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Cardio-oncology (MG Fradley, Section Editor)

Cardiotoxicity of Contemporary Breast Cancer Treatments

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Opinion statement

Treatment-related cardiotoxicity remains a significant concern for breast cancer patients undergoing cancer treatment and extends into the survivorship period, with adverse cardiovascular (CV) outcomes further compounded by the presence of pre-existing CV disease or traditional CV risk factors. Awareness of the cardiotoxicity profiles of contemporary breast cancer treatments and optimization of CV risk factors are crucial in mitigating cardiotoxicity risk. Assessment of patient- and treatment-specific risk with appropriate CV surveillance is another key component of care. Mismatch between baseline cardiotoxicity risk and intensity of cardiotoxicity surveillance can lead to unnecessary downstream testing, increased healthcare expenditure, and interruption or discontinuation of potentially life-saving treatment. Efforts to identify early imaging and/or circulating biomarkers of cardiotoxicity and develop effective management strategies are needed to optimize the CV and cancer outcomes of breast cancer survivors.

Introduction

Breast cancer is the most common cancer diagnosis and cause of cancer death among females worldwide [1], but advances in breast cancer care have led to a growing population of survivors with an estimated ~3 million breast cancer survivors in the USA [2•]. Breast cancer and cardiovascular disease (CVD) share many common risk factors such as age, obesity, and tobacco use, and breast cancer outcomes can be affected by the presence of pre-existing CVD or other cardiovascular (CV)

comorbidities [2•, 3, 4]. Furthermore, current breast cancer treatment options are associated with CV toxicities that can offset expected therapeutic benefits, disrupt the cancer treatment course, and adversely affect quality of life.

The goal of this review is to provide an update on the CV toxicities associated with contemporary breast cancer treatment.

Anthracyclines

Anthracyclines are one of the most widely used chemotherapeutic agents for the treatment of breast cancer [5]. Chronic progressive dose-dependent cardiomyopathy is the characteristic presentation of anthracycline-induced cardiotoxicity. Inhibition of topoisomerase-2β is a key mediator between interrelated pathways of injury that lead to oxidative stress, mitochondrial dysfunction, and cardiomyocyte apoptosis [6, 7]. An analysis of three studies comprised mostly of breast cancer patients showed a 5% incidence of symptomatic heart failure (HF) at a cumulative doxorubicin dose of 400 mg/m^2, increasing to 48% at 700 mg/m^2 [8]. A surveillance study on anthracycline-induced cardiotoxicity in 2625 patients (51% with breast cancer) demonstrated a median time to onset of 3.5 months after completion of anthracyclines, with almost all cases occurring within 1 year after treatment completion, at an estimated 9% increased risk per 50 mg/m^2 increment of doxorubicin [9•].

Cumulative anthracycline dose is a well-recognized risk factor for development of cardiotoxicity. Based on a recent guideline from the American Society of Clinical Oncology (ASCO), "high dose" is regarded as a cumulative dose of doxorubicin ≥ 250 mg/m^2 or epirubicin ≥ 600 mg/m^2 [10••]. In the adjuvant setting, anthracycline doses are typically below this threshold, and a significant decline of left ventricular ejection fraction (LVEF) or HF can occur in ~ 9–10% and ~ 0.6–1.3% of patients, respectively [9•, 11, 12]. Other risk factors include older age, CV comorbidities (particularly hypertension), and exposure to chest radiation therapy (RT) or other sequential cardiotoxic therapies [8, 10••, 11, 13]. Strategies to mitigate anthracycline-induced cardiotoxicity including continuous versus bolus administration, liposomal formulation of doxorubicin, and cardioprotective agents such as dexrazoxane can reduce the risk of cardiotoxicity and should be considered in patients with metastatic breast cancer requiring high doses of anthracyclines [10••]. Dexrazoxane, which chelates iron and prevents free radical generation, afforded about a 65–80% lower risk of LV dysfunction among patients receiving high doses of anthracyclines with no clear effect on treatment efficacy [14, 15].

Targeted therapies

Anti-HER2 agents

It is estimated that ~ 20–25% of all breast cancers amplify or overexpress human epidermal growth factor 2 (HER2 or ErbB2), a transmembrane tyrosine kinase receptor, conferring a poor prognosis [13]. Anti-HER2

agents have significantly improved the course and survival of patients with early or advanced HER2-positive breast cancer and formed the cornerstone of therapy. Trastuzumab was the first anti-HER2 agent approved for use in this treatment setting, and several additional targeted therapies have since been developed.

Trastuzumab

Cardiotoxicity with trastuzumab was first recognized in patients with metastatic breast cancer undergoing concurrent treatment with anthracyclines [13]. Trastuzumab is a humanized monoclonal antibody that binds to the extracellular domain IV of HER2. The mechanism of cardiotoxicity is thought to be due to interference of the cardioprotective effects of neuregulin-1/HER downstream signaling, with increased susceptibility of cardiomyocytes especially after anthracycline exposure [16]. In randomized controlled trials where trastuzumab is administered sequentially after anthracyclines, corresponding rates of LVEF decline and HF range between 4.4–18.6% and 0.8–4.1%, respectively [11, 12, 17, 18]. Retrospective claims-based studies show significantly higher rates of cardiotoxicity, up to 32–42%, among patients receiving trastuzumab with or without anthracyclines [19, 20]. This discrepancy between clinical trials versus real-world data could stem from differences in patient characteristics and/or overestimation of CV endpoints with claims-based data. The incidence of asymptomatic LV dysfunction and HF with non-anthracycline trastuzumab-based regimens is lower (3.2–9.4% and 0.4–0.5%, respectively) [18, 21•].

Cardiac dysfunction most commonly occurs within 2 years of treatment initiation [11, 17], but increased long-term HF or cardiomyopathy risk and persistent subclinical changes have also been demonstrated [18, 20, 22, 23]. Banke et al. showed that compared with chemotherapy alone, the combination of chemotherapy with trastuzumab for adjuvant treatment was associated with a twofold increased risk of late-onset HF [23]. Importantly, treatment interruption occurs in 15–20% of patients due to cardiotoxicity [11, 24]. In contrast to anthracyclines, partial to complete LVEF recovery is common and can be seen in up to 80% of patients by 6–7 months with treatment interruption, spontaneously or with medical treatment [24–26], and some patients are able to tolerate rechallenge with trastuzumab [24]. In addition to anthracycline exposure, other risk factors include older age, concomitant CV risk factors and comorbidities, and lower baseline LVEF [11, 12, 27]. There have been efforts to develop risk prediction models for trastuzumab cardiotoxicity; however, additional studies are needed to validate these models in larger populations and to demonstrate that use of these prediction models can improve CV outcomes before they can be translated into clinical practice [11, 27].

Pertuzumab

Pertuzumab binds to the extracellular domain II of HER2 and complements the activity of trastuzumab by blocking HER2 dimerization, and it is used in the neoadjuvant, adjuvant, and metastatic settings [28–31]. Long-term follow-up studies demonstrate that addition of pertuzumab

to trastuzumab does not increase the risk of cardiotoxicity beyond the risk associated with single-agent trastuzumab combined with standard chemotherapy [28–31].

Ado-trastuzumab emtansine

Ado-trastuzumab emtansine (T-DM1) is a conjugate of trastuzumab with a cytotoxic microtubule inhibitor that enables intracellular drug delivery to HER2-overexpressing cells, minimizing effects on normal tissue [32]. It is approved in the metastatic setting for patients who have progressed after prior treatment with trastuzumab and more recently has shown benefit in the early-stage setting among patients with residual disease after neoadjuvant therapy with a taxane and trastuzumab [32, 33]. In a phase III trial of T-DM1 for early breast cancer, only one (0.1%) cardiac event (severe HF or cardiac death) has been reported after a median follow-up of 40 months [33].

Anti-HER2 tyrosine kinase inhibitors

Lapatinib is an oral reversible small-molecule tyrosine kinase inhibitor (TKI) against epidermal growth factor receptor (EGFR), HER1, and HER2 and is approved for use in combination with capecitabine or letrozole in patients with progressive metastatic HER2-positive breast cancer [34]. A pooled analysis of phase I–III trials of 3689 patients showed an incidence of cardiac events of 1.6% (1.4% asymptomatic, 0.2% symptomatic) occurring at a mean of 13 weeks, with an average absolute LVEF decline of 18.8% from baseline, and partial or full recovery by 7.6 weeks in the majority of patients [35]. Trials in treatment-naïve [36, 37] and pretreated [38–40] early and advanced breast cancer patients demonstrate a low incidence of cardiac events ($<5\%$ overall, $\sim 1\%$ severe) and no intensification of cardiotoxicity when used in combination with other therapies [35]. Lapatinib has also been associated with rare arrhythmias and QTc prolongation to >500 ms in about 6% of patients, although no cases of torsades de pointes have been reported [41].

Neratinib is an oral irreversible small-molecule TKI that binds to and inhibits HER1, HER2, and HER4 and that received FDA approval in 2017 for extended adjuvant therapy of HER2-positive early-stage breast cancer after 1 year of trastuzumab [42–44]. Two trials in early and advanced HER2-positive breast cancer did not show evidence of early neratinib-related cardiotoxicity, although these trials enrolled low-risk patients with no significant cardiac comorbidities [42, 43].

Cyclin-dependent kinase 4/6 inhibitors

Cyclin-dependent kinase (CDK) 4/6 inhibitors such as abemaciclib, palbociclib, and ribociclib are used in conjunction with endocrine therapy (aromatase inhibitors (AIs) or fulvestrant) in patients with hormone receptor–positive, HER2-negative advanced breast cancer. They inhibit tumor growth by regulating the retinoblastoma pathway, causing cell cycle arrest [45]. A meta-analysis of phase II and phase III studies demonstrated a 3.5-fold increased risk of venous thromboembolism when

CDK 4/6 inhibitors were added to endocrine therapy [46]. In addition, a phase I study of ribociclib demonstrated dose-dependent QTc prolongation starting at 600 mg/day [45]. The product label for ribociclib recommends periodic QTc monitoring at baseline, at day 14, at the beginning of cycle 2 (day 28), and thereafter as clinically indicated, with dose reduction and/or interruption for QTc prolongation [47].

Endocrine therapy

Endocrine therapy with tamoxifen or third-generation AIs such as anastrozole, letrozole, and exemestane is recommended as long-term adjuvant therapy in early disease or as first-line therapy in advanced disease in women with hormone receptor–positive disease [48]. Tamoxifen is a selective estrogen receptor modulator that affects downstream estrogen signaling, while AIs interfere with endogenous estrogen production in adipose tissue. Although AIs have shown superior disease benefit over tamoxifen, there is concern that they carry a greater CV risk. A meta-analysis of RCTs estimates a 19% increased risk for CV events with AIs compared with tamoxifen, although AIs were not associated with an increased risk compared with placebo [49]. These findings suggest that the increased CV risk attributed to AIs is driven by the cardioprotective benefit of tamoxifen rather than harm associated with AIs [49]. Tamoxifen has been associated with favorable lipid changes, while AIs with unchanged or unfavorable lipid parameters [50, 51]. Incident hypertension of up to 13% [52] and evidence of significant vascular dysfunction [53] were more common with AIs. On the other hand, increased thrombogenicity has been demonstrated with tamoxifen—almost a two-fold increased risk and up to 5% rate of venous thromboembolism [51, 52]. Questions regarding the clinical implications of these cardiometabolic changes remain, as CV deaths remain unchanged and an improved overall survival has been demonstrated with AIs over tamoxifen [51, 54].

Radiation-induced ischemic heart disease

Incidental radiation of cardiac structures during breast cancer therapy creates an inflammatory and profibrotic environment that can lead to endothelial dysfunction, accelerated atherosclerosis, and myocardial fibrosis, which can manifest clinically as coronary artery disease or cardiomyopathy [55]. Survivors have a 2 to 5.9 times increased risk of radiation-induced heart disease (RIHD), augmented by factors such as younger age at exposure and treatment with other cardiotoxic therapies, CVD, and CV risk factors [56]. Darby et al. [57] demonstrated a 7.4% increased risk of major coronary events per Gy of mean heart dose (MHD), beginning within the first few years after radiation exposure and continuing after 20 years. Patients receiving left-sided versus right-sided RT have a 29% and 22% increased risk for coronary heart disease and cardiac death, respectively [58]. The left ventricular apex and left anterior descending coronary artery segments are particularly vulnerable to higher doses of radiation exposure given their proximity to the anterior chest wall [59–

61]; thus, parameters other than MHD such as left ventricular volumes receiving 5 Gy have been studied, though further validation is required [62].

Contemporary RT techniques aimed at minimizing cardiac exposure such as CT-based simulation, prone imaging, respiratory gating, heart blocks, intensity-modulated radiation therapy, and volumetric modulated arc therapy have substantially reduced the radiation dose to the heart [63]. Impact of further reduction in MHD remains unknown, given the long latency period between radiation exposure and clinical CV events. Proton therapy is an alternative radiation technique that further minimizes radiation dose to the heart beyond what is achievable with conventional photon-based radiation techniques. The RADCOMP trial (NCT02603341) is a randomized trial that will compare 10-year CV outcomes among patients undergoing proton versus photon RT.

Prevention, detection, and management of cardiotoxicity

Pre-treatment evaluation of CVD risk is recommended prior to initiation of cardiotoxic cancer treatment. This includes a comprehensive history, physical examination, and baseline LVEF assessment. Screening and active management of pre-existing CVD and/or CV risk factors according to society guidelines are recommended throughout the treatment duration [10••].

Primary prevention

Several studies have evaluated the efficacy of prophylactic renin-angiotensin system–blocking and beta-blocking agents to prevent LV systolic dysfunction associated with adjuvant anthracycline and/or trastuzumab therapy in patients with early breast cancer (Table 1). The PRADA trial [64] randomized patients receiving an epirubicin-based regimen to candesartan, metoprolol succinate, or placebo. Those on candesartan, but not metoprolol, had a small yet significant attenuation of LVEF decline as measured by cardiac magnetic resonance imaging (CMR). Of note, only 22% of patients in the PRADA trial were treated with a high-risk regimen of anthracyclines plus trastuzumab. The CECCY trial randomized a homogenous cohort of HER2-negative patients scheduled to start ACT (anthracycline, cyclophosphamide, and taxane; cumulative doxorubicin dose 240 mg/m^2) to carvedilol or placebo [65]. There was no difference in LVEF reduction among those on carvedilol versus placebo, although fewer patients developed diastolic dysfunction and troponin (Tn) elevation. In the MANTICORE study, a modest but significant attenuation in LVEF decline was noted with bisoprolol versus perindopril or placebo among patients receiving trastuzumab, although there was no difference in the primary endpoint of cardiac remodeling between the treatment groups. Notably, treatment interruption due to cardiac dysfunction was more common in the placebo group [67]. Among patients treated with anthracyclines followed by trastuzumab, a study by Boekhout et al. [66] did not demonstrate any cardioprotective benefit with candesartan, although a limitation of this study was that candesartan was not initiated until after completion of the anthracycline course. However, recent findings by Guglin et al. show that lisinopril and carvedilol are effective for preventing LVEF decline in a subset of breast cancer patients treated with

Table 1. Primary prevention trials during breast cancer treatment

Trial, *N*	Treatment	Study design	Primary outcome results	Comments
PRADA [64], *N* = 120	100% epirubicin 22.2% T 65.1% RT	1:1:1:1 randomization to candesartan, metoprolol, candesartan and metoprolol, or placebo	FU: 10–61 weeks Decline in LVEF (by CMR) from baseline to FU of – 0.8% with candesartan vs. – 2.6% with placebo; no significant difference in LVEF decline with metoprolol vs. placebo	No significant effect of candesartan or metoprolol on hsTnI (level of detection 1.2 ng/L)
CECCY [65], *N* = 192	100% ACT (Dox cumulative dose 240 mg/m^2) No T or RT	1:1 randomization to carvedilol or placebo	FU: 24 weeks > 10% decline in LVEF in 14.5% with carvedilol vs. 13.5% with placebo (NS)	Increase of TnI ≥ 0.04 ng/mL attenuated with carvedilol versus placebo (26% vs. 41.6%, $p = 0.003$) Lower incidence of diastolic dysfunction with carvedilol vs. placebo (28.5% vs. 37.2%, $p = 0.039$)
Boekhout et al. [66], *N* = 206	100% T (post-A)	1:1 randomization to candesartan or placebo	FU (median): 21 months > 15% decrease in LVEF or absolute value < 45% in 19% with candesartan vs. 16% with placebo ($p = 0.58$)	Treatment with candesartan was not initiated until after completion of anthracycline chemotherapy
MANTICORE [67], *N* = 94	100% T 23% A 41% left chest RT	1:1:1 randomization to bisoprolol, perindopril, or placebo	FU: 350 ± 18 days No difference in change in LVEDVi (by CMR) from baseline to the end of study in the bisoprolol or perindopril groups compared with placebo (+ 8 vs. + 7 vs. + 4 mL/m^2, p = NS)	Small reduction in LVEF decline from baseline to the end of study with bisoprolol compared with perindopril and placebo (– 1% vs. – 3% vs. – 5%, $p = 0.001$)
Guglin et al. [68•], *N* = 468	100% T 39% A	1:1:1 randomization to carvedilol (Coreg CR), lisinopril, or placebo	FU: 12 months > 10% LVEF decline in 29% with carvedilol vs. 30% with lisinopril vs. 32% with placebo (p = NS)	In the subset of patients with prior anthracycline exposure, > 10% LVEF decline occurred in 31% with carvedilol vs. 37% with lisinopril vs. 47% with placebo ($p = 0.009$)

T trastuzumab, *RT* radiation therapy, *FU* follow-up, *LVEF* left ventricular ejection fraction, *CMR* cardiac magnetic resonance imaging, *NS* not significant, *hsTnI* high-sensitivity troponin I, *TnI* troponin I, *ACT* anthracycline cyclophosphamide taxane, *Dox* doxorubicin, *LVEDVi* indexed left ventricular end diastolic volume

anthracyclines and trastuzumab [68•]. A common limitation of these trials was that they included mostly low-risk patients with few CV comorbidities or patients receiving low-risk treatment regimens, and this may account for the modest benefits seen with primary prevention strategies. A primary prevention strategy targeting a higher-risk patient population may yield a greater clinical benefit.

Statins have been proposed as a preventive medication for anthracycline cardiotoxicity given their multiple pleiotropic effects including both anti-inflammatory and antioxidant properties [69, 70]. In a retrospective cohort study, Seicean et al. demonstrated that statin use during anthracycline therapy was associated with a decreased risk of incident HF [71]. A prospective trial investigating the prophylactic value of atorvastatin in patients planned for adjuvant anthracycline treatment is ongoing (PREVENT, ClinicalTrials.gov Identifier: NCT01988571).

Early detection and management of treatment-related cardiotoxicity

Current recommendations for surveillance of treatment-related cardiotoxicity entail routine LVEF assessments during and after anthracycline and anti-HER2 therapy [72, 73]. A schedule of LVEF assessments at baseline and every 3 months during trastuzumab treatment is most commonly cited [73]. Adherence to this cardiac monitoring schedule is generally poor (< 50%) irrespective of age or other CV comorbidities [74, 75•]. However, the value of frequent monitoring to improve outcomes among low-risk patients has been questioned, especially among patients with HER2-positive breast cancer receiving non-anthracycline-based regimens in which the risk of cardiotoxicity is low. Potential harms of treatment interruption or false-positive findings leading to unnecessary testing associated with frequent LVEF monitoring must be balanced with the CV risks associated with LVEF declines [76]. Data from several small studies suggest that patients with asymptomatic LVEF decline can safely continue anti-HER2 therapy with close cardiac monitoring and treatment with cardiac medications, although additional safety studies are warranted [77•, 78].

Recent efforts have focused on identifying early sensitive markers of cardiotoxicity prior to the overt impairment of LV systolic function. Global longitudinal strain (GLS) via speckle tracking echocardiography (STE) is a sensitive marker of LV systolic function and can detect early signs of cardiotoxicity [79]. The predictive value of GLS for subsequent cardiotoxicity among patients receiving trastuzumab with or without prior anthracyclines has also been demonstrated [80–82]. Negishi et al. showed that a change in GLS from baseline to 6 months of 11% (95% confidence interval 8.3–14.6%) was the strongest predictor of cardiotoxicity among trastuzumab-treated patients [80]. Based on American Society of Echocardiography (ASE) guidelines, a relative decrease in GLS of > 15% is likely to reflect a clinically significant change in LV systolic function that may warrant further intervention [72]. GLS has also been used to detect subclinical signs of radiation-induced cardiotoxicity, with declines in GLS that correspond to areas receiving the highest dose of radiation [60, 83]. However, a recent study showed no significant change in GLS after contemporary breast RT among patients treated with anthracyclines and trastuzumab, which may be explained by the low mean heart dose that is delivered with contemporary RT techniques [63].

The value of more sensitive markers of cardiotoxicity is dependent on whether CV outcomes can be improved with early detection and intervention. The ICOS-ONE study compared prophylactic versus Tn-triggered initiation of enalapril for the prevention of anthracycline-induced cardiotoxicity among patients receiving a median doxorubicin equivalent dose of 180 mg/m^2. While enalapril did not decrease the risk of troponin elevation during treatment, the incidence of cardiotoxicity was lower in both groups (1.1%) compared with prior studies, suggesting the potential role of enalapril in preventing anthracycline-induced cardiotoxicity [84]. The SUCCOUR trial is a prospective trial that will compare a strategy of LVEF versus GLS-guided initiation of cardioprotective therapy for anthracycline-induced cardiotoxicity among high-risk patients (88% breast cancer) [85••].

CMR in patients receiving cardiotoxic cancer therapy can be used to provide superior image resolution for more accurate assessments of LV volumes and function and to characterize myocardial tissue [72, 86]. Detection of early stages of cardiac injury as evidenced by myocardial inflammation and edema has been demonstrated based on early gadolinium enhancement and T1/T2 mapping [86, 87]. Based on a recent study of serial multiparametric CMR assessments in the pig model, prolonged T2 relaxation time was found to be the earliest marker of anthracycline-induced cardiotoxicity, consistent with increased intracardiomyocyte edema on pathologic correlates [87]. This finding reflected a reversible stage of cardiotoxicity that—if confirmed with further studies—can have significant clinical implications in cardioprotective strategies and continued anthracycline therapy [87, 88]. CMR-based assessment of LV volumes may also help to identify the etiology of LVEF declines during cancer treatment. Cardiotoxicity as defined by reductions in LVEF is generally thought to be caused by impairment of LV contractility. However, LVEF declines in the setting of cardiotoxic cancer therapy can be attributed to isolated declines in LV preload, in which the appropriate treatment may be to provide volume repletion rather than to discontinue cancer therapy and/or initiate cardioprotective medications [89].

With regard to circulating biomarkers, several studies have demonstrated that post-anthracycline Tn elevations portend an increased risk of future cardiotoxicity [81, 84, 90]. Among patients receiving adjuvant anthracycline followed by paclitaxel and trastuzumab, Ky et al. showed that early increases in TnI and myeloperoxidase conferred up to a 46.5% increased risk of cardiotoxicity [90]. Cardinale et al. [91] showed that TnI elevations were associated with an increased risk of trastuzumab-induced cardiotoxicity and lower likelihood of LVEF recovery. The integration of circulating and imaging biomarkers, particularly among selected individuals at high cardiotoxicity risk (e.g., patients receiving sequential anthracyclines and trastuzumab), may provide the greatest predictive value of cardiotoxicity and prove to be most beneficial in clinical practice.

Despite the currently identified clinical factors that are associated with cardiotoxicity, there continues to be significant heterogeneity in the tolerance to cardiotoxic cancer therapy. This suggests that genetics may provide insight into an individual's susceptibility to cardiotoxicity. Changes in gene expression in response to cardiotoxic cancer therapy [92] and single nucleotide polymorphisms (SNPs) in genes involved in anthracycline metabolism and oxidative stress such as ABCC2, CYBA, RAC2, ABCB1, and CBR3 have been proposed as markers that

can identify patients at high risk for anthracycline-induced cardiotoxicity [93–95]. Candidate SNPs such as the HER2/neu Pro 1170 Ala polymorphism have also been identified as potential genetic markers of trastuzumab cardiotoxicity [66, 95–97]. Additional studies are needed to further explore the relationship between these genetic markers and cardiotoxicity events.

Exercise and fitness

Weight gain, decreased physical activity, and impaired exercise capacity are common changes among breast cancer patients after initial diagnosis and during treatment [98, 99]. Jones et al. showed that patients and survivors have on average 27% less exercise capacity than age-matched healthy sedentary controls [99]. Moreover, a strong inverse relationship between CVD and increasing physical activity has been demonstrated, with benefits that persisted long term [100]. The "multiple hit" model emphasizes that pre-existing CV risk factors combined with therapy-associated CV injury can lead to direct and indirect effects on the global CV system, eventually resulting in CVD [101]. Accordingly, the safety and potential CV benefits of exercise during and after treatment have previously been shown [98, 102–104]. The OptiTrain trial demonstrated that high-intensity interval training (HIIT) during treatment offered multiple benefits, including prevention of cardiorespiratory fitness decline and cancer-related fatigue and improvement in muscle strength [104]. Several prospective trials are ongoing to evaluate the effect of exercise interventions on cancer- and CV-related outcomes [105, 106].

Conclusion

As advances in cancer care continue to improve upon the cancer outcomes of breast cancer patients, more survivors will be at risk for developing late adverse CV effects from cancer treatment or overt CVD. Balancing the expected benefits of cancer treatment with treatment- and patient-specific CV risk and identifying strategies to prevent cardiotoxicity are needed to improve long-term outcomes and quality of life. Increased knowledge of imaging and circulating biomarkers has translated to earlier identification of subclinical cardiotoxicity and provides an opportunity for early intervention prior to the development of overt clinical CVD. Moreover, increasing awareness of insults to the CV system associated with cardiotoxic cancer treatment has created strides towards novel multidisciplinary approaches to the cardio-oncology care of breast cancer patients. Continued collaborative efforts within cardio-oncology will lead to better CV and cancer outcomes in cancer survivors.

Compliance with Ethical Standards

Conflict of Interest

Katherine Lee Chuy declares that she has no conflict of interest.

Anthony F. Yu has received compensation from Glenmark Pharmaceuticals, Takeda Oncology, Bristol-Myers Squibb, and Bayer for 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.

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