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

Natalie Berger¹, Charles L. Shapiro²*

¹Hematology/Oncology Fellowship Program, Icahn School of Medicine at Mount Sinai, New York, NY
²Division of Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY

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/m² (or epirubicin 300 mg/m²)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 disease3. In contrast, the European Society for Medical Oncology4, the Canadian Cardiovascular Society5, Italian Society of Cardiology and Working Group of Drug Cardiotoxicity and Cardioprotection6, the American Society of Echocardiography and European Association of Cardiovascular Imaging7, and others8,9 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\(^\text{10}\). 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\(^\text{10}\). 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\(^\text{11}\). 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\(^\text{12,13}\). 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>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Follow-up (yr)</th>
<th>Total Median Doxorubicin (mg/m(^2))</th>
<th>(\Delta) LVEF (%)</th>
<th>CHF (%)</th>
<th>Anthracyclines HR or OR(^\text{14}) (95% CI)</th>
<th>No Anthracyclines HR or OR(^\text{14}) (95% CI)</th>
<th>Cardiac Deaths (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prospective randomized trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shulman 2012 (14)</td>
<td>1107</td>
<td>5.3</td>
<td>240</td>
<td>NA</td>
<td>0.2</td>
<td>NA</td>
<td>NA</td>
<td>0.1</td>
</tr>
<tr>
<td>Advani 2016 (15)</td>
<td>664</td>
<td>6</td>
<td>240</td>
<td>-3</td>
<td>0.6</td>
<td>NA</td>
<td>NA</td>
<td>0.3</td>
</tr>
<tr>
<td>Case-Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thavendiranathan 2016 (17)</td>
<td>10,160</td>
<td>3</td>
<td>NA</td>
<td>NA</td>
<td>3.0</td>
<td>0.97 (0.73 to 1.27)</td>
<td>0.94 (0.41 to 2.20)</td>
<td>0.5</td>
</tr>
<tr>
<td>SEER Registry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doyle 2005(^\text{a}) (19)</td>
<td>5,571</td>
<td>5</td>
<td>NA</td>
<td>NA</td>
<td>3.0</td>
<td>2.8(^\text{b}) (1.25 to 1.52)</td>
<td>1.13(^\text{c}) (0.82 to 1.23)</td>
<td>NA</td>
</tr>
<tr>
<td>Pinder 2007(^\text{a}) (20)</td>
<td>8,083</td>
<td>10</td>
<td>NA</td>
<td>NA</td>
<td>3.0</td>
<td>1.26 (1.12 to 1.42)</td>
<td>0.90(^\text{d}) (0.86 to 0.99)</td>
<td>NA</td>
</tr>
<tr>
<td>Anthracyclines followed Trastuzumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prospective randomized trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advani 2016 (15)</td>
<td>710</td>
<td>6</td>
<td>240</td>
<td>-3</td>
<td>2.8(^\text{b})</td>
<td>NA</td>
<td>NA</td>
<td>0.1</td>
</tr>
<tr>
<td>Cameron 2017 (21)</td>
<td>1697</td>
<td>11</td>
<td>NA</td>
<td>NA</td>
<td>1.0(^\text{f})</td>
<td>NA</td>
<td>NA</td>
<td>0.2</td>
</tr>
<tr>
<td>Case-Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thavendiranathan 2016 (17)</td>
<td>3,250</td>
<td>3</td>
<td>NA</td>
<td>NA</td>
<td>4.2</td>
<td>3.96 (3.01 to 5.22)</td>
<td>0.81 (0.25 to 2.66)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**Abbreviations:** years (yr); left ventricular ejection fraction (LVEF); congestive heart failure (CHF); hazard ratio (HR); odds ratio (OR); not available (NA).\(^\text{a}\) Adjusted hazard or odds ratio.\(^\text{b}\)Women with early-stage breast cancer who received adjuvant non-anthracycline containing chemotherapy.\(^\text{c}\)Women with early-stage breast cancer who received no adjuvant chemotherapy.\(^\text{d}\)Sequentially or concurrently administered paclitaxel and trastuzumab.\(^\text{f}\)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. However, these are women who participated in randomized prospective trials, a group that is considered healthier than the general population.

An extensive retrospective case-control study from Ontario Canada compared over 10,000 women with breast cancer who received anthracyclines to over 92,000 healthy women without breast cancer. 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. 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).}

**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. 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. 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.

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. There are limited data to support the prognostic value of measuring GLS. However, The European Society of
Cardiac medications in asymptomatic women? 24 surrogate endpoints (i.e., with or without cardiac biomarkers or treatment of imaging will prevent CHF or cardiac deaths. Lack high-quality level I evidence that subsequent cardiac All of these recommendations are consensus-based and Likewise conflicting data use of BNP and N-terminal BNP32-34 as a predictive marker for CHF. Early indicator of cardiotoxicity did not predict for CHF31,32 therapies (trastuzumab or lapatinib), troponin I as an cancer receiving anthracyclines and HER2-targeted cataract 4-9, with or without cardiac biomarkers in asymptomatic women who received limited doses of anthracyclines4-9, and the recent ASCO Clinical Practice Guidelines on the Prevention and Monitoring of Cardiac Dysfunction in Adult Survivors. No cardiac surveillance is medically warranted with the currently availability tools for predicting risk and monitoring cardiac function.

Acknowledgements

CLS was responsible for conceptualization of article. NB was responsible for generating the first draft. CLS was responsible for multiple edits of first draft and creating Table 1. CLS and NB both read the final manuscript before submission.

References


