0.5% and cardiac deaths was 0.5%. In a multivariate analysis adjusting for age (over 65 years), diabetes, radiation, and cancer stage for the primary outcome (CHF that required hospitalization and cardiac deaths) was a hazard ratio (HR) of 0.97 (95% CI 0.73 to 1.27) for the anthracycline group. Thus, in the multivariate analysis, there was no increase in major cardiac events for the group that received anthracyclines.

In contrast, there was the group of over 3,000 women who received in the same control study, sequentially administered trastuzumab. In this case-cohort there was nearly 4-fold higher HR for major cardiac events (CHF) compared to controls that did not receive anthracyclines (HR ratio of 3.96 (95% CI 3.01 to 5.22). However, the adjusted death rates were not higher (HR ratio of 0.81(95% CI 0.25 to 2.66).

In another set of registry studies from the Surveillance Epidemiology and End Results (SEER) shows that when women with breast cancer age 65 years or older receive anthracyclines, there are slightly higher risks of developing CHF. In one study, women with breast cancer who received anthracyclines and those that did not receive chemotherapy (controls) the adjusted HR for CHF was 1.26 (95%CI 1.12 to 1.42, p<0.001) and HR of 0.90, (95%CI 0.86 to 0.99), respectively. In another study of similar design, the adjusted odds ratio (OR) for CHF was 1.38 (95% CI 1.25 to 1.52) and 1.13 (95%CI 1.03 to 1.23) for the adjuvant chemotherapy containing doxorubicin and a non-anthracycline containing adjuvant chemotherapy, respectively (Table 1)[19,20].

Table 1 also describes anthracyclines followed by trastuzumab. First, it is important to understand the benefits of adding trastuzumab to standard anthracycline-containing chemotherapy regimens. In a combined analysis of two pivotal trials the hazard ratio for mortality was 0.67 (95% CI 0.48 to 0.93, p=0.015) comparing doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) for 4 cycles every 2-weeks followed by paclitaxel (80 mg/m^2) for 12 weekly cycles with or without concurrent trastuzumab in over 3600 women with early-stage breast cancer[13]. Sequentially administration of trastuzumab, after all chemotherapy has ended, has less cardiac toxicity than concurrent administration of trastuzumab with paclitaxel, but sequential trastuzumab was less effective[15,17,21]. Thus, the preferred of administration of trastuzumab is concurrent with the paclitaxel.

In absolute terms, if 1000 HER2 over-expressing women received AC and taxanes without trastuzumab, 917 (91.7%) would survive, 6 (0.6%) would experience CHF, and 3 (0.3%) die from cardiac causes over a median of 5 years. When trastuzumab is added concurrently to anthracycline-taxane-based chemotherapy, 943 will survive, 35 (3.5%) would experience CHF and 2 (0.2%) die from cardiac causes[13]. The left ventricular dysfunction from trastuzumab improves in the majority of women with stopping the trastuzumab either with or without cardiac medications. Over 50% of these women can receive trastuzumab again without risks of cardiotoxicity[15].

Thus, the benefits in lives saved far outweighs cardiac deaths. It is extremely rare to develop late anthracycline or trastuzumab related CHF or cardiac deaths with follow-up durations of nine to ten years[15,22]. Finally, in a very recent trial six months of trastuzumab was not inferior to 12 months, and the six-month treatment had less CHF and cardiac deaths[23].

Cardiac Imaging to Monitor for Cardiotoxicity

The early detection of subclinical decreases in LVEF limits irreversible cardiac damage in Type 1 and may have a substantial impact on the reversibility of Type 2 cardiac dysfunction[24]. 2D echocardiography (ECHO) is the most common noninvasive imaging modality to monitor as it is easily performed and does not have any radiation exposure. A low baseline LVEF (*i.e.,* 50% to 55%), asymptomatic declines in LVEF during treatment, and age older than 65 years increase the risks of CHF. However, 2D ECHO has poor sensitivity for the detection of subclinical myocardial damage[9,25,26]. Newer techniques such as real-time 3D ECHO, Doppler tissue imaging, and cardiac magnetic resonance imaging have higher sensitivity for detecting myocardial damage than 2D ECHO, but their higher costs and less availability limit the use of these newer techniques[7].

The use of global longitudinal strain (GLS) which measures myocardial deformation as a percentage of change from the original dimension per unit time is a measurement on echocardiogram can identify wall motion abnormalities before detecting decreases in LVEF[27]. There are limited data to support the prognostic value of measuring GLS[7]. However, The European Society of

Cardiology[28] and others[6, 27] do not support the use of GLS alone to stop or change anthracyclines. Larger prospective studies are needed to determine if GLS can predict CHF.

The value of a baseline echocardiogram is called into question based on a retrospective study of 220 women by Mina *et al.*[29] The population was typical of a cohort of women with early-stage breast cancer with a median age was 52 years old, 2% of women had coronary artery disease, 16% had diabetes, 24% had hypertension, 35% were smokers, and 32% were obese (BMI >30). Fifteen (7%) had a wall motion abnormality on echocardiogram, 6 (3%) had LVEF of less than 50% and only in 3 (1.3%) did chemotherapy regimen change based on these findings. Prospective studies are necessary to determine the value of the baseline echocardiogram.

Cardiac Biomarkers

Cardiac biomarkers include Troponin I, B-type natriuretic peptide (BNP), and N-terminal B-type natriuretic peptide (NT-proBNP). Troponin-I has many advantages including high specificity for cardiac tissue, high sensitivity for detecting myocyte necrosis, low cost, and is minimally invasive. Cardinale et al. did the most extensive study to examine cardiac troponins to detect early chemotherapy-induced cardiotoxicity. These were individuals receiving anthracyclines before high-dose chemotherapy with autologous or allogeneic bone marrow transplant[30]. Whereas troponins sequentially collected were able to stratify high or low-risk groups for risks of CHF, these individuals were very different from women who receive limited doses of anthracyclines.

Also, in patients with early-stage HER2-positive breast cancer receiving anthracyclines and HER2-targeted therapies (trastuzumab or lapatinib), troponin I as an early indicator of cardiotoxicity did not predict for CHF[31,32]. Likewise conflicting data use of BNP and N-terminal BNP[32-34] as a predictive marker for CHF.

The Value of Repeated Cardiac Imaging in Women with Breast Cancer Receiving Limited Doses of Anthracyclines

Whereas many cardio-oncology and cardio-imaging organizations recommend subsequent cardiac imaging with or without cardiac biomarkers in asymptomatic women who received limited doses of anthracyclines[4-9], there are little data to support these recommendations. All of these recommendations are consensus-based and lack high-quality level I evidence that subsequent cardiac imaging will prevent CHF or cardiac deaths.

Are there harms to doing repeat cardiac imaging with or without cardiac biomarkers or treatment of surrogate endpoints (*i.e.,* GLS, troponins, BNP) with cardiac medications in asymptomatic women?[24] First, the frequency of CHF or cardiac deaths is very low (Table 1). Second, these surrogate endpoints lack validation for CHF and cardiac deaths in women with limited exposure to anthracyclines. Third, giving a diagnosis of a "cardiac problem" can cause distress and impact negatively on health-related quality of life, and fourth is the costs of surveillance testing when the value of that care (*i.e.,* the prevention CHF or cardiac deaths/over the total costs, including the distress and negative impact on health-related quality of life of surveillance testing) is unknown.

What to do with Women Who are Going to Receive Limited Doses of Anthracyclines?

A past medical history of hypertension, diabetes, strong family history or personal history of cardiac disease, is of older age (greater than 65 years old) or has a low baseline LVEF (50-55%) merits consideration of substituting a non-anthracycline-based regimen. All the anthracycline-based chemotherapy regimens have corresponding non-anthracycline-based regimens. If a woman develops fatigue, shortness of breath, nocturnal dyspnea, or lower extremity edema during or after receiving limited-dose anthracyclines, perform a workup that includes the cardiorespiratory systems as clinically indicated. If significant decreases in LVEF or CHF occurs, then cardiology or cardio-oncology referral is indicated. We concur with recent Breast Cancer ASCO Survivorship Guidelines[1], and the recent ASCO Clinical Practice Guidelines on the Prevention and Monitoring of Cardiac Dysfunction in Adult Survivors[2]. No cardiac surveillance is medically warranted with the currently availability tools for predicting risk and monitoring cardiac function.

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