Current Oncology Reports (2018) 20: 61
https://doi.org/10.1007/s11912-018-0710-1

BREAST CANCER (B OVERMOYER, SECTION EDITOR)

Cardiac Toxicity from Breast Cancer Treatment: Can We Avoid This?

Jesse Caron[1] · Anju Nohria[1]

Published online: 6 June 2018

Abstract

Purpose of Review Breast cancer therapies, such as anthracyclines, trastuzumab, and chest irradiation, have well-established cardiotoxicities that lead to adverse outcomes. Here, we will review strategies to mitigate these cardiotoxicities.

Recent Findings Recent consensus guidelines have established criteria for the identification and surveillance of breast cancer patients at increased risk of cardiotoxicity. Dose reduction, liposomal doxorubicin, and dexrazoxane may be considered in high-risk patients receiving anthracyclines. Anthracycline-free regimens should be considered in high-risk patients with HER-2+ breast cancer, if appropriate. Data to support the routine use of concomitant neurohormonal blockade or statins to prevent anthracycline- and trastuzumab-induced cardiomyopathy is not yet available. Strategies that minimize radiation dose to the heart such as deep inspiration and intensity-modulated radiation are recommended to prevent radiation-induced cardiotoxicity.

Summary Identification of high-risk patients, aggressive management of underlying cardiovascular risk factors, consideration of cardioprotective strategies, and routine surveillance of left ventricular function before and after therapy are recommended to reduce breast cancer treatment-associated cardiotoxicities.

Keywords Breast cancer · Cardiotoxicity · Anthracyclines · Trastuzumab · Radiation · Prevention · Surveillance · Dose · Pegylated liposomal doxorubicin · Dexrazoxane · Neurohormonal antagonists · Statins · Exercise · Cardiovascular risk factors · Echocardiography · Biomarkers

Introduction

Due to recent advances in breast cancer treatment, mortality rates from breast cancer have decreased leading to a growing population of breast cancer survivors [1]. Currently, there are more than three million breast cancer survivors in the USA [2] and cardiovascular disease is the largest cause of death among breast cancer survivors > 65 years of age [1]. While much of this increased cardiovascular risk is attributable to age, obesity, diet, and a sedentary lifestyle that predispose to both cancer and cardiovascular diseases, certain cancer treatments can also lead to adverse cardiac side effects. This review will focus on the cardiotoxicity associated with anthracyclines, HER2 antagonists, and radiation, and will discuss strategies for prevention and screening that can help reduce the long-term cardiovascular morbidity and mortality associated with breast cancer treatment.

This article is part of the Topical Collection on *Breast Cancer*

✉ Anju Nohria
anohria@bwh.harvard.edu

Jesse Caron
jpcaron@bwh.harvard.edu

[1] Cardiovascular Division, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA

Treatment-Induced Cardiotoxicities in Breast Cancer

Cardiotoxic manifestations associated with breast cancer treatment include asymptomatic left ventricular (LV) dysfunction, congestive heart failure, pericarditis, myocardial ischemia, arterial hypertension, conduction abnormalities, atrial and ventricular arrhythmias, and thromboembolic disease (Table 1) [3•]. In this review, we will focus primarily on cardiomyopathy associated with anthracyclines and HER-2 antagonists and will also discuss the risk of coronary artery disease associated with radiation therapy.

Anthracyclines

Anthracyclines, such as doxorubicin and epirubicin, are commonly used to treat breast cancer and can lead to acute and late cardiac toxicity. Acute toxicity is most likely associated with

Table 1 Major cardiotoxicities associated with breast cancer therapy

Cancer therapy	Major cardiovascular toxicity
Anthracyclines	Cardiomyopathy
HER-2 antagonists	Cardiomyopathy
Radiation	Coronary artery disease
Cyclophosphamide	Hemorrhagic myocarditis
Taxanes	Bradycardia, ischemia
Fluoropyrimidines	Vasospasm and ischemia
Tamoxifen	Thromboembolism
Aromatase inhibitors	Hyperlipidemia, hypertension, ischemia
Cyclin dependent kinase 4/6 inhibitors	QTc prolongation

increased inflammation and can lead to a pericarditis-myocarditis syndrome that is usually reversible with drug discontinuation. Cardiomyopathy is the predominant form of anthracycline cardiotoxicity and can occur months to years after anthracycline exposure. A prospective study evaluating serial echocardiograms in breast cancer patients receiving adjuvant treatment with 4 cycles of doxorubicin, cyclosphosphamide, and docetaxel revealed new LV dysfunction in 9% of patients, with 98% of cases presenting within 1 year of anthracycline treatment [4]. Anthracycline cardiotoxicity is a dose-dependent toxicity that is characterized by myocyte cell death and can advance to progressive LV dysfunction and symptomatic heart failure. Proposed mechanisms for anthracycline cardiotoxicity include: (1) increased myocardial oxidative stress via redox-cycling of the quinone moiety of anthracyclines and through the formation of anthracycline-iron complexes; (2) disruption of cellular and mitochondrial calcium homeostasis; (3) disruption of mitochondrial energetics; (4) degradation of ultrastructural proteins including titin and dystrophin; (5) direct DNA damage via inhibition of topoisomerase 2β; 6) inhibition of pro-survival pathways such as neuregulin 1 and ErbB; and (7) direct cytotoxic effects on cardiac progenitor cells diminishing repair potential after myocardial injury [5].

HER-2 Antagonists

Approximately one fifth of all breast cancers overexpress the transmembrane tyrosine kinase receptor HER-2 and are marked by a relatively poor prognosis if treated nonspecifically [6]. Currently available HER-2 antagonists include trastuzumab, pertuzumab, trastuzumab-emtansine (T-DMI), and lapatinib, with trastuzumab being used most frequently [6]. In a meta-analysis involving 10,995 patients with early stage HER-2 positive breast cancer, adjuvant trastuzumab resulted in asymptomatic LV dysfunction in 13.3% and severe symptomatic heart failure in 1.9% of patients [7]. The risk of trastuzumab-induced cardiotoxicity is further increased in patients treated with anthracyclines, followed by trastuzumab [8]. Unlike anthracyclines, trastuzumab cardiotoxicity is not dose-dependent and is characterized by myocyte dysfunction rather than necrosis. It is often reversible with discontinuation of therapy and most patients tolerate re-introduction of trastuzumab once LV function recovers [9]. Trastuzumab exerts its cardiotoxic effects via inhibition of the ErbB2 receptor tyrosine kinase/HER-2 that is expressed in breast cancer cell and cardiac myocytes. ErbB2, together with its co-receptor ErbB4, appears to be involved in myocyte growth and survival signaling pathways. Neuregulin 1 binds ErbB4 and the neuregulin 1 signaling pathway is also altered by anthracyclines. This may explain the synergistic cardiotoxicity of anthracyclines and trastuzumab [10].

Radiation

Chest irradiation has well-documented cardiotoxic effects that include pericarditis, premature coronary artery disease, valvular heart disease, arrhythmias, and restrictive/constrictive cardiomyopathy with heart failure [11]. Radiation-induced pericarditis can present within days of radiation treatment, but most radiation-induced cardiotoxicity occurs several years after exposure. The risk of radiation-induced cardiotoxicity depends upon a combination of heart radiation volume, which substructures of the heart are subject to radiation, and the total proportion of the heart included in the radiation field. Darby et al. showed a dose-dependent increase in the incidence of coronary artery events in women treated with radiation for breast cancer. Every 1 Gy increase in mean heart radiation dose was associated with a 7.4% increase in the risk of major coronary events, with no apparent threshold [12]. This risk started within the first 5 years after radiation and continued for 30 years after exposure. In the nucleus, ionized radiation causes DNA breaks which in turn lead to aberrant DNA base pairs and epigenetic changes that result in cellular damage and cell death. Radiation also increases the formation of reactive oxygen species that activate NF-κB. NF-κB mediates a pro-survival and pro-inflammatory state that leads to impaired healing and endothelial dysfunction. These inadequately healed endothelial injuries accumulate and lead to intimal thickening and accelerated atherosclerosis [13].

Risk Factors for Cardiotoxicity (Table 2)

Both anthracyclines and radiation result in dose-dependent cardiotoxicity. Patients receiving high cumulative anthracycline doses (≥ 250 mg/m^2 doxorubicin or ≥ 600 mg/m^2 epirubicin), chest radiation ≥ 30 Gy where the heart is in the radiation field, and those receiving combination therapy with low-dose anthracyclines and low-dose chest radiation are at increased risk for developing cardiotoxicity [14•]. For patients receiving low-dose anthracyclines (< 250 mg/m2 or <

Table 2 Risk factors for cardiotoxicity

1.	High-dose anthracyclines: doxorubicin ≥ 250 mg/m^2 or epirubicin ≥ 600 mg/m^2
2.	High-dose chest radiation ≥ 30 Gy with the heart in the radiation field
3.	Low-dose anthracyclines + low-dose chest radiation with the heart in the radiation field
4.	Sequential treatment with low dose anthracyclines and trastuzumab
5.	Low dose anthracyclines or trastuzumab with any of the following:
	a. Age ≥ 60 years
	b. ≥ 2 cardiovascular risk factors (hypertension, hyperlipidemia, diabetes, smoking, obesity)
	c. Pre-existing cardiovascular disease (LVEF 50–55%, prior myocardial infarction, or ≥ moderate valvular heart disease)

LVEF left ventricular ejection fraction. Modified from Armenian et al. [14•]

600 mg/m^2 epirubicin) or any dose of trastuzumab, the risk of cardiotoxicity is increased with any of the following factors [1] age ≥ 60 years at the time of treatment; (2) ≥ 2 pre-existing cardiovascular risk factors (e.g., diabetes, hypertension, tobacco use, hyperlipidemia); and (3) pre-existing cardiovascular disease (e.g., prior myocardial infarction, left ventricular ejection fraction (LVEF) 50–55% before or during treatment, and ≥ moderate valvular disease) [14•]. Patients who receive sequential treatment with low-dose anthracycline followed by trastuzumab are also at increased risk of cardiotoxicity [14•].

Prevention of Anthracycline and Trastuzumab Cardiotoxicity

Adjusting Existing Treatments to Reduce Cardiotoxicity

Anthracycline Dose Reduction

The likelihood of anthracycline cardiotoxicity increases with increasing anthracycline dose. In an analysis of 630 patients enrolled in three phase III clinical trials (two with breast cancer and one with small cell lung carcinoma), 149 patients experienced a cardiac event defined as a decline in LVEF ≥ 20% from baseline, a decline in LVEF ≥ 10% from baseline to < 50%, or symptomatic congestive heart failure [15]. The cumulative percentage of patients with a cardiac event was 7% at a dose of 150 mg/m^2 increasing to 9, 18, 38, and 65% of patients at doses of 250, 350, 450, and 550 mg/m^2, respectively. Thirty-two of these patients experienced symptomatic congestive heart failure [15]. Therefore, minimizing anthracycline exposure, especially in high-risk patients, reduces the risk of cardiotoxicity.

Anthracycline Administration Schedules

Several studies have evaluated optimal ways to administer anthracyclines to minimize their cardiotoxic effects. Von Hoff et al. found that weekly administration of doxorubicin was associated with the lowest probability of congestive heart failure (.8%) compared to doxorubicin given three times per week every 3 weeks (2.4%) or administered as a single dose every 3 weeks (2.9%) [16]. Legha et al. evaluated endomyocardial biopsies from patients treated with anthracyclines administered as a bolus versus continuous infusion given over 48 or 96 h and found that continuous infusions were associated with lower peak serum levels and fewer changes on biopsy [17]. Likewise, a meta-analysis by Smith et al. found that the risk of asymptomatic and symptomatic LV dysfunction was increased 3.0-fold and 4.3-fold, respectively, when anthracyclines were administered as a bolus rather than a continuous infusion [18].

Anthracycline Analogs

Certain anthracycline formulations may be less cardiotoxic than others. Studies have suggested that epirubicin and mitoxantrone may be less cardiotoxic than doxorubicin [18]. However, these comparisons were based on small studies that were not systematically conducted. Pegylated liposomal doxorubicin has decreased cardiotoxicity than standard doxorubicin and may be used in patients who are at increased risk or require high doses of anthracycline therapy. In a meta-analysis, Smith et al. showed that liposomal doxorubicin was associated with a lower risk of asymptomatic (OR, 0.31, 95% CI 0.2 to 0.48) and symptomatic (OR 0.18, 95% CI 0.08 to 0.38) left ventricular dysfunction compared to standard doxorubicin [18]. Similar results were found in two other meta-analyses by Van Dalen et al. [19] and Rafiyath et al. [20]. Importantly, there were no differences in cancer-specific outcomes between pegylated liposomal doxorubicin and standard formulations.

Anthracycline-Free Regimens for HER-2+ Breast Cancer

The incidence of cardiotoxicity is increased when trastuzumab is used in combination with anthracyclines. The BCIRG-006 trial compared three chemotherapy regimens: doxorubicin, cyclophosphamide and docetaxel (ACT), ACT plus

trastuzumab (ACT-H), and docetaxel, carboplatin plus trastuzumab (TCH) for the treatment of HER-2 positive breast cancer [8]. In this trial, both trastuzumab-containing regimens (ACT-H and TCH) were superior to ACT and similar to each other in terms of cancer efficacy. Importantly, TCH was associated with significantly less asymptomatic cardiotoxicity (> 10% decline in EF 9.4 vs. 18.6%, $p < 0.001$) and a lower incidence of symptomatic heart failure (0.4 vs. 2%, $p < 0.001$) compared to ACT-H [8]. Therefore, in high-risk patients, avoidance of anthracycline-based regimens should be considered for the treatment of HER-2+ breast cancer, where appropriate.

Alternatives to Trastuzumab for HER-2+ Breast Cancer

Even though 1 year of adjuvant trastuzumab is associated with increased cardiotoxicity compared with a 6-month duration (OR 2.65, $p < 0.001$), 1 year of treatment is associated with significantly improved overall and disease-free survival in women with early stage HER-2+ breast cancer [21]. Therefore, premature discontinuation of trastuzumab therapy for LV dysfunction is associated with adverse cancer outcomes. Most patients recover LV function with interruption of trastuzumab and the majority tolerate re-introduction without a further decline in LVEF [9]. However, for those patients who do not recover LV function and need continued HER-2 blockade, less toxic, but equally efficacious, alternatives to trastuzumab should be considered. The recently published phase III MARIANNE trial compared taxane plus trastuzumab (TH) to trastuzumab-emtansine (T-DM1) alone or T-DM1 plus pertuzumab in patients with advanced HER-2+ breast cancer [22]. Both T-DM1-containing regimens were non-inferior to TH in terms of progression-free survival and were associated with a lower incidence of LV dysfunction (≥ 15% decline from baseline to < 50%): 0.8% with T-DM1 alone, 2.5% with T-DM1 plus pertuzumab, and 4.5% with TH [22]. Based on these results, T-DM1 might be a less cardiotoxic alternative for high-risk patients with advanced disease who need long-term treatment with trastuzumab.

Cardioprotective Therapies

Dexrazoxane

Dexrazoxane is an effective iron chelator that reduces oxygen free radical production when administered with anthracyclines. In two randomized clinical trials of advanced breast cancer patients treated with fluorouracil, doxorubicin, and cyclophosphamide, Swain and colleagues evaluated the incidence of cardiotoxicity with concomitant administration of dexrazoxane or placebo [15]. Patients who received dexrazoxane had a significantly decreased incidence of cardiac events (defined as a decline from baseline LVEF ≥ 20%, decline in LVEF ≥ 10% from baseline and < lower limit of normal, or symptomatic CHF) compared to placebo [15]. Furthermore, they showed that dexrazoxane was cardioprotective even when it was given after patients had already received 300 mg/m^2 of anthracyclines [23]. However, due to concerns regarding decreased tumor response rates, increased myelosuppression, and an increased incidence of the development of delayed hematologic malignancies, routine use of dexrazoxane is not recommended in patients receiving anthracycline therapy. A subsequent Cochrane meta-analysis has shown no difference in oncologic response rates or in the incidence of secondary malignancies between patients receiving chemotherapy with or without dexrazoxane [24]. Despite this, the FDA currently limits the use of dexrazoxane to women with metastatic breast cancer who need > 300 mg/m^2 of anthracyclines.

Neurohormonal Antagonists

Neurohormonal blockade with angiotensin converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARB) and beta-blockers has been shown to prevent progression of left ventricular remodeling and the development of symptoms in patients with asymptomatic left ventricular dysfunction secondary to a variety of etiologies (stage B heart failure) [25]. The efficacy of these agents as cardioprotective therapies in patients at risk for developing left ventricular dysfunction (stage A heart failure) is not known and has been extensively evaluated in patients receiving anthracyclines and trastuzumab. Several randomized clinical trials have evaluated the efficacy of neurohormonal blockade, administered concomitantly with chemotherapy, to reduce the incidence of cardiotoxicity. In the Prevention of Left Ventricular Dysfunction with Enalapril and Carvedilol in Patients Submitted to Intensive Chemotherapy for the Treatment of Malignant Hemopathies (OVERCOME) trial, 60 patients treated with high-dose anthracyclines for hematologic malignancies were randomized to combination therapy with enalapril and carvedilol or placebo, administered concomitantly with chemotherapy and continued for 6 months [26]. In this trial, there was a significant reduction in LVEF decline by echocardiography (0 vs. − 3.1%, $p = 0.035$), but not by magnetic resonance imaging (MRI) (0 vs. − 3.4%, $p = 0.09$) with neurohormonal blockade compared to placebo. Interestingly, neurohormonal blockade also reduced the combined endpoint of heart failure, death, or LVEF < 45% (6.7% vs. 22%, $p = 0.036$), which was driven primarily by a decline in overall mortality. The Prevention of Cardiac Dysfunction During Adjuvant Therapy (PRADA) trial employed a 2 × 2 factorial design in which 120 breast cancer patients treated with anthracyclines ± trastuzumab were randomized to either candesartan, metoprolol, the combination, or placebo [27]. In this study, candesartan, but not metoprolol, was associated

with a reduction in LVEF decline compared to placebo (− 0.8 vs. − 2.6%, $p = 0.026$). However, a subsequent trial evaluating the cardioprotective effects of candesartan in 206 patients with early HER-2+ breast cancer treated with anthracyclines and trastuzumab, failed to show a benefit with candesartan compared to placebo [28]. The Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research (MANTICORE) trial assessed the role of neurohormonal blockade in 94 HER2+ patients with early, invasive breast cancer treated with trastuzumab [29]. In this study, patients were randomized in a 1:1:1 ratio to bisoprolol, perindopril, or placebo for 1 year. Cardiac MRI was used to assess changes in LV remodeling over 24 months. While the study failed to show a difference in its primary end-point, there was a significant attenuation in LVEF decline with bisoprolol, but not perindopril, compared to placebo (− 1 vs. − 5%, $p = 0.001$). The recently published Carvedilol Effect in Preventing Chemotherapy-Induced Cardiotoxicity (CECCY) trial evaluated the effect of carvedilol compared to placebo in 192 women with HER-2+ breast cancer treated with anthracyclines [30]. In this trial, carvedilol failed to show an improvement in the primary endpoint of ≥ 10% reduction in LVEF at 6 months compared to placebo (14.5 vs. 13.5%, $p = 1.0$). Another recent trial evaluated the efficacy of either lisinopril or carvedilol compared to placebo in 468 women with HER-2+ breast cancer and stratified patients based on prior anthracycline therapy . The primary outcome, decrease in LVEF > 10% or decrease in EF ≥ 5% to < 50%, did not differ between treatment groups (30% with lisinopril vs. 29% with carvedilol group vs. 32% with placebo). Among those who received anthracyclines, lisinopril and carvedilol appeared to be cardioprotective compared to placebo (37 vs. 31 vs. 47%, $p = 0.009$) [31].

In summary, while several trials have suggested that concomitant treatment with neurohormonal antagonists may attenuate the decline in LVEF with anthracyclines, none have shown a significant decline in hard end-points of asymptomatic or symptomatic LV dysfunction. Small trial size may in large part be responsible for the lack of conclusive results and routine prescription of concomitant neurohormonal blockade cannot be recommended at this time. However, in high-risk patients neurohormonal blockade is often recommended in clinical practice to attenuate cardiotoxicity.

Statins

Pre-clinical studies have suggested that the anti-oxidant and anti-inflammatory properties of statins may render statins cardioprotective in patients treated with anthracyclines. Two retrospective studies evaluating breast cancer patients treated with statin therapy for other indications suggested that incidental statin therapy may be cardioprotective [32] [33]. A small randomized clinical trial of 40 patients treated with anthracyclines for a variety of cancers showed that concomitant treatment with atorvastatin 40 mg daily was associated with a smaller reduction in LVEF and a smaller increase in LV end-diastolic and end-systolic dimensions compared to placebo ($p < 0.0001$; $p = 0.021$; $p = 0.001$, respectively) [34]. Larger clinical trials evaluating the efficacy of statins as cardioprotectants are currently underway.

Prevention of Chest Radiation-Induced Cardiotoxicity

Although the cardiotoxic effects of high-dose chest irradiation are well noted, protocols for chest irradiation can be modified to minimize cardiotoxic effects. The American Society of Clinical Oncology (ASCO) guidelines recommend limiting radiation dose and selecting radiation fields that exclude as much of the heart as possible [14•]. If the heart must be in the radiation field, the myocardium must be shielded appropriately. They also recommend the use of intensity-modulated radiation therapy, a technique that averts radiation to normal tissues by altering radiation energy to accurately contour the optimal radiation distribution [14•]. Deep inspiration techniques have also been found to reduce radiation doses to the heart and neighboring tissues [14•]. Peterson et al. found that deep inspiration decreased the average heart dose by 1.4 Gy compared to free breathing [35]. These techniques are currently employed by most centers and due to the latency in cardiac side effects, existing data do not reflect the effects of these modifications in radiation protocols. A recent analysis compared mean radiation doses to the whole heart in the modern era (2010–2015) to those reported in patients treated between 1974 and 1989 [36]. They showed that the average dose to the whole heart had decreased from 6 to 4.4 Gy in the modern era, with a corresponding reduction in the relative risk of cardiac mortality from 1.3 to 1.16 compared to the general population.

Exercise to Prevent Long-Term Adverse Cardiovascular Outcomes

Observational studies have shown that post-diagnosis exercise reduces all-cause mortality in women with breast cancer [37]. However, it is not known whether exercise interventions specifically improve cardiovascular outcomes in these patients. A recent prospective study of 2973 women diagnosed with non-metastatic breast cancer correlated self-reported leisure time activity with cardiovascular outcomes after a median follow-up of 8.6 years [38]. The incidence of cardiovascular events decreased with increasing activity levels ($p < 0.001$). Importantly, women who followed the cancer exercise guidelines [39] and exercised ≥ 9 metabolic equivalent (MET) hours/week had a 23% reduction in cardiovascular events

compared to those who exercised < 9 MET hours/week ($p < 0.001$) [38]. Randomized clinical trials have shown that structured exercise training improves cardio-respiratory fitness, measured by peak oxygen consumption, in cancer survivors [40]. Whether this improvement in cardio-respiratory fitness translates to a decrease in cardiovascular events is not yet known. Regardless, breast cancer patients should be encouraged to exercise on a regular basis since exercise has proven benefits with regard to cancer-related fatigue, physical fitness, and quality of life [41].

Cardiac Surveillance During the Continuum of Breast Cancer Treatment

Until recently, there were no consensus guidelines regarding cardiac surveillance in breast cancer patients undergoing treatment with cardiotoxic therapies. Establishing guidelines is essential for identifying patients at increased risk, implementing strategies to reduce risk, and for the timely detection/treatment of asymptomatic LV dysfunction (stage B heart failure) (Fig. 1).

The 2017 ASCO guideline defined general criteria to identify cancer patients at elevated risk for cardiovascular events (Table 2) [14•]. Romond et al. proposed a cardiac risk scoring system that uses age and baseline LVEF to predict probability of cardiac death or heart failure [42]. Similarly, Ezaz et al. developed a seven-factor risk score that uses type of adjuvant therapy, age, pre-existing coronary artery disease, atrial fibrillation/flutter, diabetes, hypertension, and renal failure [43]. The use of a standardized method to assess cardiovascular risk in breast cancer patients allows physicians to make informed choices regarding cancer treatment and surveillance.

It is well established that patients with ≥ 2 cardiac risk factors of pre-existing cardiovascular disease are at increased risk of cardiotoxicity [44]. Therefore, routine assessment and modification of traditional cardiac risk factors is critical before, during, and after breast cancer therapy [14•].

In non-cardiac populations with asymptomatic LV dysfunction, the severity of decline in LVEF is the strongest predictor of progression from asymptomatic (stage B) to symptomatic (stage C) heart failure [45]. Early intervention with ACEi and beta-blockers can affectively reverse LV remodeling and prevent disease progression [25]. Therefore, the ASCO guidelines recommend a baseline assessment of LVEF in patients at increased risk of cardiotoxicity [14•]. While they do not dictate routine monitoring of LVEF during chemotherapy, they leave this to the discretion of the treating physician. A prospective longitudinal study in breast cancer patients treated with anthracyclines showed that 9% of patients developed cardiotoxicity, with 98% occurring within 1 year of treatment [4]. Based on this data, the ASCO guidelines recommend monitoring LVEF once between 6 and 12 months of completing therapy in asymptomatic, high-risk patients [14•].

Some have argued that detecting cardiotoxicity prior to an overt decline in LVEF, may allow early institution of protective strategies to prevent overt cardiotoxicity. Biomarkers including cardiac troponin I and echocardiography-derived strain imaging have shown diagnostic and prognostic promise in breast cancer patients exposed to anthracyclines [46] [47]. However, routine use of these biomarkers is currently not recommended due to unclear timing of assessment, inter-assay variability, unclear cutoff values, and limited information regarding their impact on long-term cardiac outcomes [14•].

Conclusion

Breast cancer treatments including anthracyclines, HER2 antagonists, and chest irradiation are associated with significant cardiotoxicity. Optimizing treatment to balance anti-cancer efficacy and cardiovascular safety is critical to achieve the best outcomes for breast cancer patients. The emerging field of cardio-oncology represents a sustained effort to reduce the risk of cardiovascular disease following a cancer diagnosis.

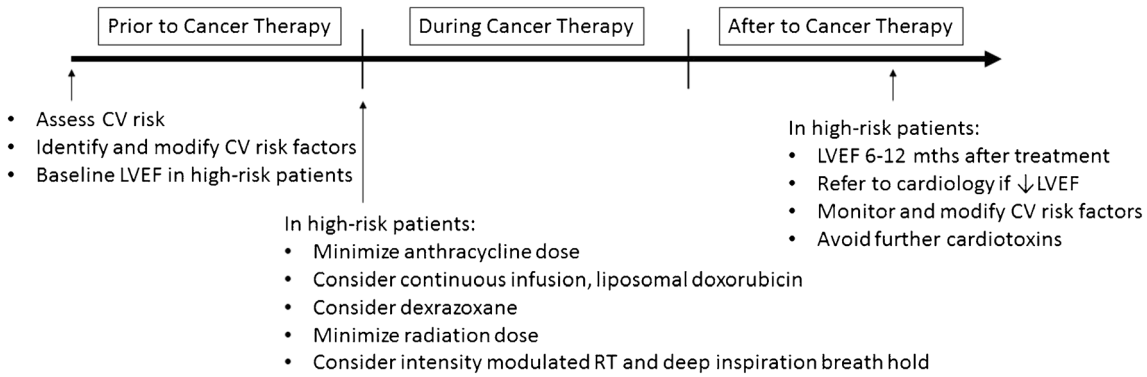

Fig. 1 Guidelines for the surveillance and prevention of cardiotoxicity in breast cancer patients

Identification of high-risk patients, aggressive management of their underlying cardiovascular risk factors, consideration of cardioprotective strategies, and routine surveillance of LV function before and after therapy are recommended by current consensus guidelines [14•]. Ongoing efforts utilizing genomic, proteomic, and metabolomic profiling will help identify markers that can be used to more accurately predict cardiovascular risk and minimize long-term side effects in the growing population of breast cancer survivors.

Compliance with Ethical Standards

Conflict of Interest Jesse Caron declares that he has no conflict of interest.

Anju Nohria has received research support from Amgen, and has received compensation from Takeda Oncology for her service as a consultant.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance

1. Patnaik JL, Byers T, DiGuiseppi C, Dabelea D, Denberg TD. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. Breast Cancer Res. 2011;13(3):R64.
2. Available from: https://www.cancer.org/cancer/breast-cancer/about/how-common-is-breast-cancer.html. Accessed on 3/15/2018.
3.• Mehta LS, Watson KE, Barac A, Beckie TM, Bittner V, Cruz-Flores S, et al. Cardiovascular disease and breast cancer: where these entities intersect: a scientific statement from the American Heart Association. Circulation. 2018;137(8):e30–66. **This article describes the common links between breast cancer and cardiovascular disease and discusses ways to address common risk factors and guidelines for surveillance and prevention of cardiotoxicity in breast cancer patients.**
4. Cardinale D, Colombo A, Bacchiani G, Tedeschi I, Meroni CA, Veglia F, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation. 2015;131(22):1981–8.
5. Geisberg CA, Sawyer DB. Mechanisms of anthracycline cardiotoxicity and strategies to decrease cardiac damage. Curr Hypertens Rep. 2010;12(6):404–10.
6. Fabi A, Malaguti P, Vari S, Cognetti F. First-line therapy in HER2 positive metastatic breast cancer: is the mosaic fully completed or are we missing additional pieces? J Exp Clin Cancer Res. 2016;35:104.
7. Bria E, Cuppone F, Fornier M, Nistico C, Carlini P, Milella M, et al. Cardiotoxicity and incidence of brain metastases after adjuvant trastuzumab for early breast cancer: the dark side of the moon? A meta-analysis of the randomized trials. Breast Cancer Res Treat. 2008;109(2):231–9.
8. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011;365(14):1273–83.
9. Yu AF, Yadav NU, Lung BY, Eaton AA, Thaler HT, Hudis CA, et al. Trastuzumab interruption and treatment-induced cardiotoxicity in early HER2-positive breast cancer. Breast Cancer Res Treat. 2015;149(2):489–95.
10. Hervent AS, De Keulenaer GW. Molecular mechanisms of cardiotoxicity induced by ErbB receptor inhibitor cancer therapeutics. Int J Mol Sci. 2012;13(10):12268–86.
11. Jacob S, Pathak A, Franck D, Latorzeff I, Jimenez G, Fondard O, et al. Early detection and prediction of cardiotoxicity after radiation therapy for breast cancer: the BACCARAT prospective cohort study. Radiat Oncol. 2016;11(54)
12. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Bronnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013;368(11):987–98.
13. Sylvester CB, Abe JI, Patel ZS, Grande-Allen KJ. Radiation-induced cardiovascular disease: mechanisms and importance of linear energy transfer. Front Cardiovasc Med. 2018;5:5.
14.• Armenian SH, Lacchetti C, Barac A, Carver J, Constine LS, Denduluri N, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol Off J Am Soc Clin Oncol. 2017;35(8):893–911. **This article describes the current consensus guidelines for the surveillance and prevention of cardiotoxicity in patients exposed to anthracyclines, trastuzumab, and radiation.**
15. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer. 2003;97(11):2869–79.
16. Von Hoff DD, Layard MW, Basa P, Davis HL Jr, Von Hoff AL, Rozencweig M, et al. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med. 1979;91(5):710–7.
17. Legha SS, Benjamin RS, Mackay B, Ewer M, Wallace S, Valdivieso M, et al. Reduction of doxorubicin cardiotoxicity by prolonged continuous intravenous infusion. Ann Intern Med. 1982;96(2):133–9.
18. Smith LA, Cornelius VR, Plummer CJ, Levitt G, Verrill M, Canney P, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. BMC Cancer. 2010;10:337.
19. van Dalen EC, van der Pal HJ, Kremer LC. Different dosage schedules for reducing cardiotoxicity in people with cancer receiving anthracycline chemotherapy. Cochrane Database Syst Rev. 2016;3:CD005008.
20. Rafiyath SM, Rasul M, Lee B, Wei G, Lamba G, Liu D. Comparison of safety and toxicity of liposomal doxorubicin vs. conventional anthracyclines: a meta-analysis. Exp Hematol Oncol. 2012;1(1):10.
21. Gyawali B, Niraula S. Duration of adjuvant trastuzumab in HER2 positive breast cancer: overall and disease free survival results from meta-analyses of randomized controlled trials. Cancer Treat Rev. 2017;60:18–23.
22. Perez EA, Barrios C, Eiermann W, Toi M, Im YH, Conte P, et al. Trastuzumab emtansine with or without pertuzumab versus trastuzumab plus taxane for human epidermal growth factor receptor 2-positive, advanced breast cancer: primary results from the phase III MARIANNE Study. J Clin Oncol Off J Am Soc Clin Oncol. 2017;35(2):141–8.
23. Swain SM, Whaley FS, Gerber MC, Ewer MS, Bianchine JR, Gams RA. Delayed administration of dexrazoxane provides cardioprotection for patients with advanced breast cancer treated with doxorubicin-containing therapy. J Clin Oncol Off J Am Soc Clin Oncol. 1997;15(4):1333–40.

24. Shaikh F, Dupuis LL, Alexander S, Gupta A, Mertens L, Nathan PC. Cardioprotection and second malignant neoplasms associated with dexrazoxane in children receiving anthracycline chemotherapy: a systematic review and meta-analysis. J Natl Cancer Inst. 2016;108(4).
25. al-Khadra AS, Konstam MA, Salem DN. Treatment of asymptomatic patients with left ventricular dysfunction. Compr Ther. 1994;20(4):257–62.
26. Bosch X, Rovira M, Sitges M, Domenech A, Ortiz-Perez JT, de Caralt TM, et al. Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: the OVERCOME trial (preventiOn of left ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies). J Am Coll Cardiol. 2013;61(23):2355–62.
27. Gulati G, Heck SL, Ree AH, Hoffmann P, Schulz-Menger J, Fagerland MW, et al. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 x 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. Eur Heart J. 2016;37(21):1671–80.
28. Boekhout AH, Gietema JA, Milojkovic Kerklaan B, van Werkhoven ED, Altena R, Honkoop A, et al. Angiotensin II-receptor inhibition with candesartan to prevent trastuzumab-related cardiotoxic effects in patients with early breast cancer: a randomized clinical trial. JAMA Oncol. 2016;2(8):1030–7.
29. Pituskin E, Mackey JR, Koshman S, Jassal D, Pitz M, Haykowsky MJ, et al. Multidisciplinary approach to novel therapies in cardio-oncology research (MANTICORE 101-breast): a randomized trial for the prevention of Trastuzumab-associated cardiotoxicity. J Clin Oncol Off J Am Soc Clin Oncol. 2017;35(8):870–7.
30. Avila MS, Ayub-Ferreira SM, de Barros Wanderley Junior MR, Cruz FDD, Goncalves Brandao SM, Carvalho Rigaud VO, et al. Carvedilol for prevention of chemotherapy related cardiotoxicity. J Am Coll Cardiol. 2018.
31. Guglin M. Lisinopril or carvedilol for prevention of trastuzumab induced cardiotoxicity—lisinopril or carvedilol for cardiotoxicity. 2018.
32. Seicean S, Seicean A, Plana JC, Budd GT, Marwick TH. Effect of statin therapy on the risk for incident heart failure in patients with breast cancer receiving anthracycline chemotherapy: an observational clinical cohort study. J Am Coll Cardiol. 2012;60(23):2384–90.
33. Chotenimitkhun R, D'Agostino R Jr, Lawrence JA, Hamilton CA, Jordan JH, Vasu S, et al. Chronic statin administration may attenuate early anthracycline-associated declines in left ventricular ejection function. Can J Cardiol. 2015;31(3):302–7.
34. Acar Z, Kale A, Turgut M, Demircan S, Durna K, Demir S, et al. Efficiency of atorvastatin in the protection of anthracycline-induced cardiomyopathy. J Am Coll Cardiol. 2011;58(9):988–9.
35. Petersen PM, Aznar MC, Berthelsen AK, Loft A, Schut DA, Maraldo M, et al. Prospective phase II trial of image-guided radiotherapy in Hodgkin lymphoma: benefit of deep inspiration breath-hold. Acta Oncol. 2015;54(1):60–6.
36. Taylor C, Correa C, Duane FK, Aznar MC, Anderson SJ, Bergh J, et al. Estimating the risks of breast cancer radiotherapy: evidence from modern radiation doses to the lungs and heart and from previous randomized trials. J Clin Oncol Off J Am Soc Clin Oncol. 2017;35(15):1641–9.
37. Lahart IM, Metsios GS, Nevill AM, Carmichael AR. Physical activity, risk of death and recurrence in breast cancer survivors: a systematic review and meta-analysis of epidemiological studies. Acta Oncol. 2015;54(5):635–54.
38. Jones LW, Habel LA, Weltzien E, Castillo A, Gupta D, Kroenke CH, et al. Exercise and risk of cardiovascular events in women with nonmetastatic breast cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2016;34(23):2743–9.
39. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc. 2010;42(7):1409–26.
40. Kampshoff CS, Chinapaw MJ, Brug J, Twisk JW, Schep G, Nijziel MR, et al. Randomized controlled trial of the effects of high intensity and low-to-moderate intensity exercise on physical fitness and fatigue in cancer survivors: results of the resistance and endurance exercise after ChemoTherapy (REACT) study. BMC Med. 2015;13:275.
41. Schmitz KH, Holtzman J, Courneya KS, Masse LC, Duval S, Kane R. Controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2005;14(7):1588–95.
42. Romond EH, Jeong JH, Rastogi P, Swain SM, Geyer CE Jr, Ewer MS, et al. Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2012;30(31):3792–9.
43. Ezaz G, Long JB, Gross CP, Chen J. Risk prediction model for heart failure and cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. J Am Heart Assoc. 2014;3(1):e000472.
44. Armenian SH, Xu L, Ky B, Sun C, Farol LT, Pal SK, et al. Cardiovascular disease among survivors of adult-onset cancer: a community-based retrospective cohort study. J Clin Oncol Off J Am Soc Clin Oncol. 2016;34(10):1122–30.
45. Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS. Natural history of asymptomatic left ventricular systolic dysfunction in the community. Circulation. 2003;108(8):977–82.
46. Cardinale D, Sandri MT, Colombo A, Colombo N, Boeri M, Lamantia G, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. Circulation. 2004;109(22):2749–54.
47. Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Cohen V, et al. Early detection and prediction of cardiotoxicity in chemotherapy-treated patients. Am J Cardiol. 2011;107(9):1375–80.