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Breast Cancer Survivorship and Cardiovascular Disease: Emerging Approaches in Cardio-Oncology

Yu Xie, MD¹, William J. Collins, MD², M. William Audeh, MD³, Stephen L. Shiao, MD, PhD⁴, Roberta A. Gottlieb, MD¹, Marc T. Goodman, PhD, MPH⁵, C. Noel Bairey Merz, MD¹, and Puja K. Mehta, MD^{1,*}

¹Cedars-Sinai Heart Institute, Barbra Streisand Women's Heart Center, 127 S. San Vicente Blvd, A3212, Los Angeles, CA, 90048, USA

²Inpatient Specialty Program, Cedars-Sinai Heart Institute, Barbra Streisand Women's Heart Center, Los Angeles, CA, USA

³Wasserman Breast Cancer Risk Reduction Program, Samuel Oschin Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA

⁴Department of Radiation Oncology, Cedars-Sinai Medical Center, Los Angeles, CA, USA

⁵Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA

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Introduction

Breast cancer is the most common non-skin cancer diagnosed in women living in the USA. During a woman's lifetime, the chance of having invasive breast cancer is approximately 1 in 8. There are nearly three million breast cancer survivors currently living in the USA. Five-year survival rates are as high as 99 % for localized breast cancer and 84 % for regional breast cancer [1]. A majority of patients are treated with either chemotherapy and/or radiation therapy after breast-conserving surgery or mastectomy. With cancer becoming curable or being treated as a chronic disease, cardiovascular disease (CVD) such as

* Puja.mehta@cshs.org.

Conflict of Interest

Yu Xie, William J. Collins, M. William Audeh, Stephen L. Shiao, and Marc T. Goodman declare that they have no competing interests. Roberta A. Gottlieb reports consulting from Takeda Pharmaceuticals and ONO Pharma USA and is a co-founder and SAB member of Tissue Netix, Inc. C. Noel Bairey Merz reports lectures from AACE, ACC-AZ chapter, Florida Hospital, Mayo Scottsdale, Mayo Cancun, Medscape, NAMS, Pri-Med, Scripps Clinic, VBWG, UCLA, UCSF, Northwestern Radcliffe Institute, Vox Media (speakers bureau), and Practice Point Communications (speaker bureau); consulting from Amgen, grant review committee from Gilead, consulting from Pfizer, grant review study section from NIH-SEP; grants from WISE CVD, RWISE, Microvascular, Normal Control, FAMRI; and consulting from Research Triangle Institute. Puja K. Mehta reports research support—Gilead, General Electric.

Compliance with Ethical Standards

Human and animal rights and informed consent

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hypertension, valvular heart disease, cardiomyopathy, and heart failure are of increasing concern. As survival time increases with more effective treatment, risk factors for CVD are now increasing in this aging population. Assessing CVD and minimizing complications from cancer therapy are important treatment goals, and several centers around the country now are providing specialty “cardio-oncology” clinics and programs to address CVD prevention and treatment in cancer. In this review, we discuss cardiovascular complications from breast cancer therapies and the monitoring and risk stratification of patients with a history of breast cancer therapy to prevent cardiovascular events.

CTRCD—definition and incidence

The 2014 American Society of Echocardiography’s (ASE) Expert Consensus defines cancer therapeutics-related cardiac dysfunction (CTRCD) as 10 % decrease in left ventricular ejection fraction (LVEF) to a LVEF $\leq$ 53 %, confirmed by repeated imaging 2–3 weeks apart [2]. The incidence of CTRCD has been previously reported to be 0–2.1 %, with rates highest in those receiving anthracycline-based regimens combined with a taxane [3]. A more recent analysis of a population-based, retrospective cohort study of 12,500 women diagnosed with invasive breast cancer demonstrated hazard ratios for heart failure and cardiomyopathy during treatment of 1.4 in patients on anthracycline alone, 4.1 in patients treated with trastuzumab alone, and 7.19 in patients treated with both agents as compared to patients who received no chemotherapy, suggesting a super-multiplicative risk of cardiotoxicity associated with the combined use of anthracycline and trastuzumab [4]. Furthermore, the women in this cohort who received anthracycline and/or trastuzumab treatment were generally younger and healthier than the remaining cohort and would have been expected to have a lower risk of CVD. This study was limited in that it used ICD-9 data to define its outcome of heart failure and cardiomyopathy.

Other studies have also suggested CTRCD rates may be higher. For example, an increase in troponin I, a measure of myocardial injury, can be seen in up to 32 % of patients after chemotherapy, and this increase is associated with decreased LVEF [5]. Elevation in troponin I carries important clinical consequences: in one study, patients who had received high-dose chemotherapy with a resulting elevation in troponin I were randomized to receive an angiotensin-converting enzyme inhibitor (ACE-I) or not. The primary end point of a 10 % decrease in LVEF was reached in 43 % of subjects who did not receive an ACE-I compared to 0 % of subjects who did [6].

A key reason for potential underestimation of CTRCD is a lag effect in which the incidence of cardiac disease increases with time after treatment may not be detectable for up to 5 years or more [4]. Furthermore, as these cancer survivors live longer and accumulate more traditional CVD risk factors, the contribution of cancer therapy to the cardiomyopathy may become difficult to distinguish from other factors.

There is also increasing recognition of a high rate of subclinical cardiac dysfunction among breast cancer patients. One study demonstrated that doxorubicin-induced subclinical cardiomyopathy affects approximately one in four patients [7]. This may put patients at increased risk for future cardiac events and may also contribute to the lag effect.

Chemotherapy agents and toxicity

CTRCD can be further classified based on symptoms (asymptomatic vs. symptomatic), degree of reversibility (as defined with respect to the nadir and baseline), and mechanism of cardiotoxicity.

Reversible CTRCD is defined by an improvement to within 5 percentage points of baseline LVEF. Partially reversible CTRCD is defined by improvement of 10 percentage points from the lowest LVEF value but still >5 percentage points below the baseline. Irreversible CTRCD is defined by improvement by <10 percentage points from the nadir and remaining >5 percentage points below the baseline [2].

The mechanism of cardiotoxicity and onset of cardiac dysfunction vary among different chemotherapy agents used in breast cancer. Therefore, these groups of agents will be discussed separately below.

Type I CTRCD: agents that directly cause cardiac damage

Anthracycline-induced cardiotoxicity associated with breast cancer therapy was first described in the 1960s and was recognized to be dose dependent [8]. Heart failure, especially systolic heart failure, was recognized as a major consequence of anthracycline-based therapy, and this led to a change to limit the dose of anthracycline agents [9]. Anthracyclines (doxorubicin, epirubicin, and idarubicin), as well as mitoxantrone (an anthracenedione antineoplastic agent), all cause a dose-dependent immediate toxicity to cardiomyocytes [10]. The incidence of cardiotoxicity increases with increasing doses of doxorubicin and epirubicin above 550 and 900 mg/m², respectively [11]. Cardinale et al. [12•] recently reported that in 2625 patients receiving anthracycline-based therapy, the incidence of cardiomyopathy was 9 % at a median follow-up of 5.2 years. Eleven percent of patients with cardiotoxicity in this cohort had full recovery, and 71 % had partial recovery with heart failure therapy, which was initiated when LVEF decreased >10 % or was <50 %. Anthracycline-induced cardiotoxicity was dose dependent, typically occurred within the first year, and also depended on the LVEF at the end of treatment.

Cardiomyocytes have a poor antioxidant defense system, making them more vulnerable to oxygen free radicals, which are thought to be the primary pathogenesis of type I CTRCD [13]. Oxygen free radicals [14] from doxorubicin semiquinone interaction with intracellular iron and from mitochondrial dysfunction [15] form peroxynitrite radicals after anthracycline induction of inducible nitric oxide synthase [16]. These free radicals contribute to mitochondrial dysfunction, activate matrix metalloproteinases [11], and lead to apoptosis [7]. Studies in mice demonstrated doxorubicin forms complexes with topoisomerase-II β and DNA in cardiac cells to induce deoxyribonucleic acid double strand breaks followed by transcriptional changes and cell death [17]. Consistent with this, electron microscopy of endomyocardial biopsies after anthracycline treatment demonstrates vacuolar swelling, mitochondrial swelling, and myofibrillar disarray [18]. Doxorubicin has also been shown to deplete c-kit⁺ cardiac progenitor cells in mice, resulting in microvascular disease and cardiac fibrosis in response to exercise [19].

Once these agents induce cellular damage that leads to myocyte apoptosis, the damage is thought to be irreversible. Therefore, agents causing type I CTRCD are associated with significant mortality and morbidity [20, 21].

Type II CTRCD: agents that indirectly cause cardiac damage

Type II chemotherapy agents have a more variable effect on cardiac function than type I agents, and often there is significant delay (up to years) from exposure to the time cardiac dysfunction that is detectable and/or clinically manifests (the lag effect).

Agents in this class, trastuzumab being the primary example, do not typically cause cellular damage when endomyocardial biopsies are examined under electron microscopy but do seem to have a cumulative dose-dependent effect, although the associated cardiac damage may be reversible [22]. Aside from trastuzumab, other type II agents include tyrosine kinase inhibitors (TKIs), such as bevacizumab, sunitinib, and sorafenib, that target vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor (VEGFR). TKIs affect a broad spectrum of kinases that play important roles in normal cardiac function. These agents are associated with severe hypertension, ischemic events, and impairment of ventricular contractility [23].

Isolating the morbidity associated with type II CTRCD agents can be difficult as they are often used simultaneously or serially with agents that cause type I CTRCD. For instance, Tan-Chiu et al. [24] analyzed data from 1664 patients with breast cancer who received doxorubicin and had a subsequently normal posttreatment LVEF, half of which were then randomized to receive trastuzumab as adjuvant therapy and the other half were not. Their results showed that the trastuzumab group had an increased incidence of CHF and other cardiac events (3.3 % absolute increase in events over 3 years). Whether this was an independent effect of trastuzumab or a consequence of its use in conjunction with an anthracycline is unclear.

Radiation therapy and toxicity

Radiation exposure is associated with increased risk of ischemic heart disease in patients with breast cancer in a dose-dependent manner with a lag time of up to 20 years [25••]. Radiation to the left breast is of particular concern given its anatomical proximity to the heart, and studies have shown increased incidence of perfusion defects, CAD diagnosis, and myocardial infarction in patients receiving left-sided compared to right-sided radiotherapy although no associated increase in cardiovascular-related mortality has been reported [26, 27]. Angiography studies have found that a dose-dependent relationship exists for the amount of radiation and volume of coronary arteries in the field with the proximal to the mid right coronary artery and mid to distal branches of the left anterior descending artery, most likely to be affected given their anterior anatomic location [28]. Many of the studies looking at the effects of RT on the heart examined retrospective data from older radiation techniques. Recent advances such as CT guidance of tangential radiation treatment and respiratory gating for left-sided breast cancer have allowed both the dose and duration of radiation to be reduced with several studies showing that the lower doses of RT do not appear to affect

cardiac function in the same manner as higher radiation doses, though the long-term effects of low-dose radiation remain uncertain [29].

Who is at risk?

Risk factors for anthracycline toxicity include history of prior radiation, total cumulative dose of chemotherapy (dose effect), higher single doses, and concomitant use of trastuzumab or taxol. Non-cancer-related traditional cardiovascular risk factors include age, sex, tobacco use, hypertension, diabetes, and chronic kidney disease. Some risk factors for breast cancer, for example, tobacco use, overlap with those for CVD. Thus, some women with breast cancer may already be at a higher CVD risk prior to exposure to cardiotoxic chemotherapy and chest wall radiation therapy than women without breast cancer [10]. Further, as survival time increases with more effective treatment, age-related risk factors for CVD rise in this population. One cohort study found CVD to be the primary cause of death in women age 66 or older with breast cancer, just above breast cancer itself (15.9 vs. 15.1 %) [30].

Screening and monitoring for cardiotoxicity

While a number of expert groups have proposed guidelines for screening and treatment of cardiotoxicity after breast cancer therapy, evidence-based guidelines are lacking [31••, 32]. The first step in screening and monitoring for cardiotoxicity is taking a complete history and physical exam and having an overall higher index of suspicion in these patients. When suspected, the two main modalities to detect and monitor cardiac dysfunction are endomyocardial biopsy and cardiac imaging. Although there is still a role for endomyocardial biopsy, it has been largely replaced by transthoracic echocardiogram (TTE) due to its non-invasive nature, wide availability, reproducibility, lower cost, lack of radiation, and ability to obtain functional data.

It is recommended that all patients should have a baseline screening TTE done prior to initiation of chemotherapy with agents known to cause CTRCD (grade IA from European Society for Medical Oncology (ESMO) guidelines) [31••]. This recommendation serves as a useful comparison for future studies [33, 34] and, even more importantly, identifies those with pre-existing compromised cardiac function so that their treatment regimen may be modified. Newer techniques to aid in identification of cardiotoxicity include the use of biomarkers [35•] and risk prediction models [36] to risk-stratify patients beginning chemotherapy, to allow for potential dose adjustments and preventative therapy. Aside from the measurement of serum troponin levels before and after each cycle of therapy, tools for the early detection of deleterious cardiac effects before a drop in LVEF is recognized (grade IIIB; Fig. 1) have yet to be integrated into standard care [31••].

Patients should have serial assessment of cardiac function with TTE during and after treatment. ESMO guidelines recommend assessment of cardiac function at baseline and at 3, 6, and 9 months during treatment as well as at 12 and 18 months after initiation of treatment (grade IA; Fig. 1). Thereafter, recommended monitoring with TTE is annual or biannual depending on the clinical indication [31••].

A TTE should include assessment of left ventricular ejection fraction (LVEF), wall motion, diastolic dysfunction, and strain. American Society of Echocardiography (ASE) and European Association of Echocardiography (EAE) both recommend calculating LVEF using the modified biplane Simpson's technique in combination with the wall motion score index [24, 37–39]. Early signs of cardiac dysfunction often manifest as diastolic dysfunction or strain. However, it is less clear whether chemotherapy should be adjusted based on subtle changes in diastolic function or strain. Furthermore, diastolic dysfunction is largely affected by volume status, which can fluctuate greatly in a cancer patient undergoing chemotherapy (nausea/vomiting, volume with chemo) [37].

There is now improved commercial software for monitoring early signs of cardiomyopathy. The ASE's Expert Consensus published in 2014 recommended acquiring and analyzing cardiac strain in apical, two-, three-, and four-chamber views over 3 cardiac cycles and analyzing for segmental and global strain [2, 40–42]. The normal range for left ventricular global longitudinal strain (GLS) is –15.9 to –22.1 % (mean –19.7 %; 95 % CI –20 to –18.9 %); global circumferential strain ranges from –20.9 to –27.8 % (mean –23.3 %, 95 % CI –24.6 to –22.1 %); and global radial strain ranges from 35.1 to 59.0 % (mean 47.3 %, 95 % CI 43.6 to 51.0 %) [43]. At this point, there is no consensus on how to manage patients who show changes in strain.

While TTE is the current mainstay for monitoring cardiotoxicity, cardiac magnetic resonance imaging (CMRI) is an emerging modality that can provide important information on cardiac dysfunction, early myocardial damage, and fibrosis, which can be missed on TTE, as evidenced in other disease states [44].

Prevention and treatment of cardiotoxicity

Exercise

The usual decline in cardiopulmonary reserve with aging is accelerated during chemotherapy. The disease and treatment burden has been shown to contribute to both weight gain [45] and decrease in physical activity [46, 47] in breast cancer patients, thus potentially raising CVD risk. In 5721 asymptomatic women who underwent baseline evaluation in the St. James Women Take Heart Project, exercise tolerance measured by metabolic equivalents on treadmill testing predicted a 17 % increase in Framingham Risk Score-adjusted mortality with each unit decline in MET level [48].

Several studies have shown exercise training in women with breast cancer improves cardiopulmonary function [49, 50]. Furthermore, a Cochrane review in 2012 showed benefit of a regular exercise program on quality of life in cancer patients [51].

Taken together, these reports underscore the importance of cardiovascular fitness to women with breast cancer. At every follow-up visit, clinicians should encourage breast cancer survivors to engage in an exercise routine. All breast cancer patients should aim for the recommended AHA physical activity level, which includes moderate-intensity aerobic or endurance physical activity for 30 min or more for 5 days each week or vigorous-intensity

aerobic physical activity for 20 min or more for 3 days a week among those aged 18 to 65 years of age [52].

Pharmacologic therapy

The main treatment goals of managing chemotherapy-induced cardiomyopathy have in general focused on the management of the associated heart failure with routine heart failure therapies used in non-cancer patients, though these agents have not been rigorously studied in cancer patients. The 2013 ACC/AHA heart failure guidelines recommend the use of ACE-I for patients with current or previous symptoms of HF and reduced LVEF, unless contraindicated. Angiotensin II receptor blockers (ARBs) can be used if there is ACE-I intolerance (class I recommendation, level A evidence). Beta-blockers (bisoprolol, carvedilol, or metoprolol succinate) are recommended for patients with current or previous symptoms of HF and reduced LVEF, unless contraindicated (class I recommendation, level A evidence). Loop diuretics are recommended for patients with reduced LVEF and volume overload (class I recommendation, level C evidence). Aldosterone antagonists are recommended for all patients with NYHA FC II–IV and LVEF $\geq 35\%$, unless contraindicated. Patients with NYHA FC II should have a prior history of hospitalization or elevated BNP to be placed on an aldosterone antagonist. All patients should have close monitoring of their potassium and renal function (class I recommendation, level A evidence). Hydralazine with isosorbide dinitrate is recommended for African-American patients with NYHA FC III–IV and reduced LVEF, unless contraindicated (class I recommendation, level A evidence). Hydralazine with isosorbide dinitrate is recommended for patients who are intolerant of ACE-I or ARBs (class I recommendation, level B evidence). Digoxin can be helpful in patients with decreased LVEF to reduce HF-related hospitalization (class I recommendation, level B evidence) [53].

The 2013 ACC/AHA heart failure guidelines also recommend implantable cardioverter-defibrillator (ICD) therapy for primary prevention of sudden cardiac death in patients with non-ischemic cardiomyopathy who have an LVEF $\geq 35\%$, have a NYHA functional class II or III, on goal-directed medical therapy, and have life expectancy of greater than 1 year (class I recommendation, level A evidence). Cardiac resynchronization therapy (CRT) is recommended in patients with LVEF $\geq 35\%$, sinus rhythm, left bundle branch block (LBBB) with a QRS ≥ 150 ms, and NYHA functional class II, III, or ambulatory class IV symptoms, on goal-directed medical therapy (class I recommendation, level A evidence for NYHA FC III/IV; class I recommendation, level B evidence, NYHA FC II). This has been significantly updated since the 2005 ACC/AHA guideline [53, 54].

Given these guidelines are not specifically for cancer treatment-related cardiomyopathy, further studies are warranted. Several randomized controlled trials of standard heart failure pharmacotherapies in breast cancer have been proposed [55, 56].

ACE-I/ARB

In a study of 114 women who had elevated troponin I after chemotherapy randomized to receive enalapril vs. no enalapril, no one in the enalapril group had a $>10\%$ decline in LVEF compared to 43 % of placebo-controlled patients [6].

An ACE-I or ARB should be prescribed per ACC/AHA [54] and ESC [57] heart failure guidelines for those with signs of heart failure after breast cancer chemotherapy. It may be reasonable to consider starting ACEi-I/ARB prophylactically if the risk of cardiotoxicity is felt to be increased in a select patient although clinical trials are needed to establish efficacy. Specifically, ESMO guidelines recommend starting enalapril for 1 year for any patient with elevated troponin during treatment (Fig. 1) [31••]. Emerging data in acute coronary syndrome populations suggest that a lower high-sensitive troponin cutoffs may need to be applied to women as compared to men [58–60].

Beta-blockers

Carvedilol blocks beta-1, beta-2, and alpha-1-adrenoceptors and has antioxidant and anti-apoptotic properties [61, 62]. In animal models, carvedilol has been shown to decrease free radical release and apoptosis [63–65]. In a trial of 50 cancer subjects (34 of which had breast cancer) with normal EF by TTE randomized to placebo vs. carvedilol 12.5 mg orally daily for 6 months prior to starting six rounds of anthracycline chemotherapy, 24 % ($n=5$) of patients in the control group had LVEF ≤ 50 % at the end of the 6-month follow-up period vs. 4 % ($n=1$) in the carvedilol group. Both systolic and diastolic diameters were significantly increased compared with basal measures in the control group. In this small study, there was a trend towards a therapeutic benefit of carvedilol to prevent anthracycline-induced cardiomyopathy, though it must be noted that the control group had significantly lower mean EF at the outset (68.9 vs. 52.3; $p<0.001$) [66].

The same study group has also shown protective effects of traditional heart failure therapies nebivolol [67] and spironolactone [68] in anthracycline-induced cardiomyopathy in small randomized clinical trials.

Traditional risk factors: hypertension, hyperlipidemia, diabetes mellitus, smoking

CVD risk factor reduction with appropriate control of blood pressure, cholesterol, and blood glucose as well as cessation of smoking is recommended in all patients for primary prevention of CVD [69]. Statin use may have a particularly important role in prevention of LVEF decline [70] and is recommended in all patients without a contraindication. Statins may have an antioxidant effect outside of cholesterol lowering that may prevent cardiac damage from chemotherapy [71], and several studies show a benefit of statins with respect to cancer survival and all-cause mortality [72]. Statin is particularly relevant for prevention of anthracycline-induced cardiotoxicity, as it inhibits Rac1 which mediates ROS formation caused by the topoisomerase-2 β -DNA complex, as discussed above [73]. In vitro studies have shown that lovastatin downregulates Rac1 signaling, leading to reduced topoisomerase 2-mediated cell damage [74], and that pitavastatin attenuates DNA damage and p53 accumulation in cardiomyocytes caused by anthracyclines [75]. In a small observational study, breast cancer patients treated with anthracyclines experienced a reduced risk of heart failure and cardiac-related mortality if they used statins [76•]. Investigators from the only published trial examining the prophylactic use of statins in patients with anthracycline-treated hematologic malignancies reported that 40 mg/day atorvastatin administered before chemotherapy and continued for 6 months protected against reduced ejection fraction [71].

Discontinuation of cancer therapy

In addition to dose limits for anthracycline therapy as previously discussed [11], algorithms have also been proposed by the ESMO Clinical Practice Guideline for when to hold or discontinue treatment with trastuzumab based on serial LVEF measures [31••]. Decisions to modify or stop cancer therapy should be arrived at jointly by the patient, the oncologist, and the cardiologist.

Knowledge gaps

There remain many unanswered questions for further investigation. In women with cardiac risk factors who require chemotherapy, does pre-treatment with known, effective therapies for CHF such as beta-blockers or ACE-I reduce the risk of myocardial dysfunction from chemotherapy? Is coronary microvascular dysfunction, without overt obstructive coronary atherosclerosis, a long-term consequence of combination chemotherapy and radiation in women? In young women undergoing left breast radiation, would treatment with aspirin and/or a statin be beneficial in the long-term? Is CMRI a better modality for early detection and specific management of toxicity?

Conclusion

It is now well recognized that standard therapies for breast cancer including anthracyclines, trastuzumab, and radiation therapy put patients at increased risk for future cardiac events. It is thus imperative that these patients undergo baseline screening as well as serial follow-up, generally with TTE, to ensure timely diagnosis of heart disease. Standard heart failure therapies such as beta-blockers, ACE-I, and ARB appear to have similar therapeutic effects in patients with heart failure secondary to therapy for breast cancer, though large randomized control trials have yet to be completed. Risk factor modification is beneficial in CVD prevention and should be addressed at baseline and at follow-up visits in patients with a history of breast cancer. Future opportunities include work to standardize a specialized and multidisciplinary approach to screening and treatment. Registries to better understand the true incidence of cardiovascular disease and the utility of current treatments would be invaluable for this growing population of breast cancer survivors.

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This is a retrospective case-control study showing potential protective effect of continuous statin use through anthracycline therapy.

Opinion statement

Cardiovascular disease (CVD) and breast cancer cause substantial morbidity and mortality in women and are major public health concerns in the USA. While aggressive screening and targeted, advanced treatment for breast cancer have had a measurable impact on breast cancer survival, treatment is not without significant cardiotoxic effects. Anthracycline-based chemotherapy can lead to left ventricular dysfunction and failure, as well as a decline in exercise tolerance and cardio-pulmonary reserve despite preserved ejection fraction. Trastuzumab, a newer monoclonal antibody targeting the Her2 receptor used in the treatment of Her2+ cancer, is also linked to left ventricular dysfunction, although the long-term cardiac effects are presently unclear. Radiation treatment particularly for left-sided breast cancer has been associated with increased rates of ischemic heart disease. As women have increasing survival and cure rates from early breast cancer, long-term consequences on the heart that are secondary to therapy are a major concern. These need to be identified, treated, and avoided when possible. Further research and clear surveillance guidelines are needed to aid the practicing clinician in CVD prevention in breast cancer survivors.

Fig. 1.

Algorithm for the management of cardiotoxicity in patients receiving anthracyclines.

Adapted with permission from Curigliano G. et al. [31••]. *ECHO* echocardiogram, *CTh* chemotherapy, *TnI* troponin I, *LVD* left ventricular dysfunction.