

# Cardio-Oncology

## An Update on Cardiotoxicity of Cancer-Related Treatment

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**Abstract:** Through the success of basic and disease-specific research, cancer survivors are one of the largest growing subsets of individuals accessing the healthcare system. Interestingly, cardiovascular disease is the second leading cause of morbidity and mortality in cancer survivors after recurrent malignancy. This recognition has helped stimulate a collaboration between oncology and cardiology practitioners and researchers, and the portmanteau cardio-oncology (also known as onco-cardiology) can now be found in many medical centers. This collaboration promises new insights into how cancer therapies impact cardiovascular homeostasis and long-term effects on cancer survivors. In this review, we will discuss the most recent views on the cardiotoxicity related to various classes of chemotherapy agents and radiation. We will also discuss broadly the current strategies for treating and preventing cardiovascular effects of cancer therapy. (*Circ Res.* 2016;118:1008-1020. DOI: 10.1161/CIRCRESAHA.115.303633.)

**Key Words:** cancer and stroke ■ cardiac dysfunction ■ cardiology ■ cardiotoxicity ■ oncology

### What Does Cardiotoxicity Mean?

As the population of cancer survivors grows, it is even more important for providers to be aware of the cardiac complications of cancer treatment.<sup>1</sup> There are many recognized adverse cardiovascular effects of cancer therapies (Figure 1), though there remains a lack of true consensus over definitions for cardiotoxicities. Most current definitions of cardiotoxicity in guideline statements and in clinical trials focus narrowly on changes in resting myocardial systolic function, such as left ventricular ejection fraction (LVEF) and the development of heart failure (HF) symptoms. However, chemotherapy and radiation are known to affect more than just resting LVEF and have a broad range of effects on the entire cardiovascular system. Although changes in ejection fractions remain the gold standard for reporting chemotherapy-induced cardiotoxicity, there is a need to broaden the definition to include direct effects on cardiac structure (eg, fibrosis), diastolic function, cardiac conduction and arrhythmias, systemic and pulmonary vascular function and hemodynamics, hemostasis and thrombosis, as well as cardiac response to injury and stress. Changes in myocardial strain and specific cardiovascular biomarkers (eg, troponin I and natriuretic peptides) during cancer treatment can represent subtle perturbations on the cardiovascular system that are prognostic for the development of HF before a drop in LVEF.<sup>3-5</sup> In general, cardiotoxicity is a broad term that should encompass not only changes in resting cardiac parameters but also dynamic functional assessments of the cardiovascular systems (coronary blood flow reserve, recruitable stroke work, maximal functional capacity [VO<sub>2</sub>]). Dynamic cardiovascular

assessments are important because we know that many cancer survivors have diminished exercise capacity that significantly impact quality of life.<sup>6</sup> The ultimate goal of the cardio-oncology community is to identify chemotherapy cardiotoxicities with a broad definition—not to impede or disrupt oncology regimens, but to begin medical therapy or lifestyle interventions sooner with hopes to improve survivorship outcomes.

### Anthracyclines

Anthracyclines are a class of antibiotics discovered over 50 years ago that are used to treat many different cancers including lymphoma, leukemia, sarcoma, and breast cancer.<sup>7</sup> Anthracyclines are derived from *Streptomyces bacterium* and are among the most effective anticancer drugs to date.<sup>8</sup> Commonly used anthracyclines include doxorubicin, mitoxantrone, epirubicin, idarubicin, and daunorubicin. Anthracyclines exhibit anti-neoplastic properties by 4 main mechanisms. Anthracyclines disrupt DNA and RNA synthesis by intercalating between base pairs, inhibit topoisomerase II (leading to DNA breaks and preventing ligase repair),<sup>7</sup> cause histone eviction attenuating DNA repair,<sup>9</sup> as well as creating iron-mediated free radicals which damage the DNA.<sup>10</sup>

Although anthracyclines remain an effective and commonly used therapy, their use is limited by cardiotoxicity. HF and left ventricular (LV) dysfunction are the dreaded short and long-term complications of anthracycline exposure occurring in 5% to 23% of patients, causing diminished exercise capacity and progressive HF symptoms.<sup>11,12</sup> The risk for early and late anthracycline toxicity is largely a function of cumulative

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**Nonstandard Abbreviations and Acronyms**

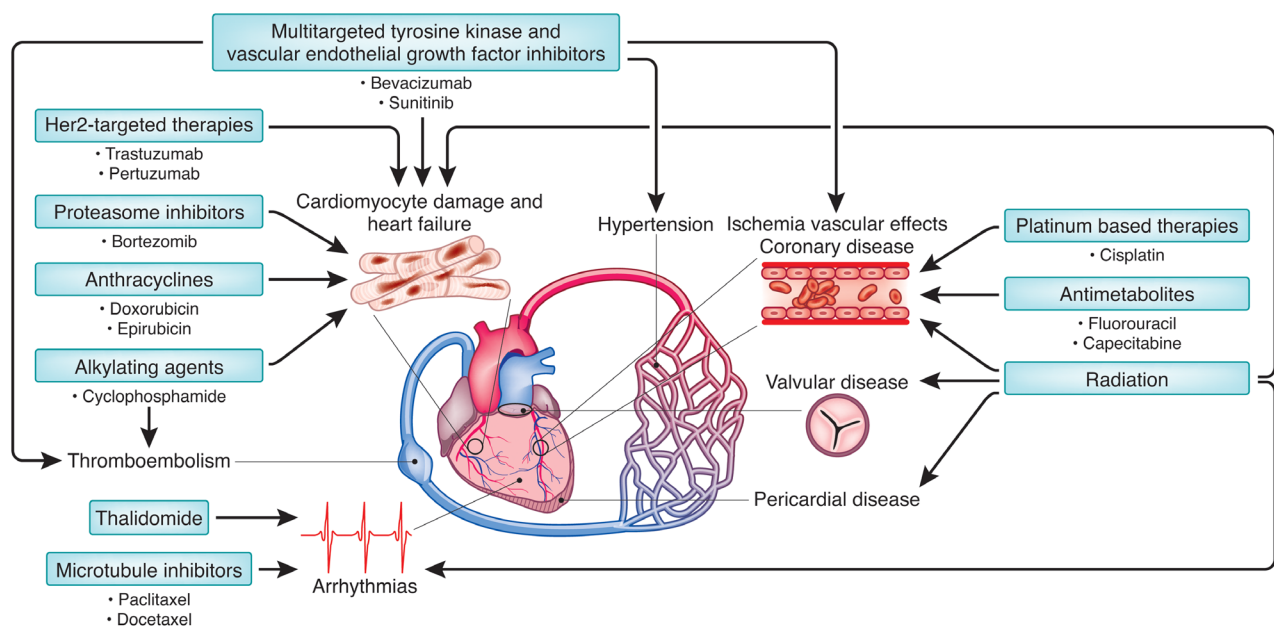
<b>ACE</b>	angiotensin-converting enzyme
<b>AIC</b>	anthracycline-induced cardiotoxicity
<b>BB</b>	$\beta$ -blocker
<b>5-FU</b>	5-fluorouracil
<b>HF</b>	heart failure
<b>LV</b>	left ventricle
<b>LVEF</b>	left ventricular ejection fraction
<b>MDR</b>	multidrug resistance
<b>RIHD</b>	radiation-induced heart disease
<b>TKI</b>	tyrosine kinase inhibitor
<b>Top2</b>	topoisomerase 2
<b>VEGF</b>	vascular endothelial growth factor

anthracycline exposure.<sup>13</sup> At a cumulative dose of 400 mg/m<sup>2</sup>, there is a 5% risk of developing HF, which increases to 25% at 700 mg/m<sup>2</sup>.<sup>13</sup> In patients with additional risk factors, such as age at 2 extremes (age <18 and >65 years), prior cardiac pathology (hypertension, LV hypertrophy, coronary artery disease), diabetes mellitus, or prior radiation exposure, the recommended total cumulative exposure is decreased to 450 mg/m<sup>2</sup> to reduce the risk of LV dysfunction. Even at low cumulative doses, such as standard-dose therapy for breast cancer,  $\approx$ 20% of patients experience reduced LV systolic function (with a drop in >10 U in LVEF) within the first 6 months of treatment.<sup>4</sup> Thus, every exposure to an anthracycline carries some risk of inducing cardiac dysfunction.

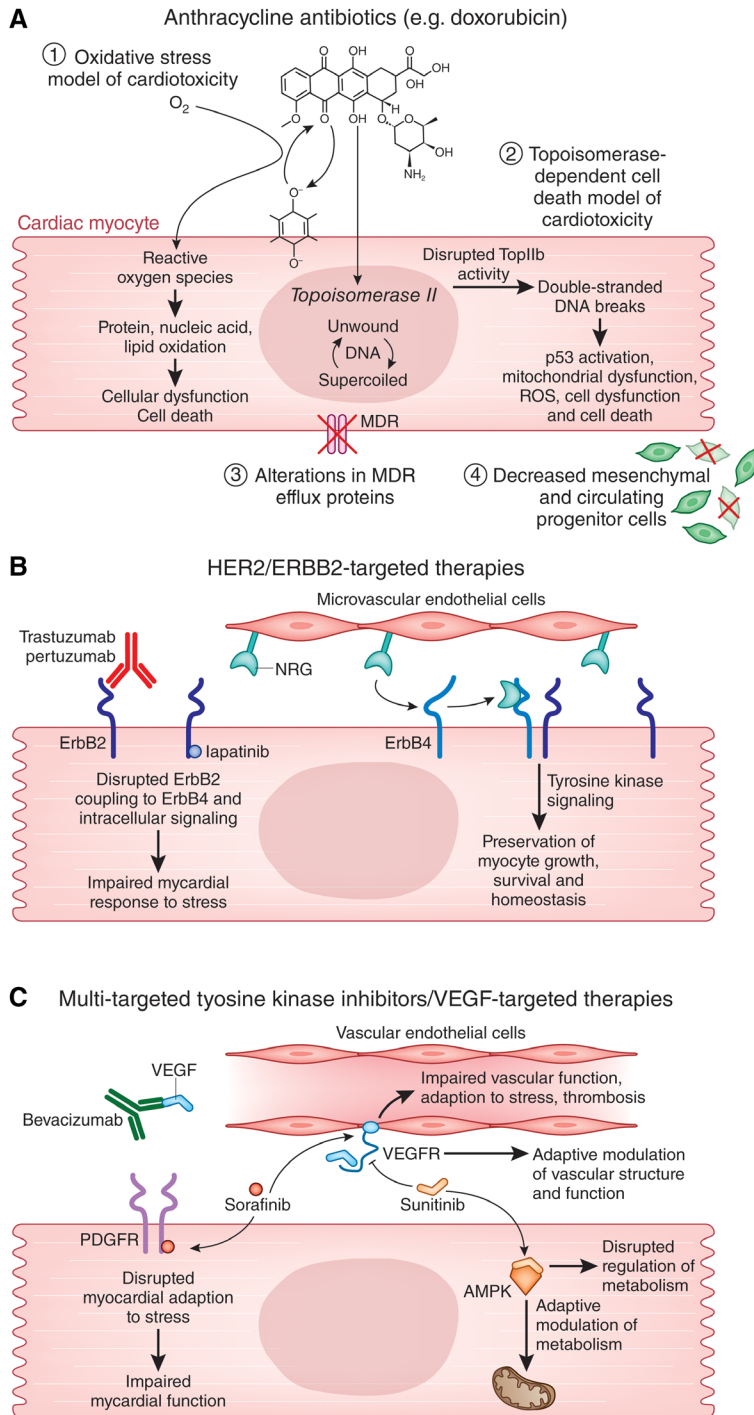
The mechanism of anthracycline-induced cardiotoxicity (AIC) has been investigated for decades. Anthracyclines induce multiple forms of cellular injury to cardiac myocytes and endothelial cells that have been attributed to the excess free radical production induced by the quinone group<sup>14</sup> (Figure 2). Recent attention has turned to the role of topoisomerase 2

(Top2) as a molecular target responsible for both anthracycline's anticancer property and a contributor to AIC. DNA topoisomerases are essential enzymes required for transcription, replication, or recombination. Two Top2 isoenzymes are expressed in humans: Top2 $\alpha$  and Top2 $\beta$ . Top2 $\alpha$  is highly expressed in rapidly proliferating cells, whereas Top2 $\beta$  is expressed in quiescent cells, such as the myocardium<sup>15</sup> (Figure 2). Notably, mice lacking Top2 $\beta$  are protected from anthracycline-induced DNA damage and cardiomyocyte death.<sup>10</sup> A recent genome-wide association study identified retinoic acid receptor gamma as an AIC susceptibility gene,<sup>16</sup> where genetic variants of retinoic acid receptor gamma alter retinoic acid effects on Top2 $\beta$  expression in vitro. These findings have led to several new lines of investigation as to whether alterations in Top2 $\beta$  can provide more cardioprotection during anthracycline treatment. Theoretically, if an anthracycline chemotherapy can be developed that selectively targets Top2 $\alpha$  over Top2 $\beta$  or allows for only tissue-specific modulation of Top2 $\beta$ , then the cardiotoxic effects of anthracyclines could be attenuated.<sup>17</sup> In addition, we may improve our prediction of risk for AIC using Top2 $\beta$  expression.<sup>17</sup> The role of Top2 $\beta$  in AIC has opened a new avenue of research into cardioprotective strategies during anthracycline exposure.

Dexrazoxane, a derivative of EDTA, chelates iron and thus reduces the number of metal ions complexed with anthracycline and, consequently, was developed to provide cardioprotection against AIC by the reduction in superoxide radicals. Dexrazoxane was found to provide cardioprotection from AIC in women with advanced breast cancer.<sup>18</sup> Recent data suggest an alternative mechanism, where dexrazoxane binding to Top2 $\beta$  leads to Top2 $\beta$  degradation.<sup>19</sup> Dexrazoxane is not broadly used to prevent AIC, in part because of the concerns of diminished antitumor effects, as well as a role in promoting secondary malignancy. Perhaps, the new insights into



**Figure 1.** An overview of the cardiovascular side effects of chemotherapy and radiation.



**Figure 2.** Molecular pathways involved in cardiotoxicity related to anthracyclines, HER2-targeted and tyrosine kinase inhibitors/vascular endothelial growth factor (VEGF) inhibitors. **A**, Anthracycline causes cardiotoxicity through many mechanisms; however, outlined are 4 common pathways. (1) Oxidative stress induces multiple forms of cellular injury to cardiac myocytes because of excess free radical production induced by the quinone group. (2) Modulation in topoisomerase 2 $\beta$  activity. (3) Alteration in the multidrug-resistant (MDR) efflux proteins, leading to higher levels of intracardiac levels of anthracycline. (4) Decreased mesenchymal progenitor cells (MPCs) and circulating progenitor cell (CPCs) population. **B**, HER2/ERBB2-targeted therapies disrupt the paracrine signaling with neuregulin (NRG) and the ERBB2 receptors forming homo- and heterodimers important for normal myocyte growth, survival, and homeostasis. **C**, The multitargeted tyrosine kinase inhibitors (TKIs) and VEGF-targeted therapies disrupt endothelial cell receptor signaling causing impaired vascular function, exaggerated hypertension, and increased thrombosis. TKIs inhibit several tyrosine kinases, including adenosine monophosphate-activated protein kinase (AMPK) and platelet-derived growth factor (PDGFR), which cause alterations in mitochondrial metabolism and the myocyte's ability to adapt to stress. ROS indicates reactive oxygen species.

dexrazoxane's effects on Top2 $\beta$  as a mechanism for prevention of AIC will lead to a re-examination of its clinical utility.

Another contributing factor in AIC is the function of membrane transport systems that modulate the intracellular myocyte concentration and exposure to anthracycline. The cellular efflux of anthracyclines is in part regulated by the expression of the membrane transporter in the ATP-binding cassette (ABC) family, including multidrug resistance (MDR) proteins (also known as p-glycoprotein; Figure 2). The role of MDR proteins in determining cardiotoxicity in humans has been demonstrated by candidate gene as well

as genome-wide association studies showing an interaction between MDR1 polymorphisms and cardiotoxicity.<sup>20,21</sup> A recent study confirmed that breast cancer patients who developed AIC had 2-fold lower levels of ABCB1 (adenosine triphosphate-binding cassette B1) mRNA expression, encoding the MDR1.<sup>20</sup> This has immediate clinical importance in cancer patients receiving other medications that are MDR substrates, such as calcium-channel blockers (ie, verapamil, diltiazem) which may increase the intracellular levels of cardiotoxic chemotherapy, potentially increasing the risk of cardiotoxicity.<sup>20</sup>



A more recent finding is that anthracycline exposure decreases the number of cardiac mesenchymal progenitor cells, as well as circulating progenitor cell populations,<sup>22</sup> and thus reducing cardioreparative capacity when the heart is exposed to stress<sup>23</sup> (Figure 2). This may explain the delayed onset of HF that is often observed in children exposed to anthracyclines. In response to preclinical findings of reduced mesenchymal progenitor cells in AIC, the National Institutes of Health Cardiovascular Cell Therapy Research Network is planning a prospective clinical trial (Stem cell treatment for end-stage cardiac failure [SENECA]) investigating the safety of allogeneic mesenchymal cells for patients with anthracycline-induced HF.<sup>24</sup> This study will lay the foundation of cellular therapies as a potential strategy to reverse cardiac dysfunction associated with AIC. Even though anthracyclines have been an effective therapy for over 50 years, the continued insight into the molecular pathways is leading to innovative strategies to reduce and or treat AIC.

### Trastuzumab and HER2-Targeted Agents

HER2-targeted agents are a class of drugs that specifically target and inhibit HER2/*neu* receptors (also known as ERBB2). Before HER2-targeted therapy, HER2-positive (HER2<sup>+</sup>) breast cancer patients had a poor prognosis secondary to the aggressive nature of the rapidly growing cancer. Trastuzumab was the first HER2-targeted agent approved by the Food and Drug Administration in 1998 for advanced metastatic cancer and later expanded for the treatment of early-stage HER2<sup>+</sup> breast cancer in 2007.<sup>25</sup> Trastuzumab is a humanized monoclonal antibody that blocks the activation of specific epidermal growth factors with the HER2/*neu* receptor. Inhibiting epidermal growth factors/HER2 ligand receptor activity disrupts the phosphorylation of intracellular tyrosine kinases that are critical regulators of cell growth and survival. The initial clinical studies of trastuzumab showed that it improved overall survival in late-stage (metastatic) breast cancer from 20.3 to 25.1 months.<sup>26</sup> Subsequent studies demonstrated that trastuzumab in early-stage breast cancer reduces the risk of cancer returning after surgery by an absolute risk of 9.5% and the risk of death by an absolute risk of 3%. Although trastuzumab improves breast cancer response rates in early-stage breast cancer, there was a slight increased risk of cardiac dysfunction with an absolute 2.1% risk in reduction in LV function, which usually resolved if therapy was stopped.<sup>27</sup> Even though the clinical significance of the asymptomatic LV dysfunction with trastuzumab remains unknown, it is worthwhile for clinicians to be cognizant of the change.

HER2-targeted agents can cause asymptomatic cardiac dysfunction and less often symptomatic HF in some patients.<sup>28</sup> The cardiac dysfunction observed with HER2-targeted agents is because of disruption in signaling between the HER2 (ERBB2) receptor and ligand growth factor named neuregulin (Figure 2). The ligand–receptor neuregulin-ERBB2 signaling pathway on cardiomyocytes is critical for normal myocyte growth, survival, and homeostasis.<sup>29,30</sup> HER2-targeted agents may trigger a decline in the ejection fraction because of effects on myocyte neuregulin-ERBB2 signaling that are required for cardiac repair and myocyte homeostasis. Neuregulin/ERBB signaling regulates other functions in the cardiovascular system, including

vasomotor tone and sympathetic output. Breast cancer patients treated with HER2-antagonist experienced increased levels of norepinephrine along with increases in blood pressure and heart rate.<sup>31</sup> In preclinical models, the expression and activity of  $\beta$ -adrenergic receptor activity is coupled to ERBB2 expression,<sup>32</sup> and ERBB2 activation is a critical modulator of the toxicity of chronic exposure to  $\beta$ -adrenergic receptor agonists.<sup>32,33</sup> Thus an additional mechanism of HER2-targeted therapy altering cardiac function may be because of the chronic increases in sympathetic tone. Further investigation is needed to evaluate the effects of HER2-targeted therapies on sympathetic tone, as well as examine the potential role of  $\beta$ -blockers (BBs) in mitigating the Her2-related cardiac dysfunction.

Newer HER2-targeted agents have emerged in the last several years. Lapatinib is an oral HER2-targeted small molecule, dual tyrosine kinase inhibitor (TKI) of HER2/*neu* receptor and the epidermal growth factor receptor (Figure 2). Pertuzumab is another HER2-targeted agent designed to overcome trastuzumab resistance caused by the formation of HER2:HER3 heterodimers<sup>34</sup> (Figure 2). Ado-Trastuzumab emtansine is one of the newest Food and Drug Administration-approved HER2-targeted therapies used in the treatment of metastatic breast cancer that is resistant to trastuzumab.<sup>35</sup> Ado-Trastuzumab emtansine works as an antibody–drug conjugate with a monoclonal antibody to the HER2 receptor bound to several molecules of mertansine, an anti-microtubule agent. This antibody–drug conjugate allows for preferential intracellular drug delivery to HER2<sup>+</sup> tumor cells.<sup>34</sup> The fact that mertansine is only released after the antibody–drug conjugate has been taken up by a tumor cell theoretically reduces toxic effects while maintaining antitumor efficacy. The clinical trials of the newer HER2-targeted agents mentioned above have exhibited little signal for cardiotoxicity.<sup>35</sup> However, long-term follow-up is needed because these agents are used in broader patient populations.

Routine monitoring of cardiac function during treatment with HER2-targeted therapies has become standard practice. Many pivotal clinical trials assessed LVEF by either multigated acquisition scans or echocardiograms every 3 months to look for significant changes in cardiac function.<sup>36–39</sup> Current Canadian consensus guidelines recommend LVEF assessment every 3 months while on HER2-targeted therapy and initiation of HF therapy if LVEF falls below 40% and consideration of therapy if a drop of >10 points below baseline with LVEF <50%.<sup>40</sup>

HER-targeted therapies have significantly improved outcomes in breast cancer patients and are being expanded to treat advanced-stage gastric cancers that overexpresses HER2<sup>+</sup> receptors.<sup>41</sup> With the continued use of HER-targeted therapies, we anticipate the potential cardiovascular effects caused by the overlap in the HER/ERBB biology between various tumors and the cardiovascular system. One of the main goals is to better understand which patients are at highest risk of HER-related cardiotoxicity, optimal monitoring for toxicity, treatment to reverse cardiac dysfunction, and eventually strategies to prevent cardiovascular toxicity.

### Multitargeted Tyrosine Kinase Growth and Angiogenesis Inhibitors

The recognition of angiogenesis signaling as a general requirement for tumor growth has led to a growing array of cancer

therapies that inhibit the signals involved in tumor growth and angiogenesis. The first of these developed were antibody-based inhibitors of vascular endothelial growth factor (VEGF), and more recently, small molecules have been selected for their ability to inhibit VEGF receptor tyrosine kinase, as well as other receptor and nonreceptor tyrosine kinases. The cardiovascular effects of cancer treatments targeting angiogenesis are clinically important and biologically fascinating given the fundamental role of angiogenesis in cardiovascular function. VEGF plays an important role in angiogenesis, endothelial cell survival, vasodilatation, and cardiac contractile function.<sup>42</sup> Thus, on-target cardiovascular effects of VEGF-targeted angiogenesis inhibitors such as increased blood pressure<sup>43</sup> are expected. Other toxicities that are at least in part caused by on-target effects include promotion of thromboembolism and cardiac contractile dysfunction. The cardiovascular effects of small-molecule TKIs are more complicated because of their poor selectivity compared with monoclonal antibody-based biologics. Thus, evaluation of the mechanism for the effects of these multi-TKIs on cardiovascular function requires consideration for possible off-target effects.

Hypertension during treatment with VEGF-targeted angiogenesis inhibitors is the most common cardiovascular effect and demonstrates a critical role of VEGF and related signaling pathways in the control of blood pressure. The hypertensive effect seems to be dose-related because it is more frequent in patients treated with a higher dose of the anti-VEGF cancer agents.<sup>44,45</sup> Interestingly, VEGF polymorphisms seem to be associated with the risk of anti-VEGF-induced hypertension as well as the antitumor efficacy, supporting the notion that hypertension may be a marker of treatment response.<sup>46,47</sup>

Several mechanisms of anti-VEGF-induced hypertension have been proposed, including an increase in vascular resistance, stiffness, and rarefaction.<sup>48</sup> VEGF signaling plays an important role in cardiovascular physiology, modulating vasomotion and glomerular function.<sup>49,50</sup> VEGF activates vascular eNOS (endothelial nitric oxide synthase) via the PI-3kinase/PKB/Akt pathway, and this is one mechanism for VEGF-mediated vasorelaxation.<sup>51</sup> Mice lacking VEGF demonstrate abnormal glomerular pathology, with loss of podocytes and disruption of the basement membrane.<sup>52,53</sup> This, together with thrombotic microangiopathy in the glomeruli, correlates clinically with proteinuria observed in patients treated with VEGF inhibitors.<sup>52,54</sup>

VEGF-targeted therapies are associated with a 3-fold increase in risk for arterial thromboembolic events (stroke, transient ischemic attacks, myocardial infarction, angina, and other arterial events).<sup>55</sup> Platelet activation is accompanied by release of VEGF, and this seems to regulate endothelial cell survival and repair of the vasculature.<sup>55</sup> Inhibition of VEGF thus likely promotes microvascular injury and potentiates thrombosis.

Cardiac systolic dysfunction has been observed in patients treated with bevacizumab (an anti-VEGF antibody), though this seems to occur more commonly during treatment with sunitinib and other multi-TKIs (discussed in more detail later). VEGF signaling mediates the adaptation of the heart to pressure overload.<sup>56</sup> Suppressing of VEGF in the setting

of pressure overload leads to more rapid deleterious cardiac remodeling and HF in mice. Thus, adaptation of the heart to pressure overload seems to require VEGF-regulated microvasculature growth in proportion to cardiac myocyte metabolic and growth changes.

Small-molecule multi-TKIs seem to more frequently cause cardiac dysfunction and HF when compared with therapies that only target VEGF receptors. Clinical trial meta-analysis, using trial definitions of cardiac toxicity, concluded that the incidence of ventricular dysfunction and HF is relatively low and similar among the established TKIs.<sup>57</sup> However, retrospective analyses of a single-center data report cardiac dysfunction in  $\approx 10\%$  of patients receiving sunitinib<sup>58</sup> or 50% to 70% for a wider range of TKIs in prospective studies where more careful cardiac phenotyping was used.<sup>59</sup> Preclinical models of toxicity have demonstrated effects of TKIs on mitochondrial injury and cardiomyocyte apoptosis in both mice and cultured rat cardiomyocytes.<sup>58,60</sup> TKIs inhibit several tyrosine kinases, including adenosine monophosphate-activated protein kinase (AMPK) and platelet-derived growth factor (PDGFR; Figure 2), which may explain the higher rate of clinical cardiac toxicity than more selective VEGF-targeted therapies. Mice lacking PDGF receptor expression respond to pressure overload induced by surgical aortic constriction with accelerated cardiac remodeling and with impaired vascular growth and function.<sup>61</sup> Mice lacking AMPK $\alpha 2$  similarly are normal in the unstressed condition, but experience accelerated remodeling and HF after pressure overload. It is interesting that in each of these animals, the phenotype of cardiac dysfunction is not manifested unless the animals are subjected to pressure overload. This would suggest that the hypertensive effect of angiogenesis inhibitors may be requisite for induction of contractile dysfunction.

It is unclear whether TKI-associated cardiac dysfunction is reversible. In early reports of patients treated with sunitinib, the best studied of the TKIs, HF and LV dysfunction generally responded to temporary suspension and initiation of medical therapy.<sup>58</sup> However, the preclinical data in animals and cells supports a proapoptotic effect of sunitinib that accordingly should lead to some degree of irreversible cardiac damage. Persistent cardiac dysfunction has been noted in some people treated with sunitinib.<sup>60,61</sup> At least one case of fatal cardiac dysfunction has been reported with axitinib,<sup>57,59</sup> a TKI designed against mutant gene BCR-ABL1 (breakpoint cluster region-Abelson 1 gene) that also has inhibitory effects on VEGF and PDGF. Larger meta-analyses have found cardiac dysfunction and HF to be a common problem with TKIs, and more work is needed to help discern appropriate screening and monitoring for cardiotoxicity.<sup>62</sup>

### Platinum-Based Chemotherapy Agents

Emerging data indicates that vascular toxicity is one of the most concerning consequences of platinum-based chemotherapy.<sup>63,64</sup> Cisplatin is a common chemotherapy used to treat many solid tumors (genitourinary, gastrointestinal, lung, and head and neck). With close to 90% cure rates in testicular cancer patients treated with platinum-based agents, cardiovascular disease has emerged as one of the significant consequences

facing survivors.<sup>65</sup> Platinum-based antineoplastic agents cause crosslinking of DNA.<sup>66,67</sup> They act on the adjacent N-7 position of guanine, forming 1, 2 intrastrand crosslink, impeding cellular processes, such as replication and transcription. Ultimately, the crosslinks inhibit DNA repair and DNA synthesis in cancer cells, leading to cellular apoptosis. Platinum-based antineoplastic agents are sometimes described as alkylating-like because of similar effects as alkylating antineoplastic agents, although they do not have an alkyl group.

Vascular toxicity is one of the most important late consequences of cisplatin-based chemotherapy in the treatment of men with advanced testicular cancer.<sup>65</sup> The major cardiovascular issues that have been studied include hypertension, dyslipidemia, early atherosclerosis, coronary artery disease, Raynaud's phenomenon, and thromboembolic events<sup>68</sup> (Figure 1). Survivors of testicular cancer have an increased risk of developing both an unfavorable cardiac risk factors (obesity, hypertension, hyperlipidemia, diabetes mellitus) and cardiovascular disease.<sup>69</sup> Although the observed increase in cardiovascular disease may be due in part to the accelerated development of cardiac risk factors, other mechanisms, including direct vascular toxicity from the chemotherapy and radiation, are emerging as an area of mechanistic intrigue with potential for therapeutic interventions.

Cisplatin is incompletely eliminated after treatment, and platinum is measurable in the serum several years after therapy.<sup>70</sup> Because of detectable circulating platinum, it is possible that a small amount of cisplatin continuously acts on the endothelium, leading to endothelial dysfunction, and late adverse effects on the vascular system. Studies reveal that endothelial dysfunction develops in patients treated with cisplatin for testicular cancer.<sup>71</sup> Increased biomarkers of endothelial injury, von Willebrand factor, tissue-type plasminogen activator, and plasminogen activator inhibitor type 1 were reported after cisplatin exposure when compared with healthy controls.<sup>72</sup> Additionally, the incidence of coronary artery disease (CAD) seems to be higher for testicular cancer survivors with 2 specific polymorphisms in the plasminogen activator inhibitor type 1 gene (4G/4G and 4G/5G; 6% and 4.9%, respectively) than in those with the 5G/5G polymorphism (2.6%).<sup>73</sup> Cisplatin induces upregulation of intracellular adhesion molecule-1, tissue-type plasminogen activator, and plasminogen activator inhibitor type 1 in endothelial cells in vitro, suggesting an endothelial activation shortly after chemotherapy exposure.<sup>74</sup> Thickening in the carotid intima-media wall, as well as increased plasma levels of von Willebrand factor, has been observed shortly after cisplatin-based chemotherapy.<sup>63</sup> Increased levels of intracellular adhesion molecule-1, circulating endothelial cells, and impaired flow-mediated dilatation were also observed more frequently after cisplatin-based chemotherapy in patients treated for testicular cancer.<sup>75</sup> Further work is needed to determine whether the early endothelial dysfunction observed after platinum-based exposure explains the increased risk of premature atherosclerosis in testicular cancer survivors.

Human clinical trials of platinum-based chemotherapy, without concurrent anthracyclines, have not demonstrated a significant signal for development of systolic

dysfunction.<sup>76</sup> However, in a rodent animal treated with cisplatin developed cardiotoxicity with LV dysfunction and depressed cardiomyocyte contraction because of mitochondrial abnormalities, enhanced endoplasmic reticulum stress response, and apoptosis.<sup>77</sup> Even though HF is not a commonly described side effect in patients treated with platinum agents, preclinical evidence demonstrates the possibility of cardiomyocyte dysfunction through alternations in mitochondria that may warrant further investigation in long-term survivors.

### Microtubule Inhibitors

Microtubule inhibitors are generally known as taxanes (paclitaxel and docetaxel).

Taxanes exert antineoplastic effect by disrupting the microtubule function. Microtubules are essential for cell division, and taxanes stabilize guanosine diphosphate-bound tubulin in the microtubules, thereby inhibiting the process of cell division, freezing mitosis.<sup>78</sup> Taxanes are used in the treatment of many solid tumors, including breast and ovarian cancer.<sup>79</sup> When paclitaxel was first introduced in clinical trials, its cardiotoxicity was unexpected. Arrhythmias are the most commonly observed toxicity by taxanes (Figure 1).<sup>79</sup> Bradycardia and heart block suggest that microtubules can play a role in calcium handling. Researchers found that paclitaxel exposure decreases calcium amplitude and contraction in isolated cardiomyocytes, but shortens the time from the maximum contracted state to relaxation.<sup>80</sup> Generally, bradyarrhythmias are asymptomatic and self-limited from taxane exposure. Supraventricular arrhythmias, including atrial fibrillation, atrial flutter, and atrial tachycardias, have also occurred with taxanes.<sup>79,81,82</sup> Although the pathogenesis of these arrhythmias may be multifactorial, studies implicate paclitaxel drug delivery vehicle (polyethoxylated castor oil) inducing histamine release as another precipitating factor.<sup>79,81,82</sup>

Paclitaxel, similar to colchicine, is microtubule-stabilizing agent, and in normal postmitotic cardiomyocytes, microtubule density is low; thus, taxane agents are not thought to hinder cardiomyocyte contraction.<sup>83</sup> However, small clinical trial data demonstrate that taxane exposure may contribute to LV dysfunction.<sup>76,84</sup> A preclinical investigation of paclitaxel exposure alone versus in conjunction with trastuzumab identified that concomitant inhibition of ERBB2 receptors and paclitaxel treatment has an additive worsening effect on adult cardiomyocytes, mainly discernible in changes of myofibrillar structure and function, but not causing myocyte cell death.<sup>85</sup> Both paclitaxel and trastuzumab modulated the MAPK/Erk1/2 (mitogen-activated protein kinase/extracellular signal-regulated kinase 1 and 2) signaling within cardiac myocytes, which are common pathways required for normal myocardial homeostasis.<sup>85</sup> Also cardiomyopathy is reported in patients treated with combined regimens paclitaxel and doxorubicin. Cardiac dysfunction developed in  $\leq 20\%$  of patients treated with paclitaxel plus doxorubicin.<sup>86</sup> The development of HF occurred at cumulative doses much lower than would be expected with doxorubicin alone.<sup>87–89</sup> The data with trastuzumab and doxorubicin raises concern that taxanes may contribute to higher incidence of cardiac dysfunction when they are used in conjunction with known cardiotoxic agents. This work highlights the need for further preclinical mechanistic studies and prospective studies



investigating the cardiac effects of multiple concurrent chemotherapy agents to elucidate the synergistic effects on the cardiovascular system.

### Antimetabolites

Antimetabolites are a class of drugs that interfere with the DNA and RNA growth by substituting the normal building blocks of DNA/RNA and thus damage proliferating cells during the S phase of mitosis.<sup>90</sup> Common antimetabolites include 5-fluorouracil (5-FU), capecitabine, cytarabine, gemcitabine, methotrexate, and hydroxyurea, which are commonly used to treat leukemia, ovarian, breast, gastrointestinal, and other solid tumors. Fluorouracil is widely used antimetabolite, with an incidence of cardiotoxicity ranging from 1% to 7.6%.<sup>90</sup> The most commonly described cardiac effects are myocardial ischemia, angina, chest pain, and ECG changes (ST-segment changes and T-wave abnormalities; Figure 1). The incidence of ischemia related to 5-FU is higher in patients with underlying coronary disease (4.5%) compared with patients without known disease (1.1%).<sup>91</sup> In general, a rechallenge of 5-FU usually reproduces the ischemic syndrome/symptoms. Cardiotoxicity typically occurs early (during the first to third dose) and is more common after higher doses and continuous infusions.<sup>92</sup> Prophylactic regimens with antiplatelet agents, nitroglycerin, or calcium-channel blockers are not currently recommended by standard guidelines. Although controversial, there are 2 small trials on the prophylactic use of calcium-channel blockers or nitrates in the setting of 5-FU or capecitabine, which showed an improvement in anginal symptoms.<sup>93,94</sup>

The pathophysiology of 5-FU and capecitabine cardiotoxicity appears multifactorial. Recent studies implicate several mechanisms as the cause of antimetabolite toxicity: endothelial injury followed by thrombosis, increased metabolism leading to energy depletion and ischemia, oxidative stress causing cellular damage, coronary artery spasm leading to myocardial ischemia, and diminished ability of red blood cells to transfer oxygen, resulting in myocardial ischemia.<sup>95</sup> In general, 5-FU and capecitabine are safe to use in patients with heart disease. However, providers need to be aware of potential symptoms and cardiovascular side effects where collaborative cardio-oncology management may help minimize interruptions in the chemotherapy regimen.

### Proteasome Inhibitors

The ubiquitin–proteasome system regulates protein turnover in addition to activation of cell signaling pathways, including growth and survival in some tumors. Cancer therapies targeting the proteasome pathway are in use and have been associated with cardiac dysfunction, including HF (Figure 1). The proteasome plays a fundamental role in maintenance of cardiac structure and function.<sup>96</sup> It is remarkable how well most proteasome inhibitor–treated patients tolerate this treatment. Bortezomib (Velcade) was the first proteasome inhibitor put to clinical use for suppression of plasma cell proliferation in multiple myeloma.<sup>97</sup> There are relatively few reports of HF occurring during treatment with bortezomib.<sup>98</sup> Newer proteasome inhibitors are being developed, including carfilzomib, an irreversible proteasome inhibitor now approved as second line therapy for relapsed multiple myeloma. Although this

therapy seems to be more active in resistant myeloma cases than previous treatments, there may be a greater likelihood of cardiac events, including HF, sudden cardiac death, and acute coronary syndrome.<sup>99</sup> The cardiac safety of carfilzomib and other proteasome inhibitors will become clearer as greater experience accumulates with these therapies.

### Radiation-Induced Heart Disease

Radiation therapy improves cancer-related outcomes in a variety of malignancies, including but not limited to lymphoma, breast, lung, and head and neck cancers. Radiation-induced heart disease (RIHD) is a serious side effect of cancer treatment, which may manifest as pericarditis (acute and subacute), pericardial effusions or late sequelae that affect the entire cardiovascular system.<sup>100</sup> Late effects of radiation-related toxicity manifests at a median of 10 to 15 years after exposure and contribute to the development of pericardial disease (constrictive pericarditis), restrictive cardiomyopathy, valvular abnormalities, premature coronary disease, peripheral vascular disease, cardiomyopathy (systolic and diastolic), arrhythmias, and autonomic dysfunction<sup>100–107</sup> (Figure 1). The incidence and severity of cardiac disease increases with higher radiation dose, larger volume exposed, younger age at time of exposure, greater time elapsed since treatment, use of other adjuvant chemotherapy, type of radiation source, and concurrent metabolic risk factors (hypertension, smoking, obesity, diabetes mellitus).<sup>100</sup>

The proximity of the heart to the chest wall in breast cancer and Hodgkin's lymphoma increases the occurrence of RIHD. In general, patients with left-sided breast cancer have higher risk of direct exposure of radiation beams to the heart because of the anatomic location of the heart. Some studies demonstrated increased morbidity and mortality from cardiovascular disease after treatment for left-sided breast cancer patients compared with those patients treated for right-sided breast cancer.<sup>108–110</sup> However, later reports from the 1986 to 1993 SEER (Surveillance, Epidemiology, and End Results) database demonstrated that there was no difference in cardiac morbidity between left- versus right-sided breast cancer when treated surgery plus radiation.<sup>111</sup> Interestingly, after 1979, radiotherapy to either the left or right side of the internal mammary chain was associated with increased risk of valvular heart disease and HF, but no increased risk of myocardial infarction when compared with patients without radiation.<sup>112</sup> This decreased risk in myocardial infarction is attributed to change in radiation techniques as discussed later.<sup>112</sup>

In addition to breast cancer patients, Hodgkin's lymphoma survivors treated between 1965 and 1995 have an increased risk of radiation-induced myocardial infarction and HF that is 3 to 5-fold higher than the general population after a median follow-up of  $\approx 19$  years.<sup>113</sup> The same study demonstrated that anthracycline exposure further increased the risks of HF and valvular disorders from mediastinal radiotherapy, suggesting additive cardiotoxic effect.<sup>113</sup> In a retrospective analysis of 1279 Hodgkin's survivors treated with mediastinal radiation demonstrated a cumulative increase in cardiac disease from 2.2% at 5 years and 15% at 20 years.<sup>114</sup> Hodgkin's survivors have increased standard incidence ratio for coronary artery bypass graft (3.19), percutaneous intervention (1.55), implantable defibrillator/pacemaker

placement (1.9), valve surgery (9.19), and pericardial surgery (12.91) when compared with age-matched controls.<sup>114</sup>

In addition to cardiac effects, Hodgkin's survivors who are treated with mediastinal and neck radiation exhibit higher rates of cerebrovascular disease. A recent retrospective study demonstrated that 2201 Hodgkin's survivors treated between 1965 and 1995 had increased standardized incidence ratio of 2.2 for stroke and 3.1 for transient ischemic attack compared with a general population.<sup>115</sup> Hypertension, diabetes mellitus, and hypercholesterolemia were associated with increased occurrence of ischemic cerebrovascular disease while chemotherapy treatment was not.<sup>115</sup> Beyond Hodgkin's lymphoma survivors, a study of childhood survivors of acute lymphoblastic leukemia, and brain tumors who received radiation, showed a significantly higher relative risk of stroke at a mean follow-up of 18 years.<sup>116</sup> Thus, in cancer survivors treated with radiation, we must be aware of the spectrum of vascular disease, both cardiovascular and cerebrovascular and aggressively treat modifiable risk factors.

The pathophysiology related to RIHD is not clearly delineated; however, the final common histology is related to the fibrosis within the myocardium, valves, vasculature, and pericardium. Radiation is thought to induce tumor damage through the formation of reactive oxygen species, which disrupts DNA synthesis and repair in highly replicating cells.<sup>117</sup> Because cardiac myocytes are well-differentiated cells, they are perceived as relatively radiation-resistant.<sup>117</sup> However, experimental evidence suggests that RIHD is the result of indirect myocyte injury caused by microvascular and macrovascular damage. The mechanism of RIHD has been explored through experimental work from animals demonstrating 3 phases of injury. Small to medium sized arteries exhibit acute inflammatory changes with neutrophilic invasion in all layers of the heart  $\approx$ 6 hours after exposure to radiation.<sup>103,118</sup> During the latent phase (2 days from exposure), the experimental animals have grossly normal-appearing myocardium and pericardium; however, electron microscopy reveals progressive capillary luminal destruction from fibrin and platelets.<sup>103,118</sup> The alterations in the microcirculation leads to ischemia and fibrosis.<sup>103</sup> Although the animal experiments were not always conducted with fractionated radiation, the histological changes observed were identical to those described in humans, although timing of the pathological changes is different.

The cusps and leaflets of heart valves undergo fibrotic changes with and without calcifications when exposed to radiation. This cannot be explained by microvascular changes because the valves are largely avascular.<sup>119,120</sup> Although pathophysiology of radiation-induced valvular disease is not well understood, left-sided valves are more commonly affected than right-sided valves. Because left-sided valves are more commonly affected by radiation exposure suggest that higher systemic pressure plays a role in the pathogenesis.<sup>120,121</sup>

Recent studies suggest that RIHD is diminishing in patients treated in the 1980s and 1990s compared with earlier decades.<sup>122,123</sup> The decrease in RIHD is likely related to the changes in radiation techniques, such as switch from Cobalt 60 teletherapy to linear accelerators, which is known to decrease the variation of doses at field edges (also known as

wide penumbra).<sup>123</sup> Additionally, Hoening et al showed that the elimination of internal mammary node radiation therapy fields reduced the risk of CAD significantly in breast cancer patients.<sup>112</sup> Computed tomography simulation planning is often used to exclude the cardiac silhouette from tangential beams of radiation, which reduces the exposure to heart. Prone patient positioning and respiratory gating are alternative strategies used to reduce the cardiac exposure in breast cancer patients treated with radiation.<sup>123,124</sup> Additionally, there have been a few studies that show CAD risk factors, such as smoking, hypertension, diabetes mellitus, and hypercholesterolemia, act synergistically with radiation therapy to increase the known cardiac complications. Thus, healthcare providers need to aggressively treat cardiac risk factors during radiation treatment to decrease long-term cardiac effects. Ultimately, as the radiation techniques improve and cardiac risk factors are modified, the cardiovascular complications will likely decrease for survivors.

### Treatment for Chemotherapy-Related Cardiotoxicity

Currently, there are no formal guidelines from the American College of Cardiology, American Heart Association, or the Heart Failure Society of America regarding the treatment and management of chemotherapy/radiation-induced cardiotoxicity. However, the European Society of Medical Oncology recommends serial cardiac monitoring and initiation of angiotensin-converting enzyme (ACE) inhibitor and BB in patients who develop LV dysfunction or prophylactically in patients at high risk of cardiotoxicity.<sup>125</sup> The European Society of Medical Oncology recommendations are based on several small studies demonstrating improvement in cardiac function with the initiation of neurohormonal antagonist in patients with chemotherapy-induced cardiomyopathy and the preservation of cardiac function from prophylactic use of ACE/BB therapy.<sup>12,126</sup> One of the critical factors in cardiac recovery from AIC is the prompt initiation of standard HF therapy. Cardinale et al demonstrated that the time elapsed from the end of chemotherapy to the start of HF therapy (time-to-treatment), with ACE and, when tolerated, with BB, is a crucial variable for recovery of cardiac dysfunction in patients treated with anthracyclines.<sup>12,127</sup>

Despite the use of HF guideline-based medical therapy, AIC is often irreversible if not identified early and can lead to progressive end-stage HF. Analysis of heart transplant data from the United Network of Organ Sharing demonstrated that over the last 24 years, there was a statistically significant increasing trend in the number of AIC patients who required heart transplantation.<sup>128</sup> Chemotherapy-induced cardiomyopathy has been reported in  $\leq$ 10% of cancer survivors, progressing to end-stage HF in 2% to 4%.<sup>129</sup> Because newer chemotherapy agents have shown cardiotoxic potential and cancer mortality is decreasing, the number of cancer survivors with chemotherapy-induced cardiomyopathy requiring orthotopic heart transplantation is likely to rise.<sup>130</sup> The United Network of Organ Sharing data illustrates that AIC is a relevant problem leading to severe HF.<sup>128</sup> A previous study revealed that the prognosis for AIC is worse than ischemic and other forms of idiopathic cardiomyopathy; thus, it is important to understand treatment options and outcomes of advanced HF



in cancer survivors.<sup>131</sup> Although some transplant programs may have center specific guidelines on how long cancer survivors need to be in remission before heart transplant listing, the International Society of Heart and Lung Transplant committee published a recent update addressing a case-by-case approach for cancer survivors who develop end-stage HF. The guidelines state that preexisting neoplasms are diverse, and many patients may achieve cure or remission with appropriate treatment.<sup>132</sup> In these patients needing cardiac transplantation, collaboration with oncology specialists should occur to stratify each patient as to their individual risk of tumor recurrence. Cardiac transplantation should be considered when tumor recurrence is low based on tumor type, response to therapy, and negative metastatic work-up.<sup>132</sup> The specific amount of time to wait for a transplant after cancer remission will depend on the aforementioned factors, and no arbitrary time period for observation should be used (Class I, Level of Evidence: C).<sup>132</sup>

Retrospective data shows that patients with chemotherapy-induced HF benefit from advanced HF therapies, including cardiac-resynchronization therapy, ventricular assist devices, and orthotopic heart transplant with similar outcomes to patient with other forms of HF.<sup>133</sup> Two studies demonstrate that cancer survivors who need OHT because of chemotherapy-related cardiomyopathy have similar outcomes to other causes of cardiomyopathy both at short and long-term follow-up of 10-years. Interestingly, there is no increased risk of death because of recurrent malignancy in this population.<sup>128,130</sup> Similar to OHT, AIC patients who needed mechanical support, such as ventricular assist device, had similar survival to other etiologies of HF; however, it seems that AIC patients more commonly needed additional right ventricular support in conjunction with left ventricular assist device.<sup>134</sup> Additionally, as discussed earlier, cell therapy may play a role in the future treatment of AIC unresponsive to medical therapy.<sup>23</sup> In the coming years, we will gain further insight into the therapeutic role of progenitor cells in the treatment of AIC.

Several studies have examined both trastuzumab-induced and TKI-induced systolic dysfunction. In the early stages of trastuzumab-induced cardiotoxicity, withdrawal or discontinuation of the drug ( $\approx 4$ –8 weeks) can reverse the systolic dysfunction with the initiation of standard HF therapy (ACE inhibitor and BB).<sup>126</sup> Although the true reversibility of trastuzumab-induced cardiotoxicity is under debate, there is general agreement that conditions improve in most patients after trastuzumab withdrawal and treatment of cardiac symptoms.<sup>135</sup> A rechallenge of trastuzumab once LVEF recovers on HF therapy has been reported to be well-tolerated.<sup>126</sup> A study by Ewer et al demonstrated that 25 patients were rechallenged with trastuzumab after recovery of LVEF ( $>50\%$ ), and 22 (88%) maintained stable LVEF during a median follow-up of 8.4 months. In general, a rechallenge with trastuzumab (other HER2-targeted therapy) is mostly recommended for patients with advanced-stage disease or after careful evaluation of risks/benefits have been discussed with the patient.<sup>28</sup> As discussed earlier, there is limited data on whether TKI-induced systolic dysfunction is reversible and the best therapeutic options for treatment other than the standard HF guidelines. Because higher levels of cardiac dysfunction were noted in

sunitinib-treated patients with underlying CAD and hypertension, the European guidelines recommend aggressive risk factor control, with careful cardiac monitoring in these patients.<sup>136</sup>

### Prevention of Cardiotoxicity

In the context of anthracyclines, there are a few oncology-based strategies to reduce the likelihood of AIC. In patients who are thought to exceed the recommended lifetime cumulative dose of anthracycline, an oncologist may use liposomal-encapsulated formulation of doxorubicin. Liposomal-encapsulated anthracyclines appear to preferentially distribute in tumors because of vascular permeability in malignant tissue. Two liposomal-encapsulated doxorubicin formulations are currently in use, which improve the relative delivery of drug to tumors versus other organs, including the heart. Doxil (pegylated formulation; Janssen Products, Titusville, NJ) and Myocet (nonpegylated formulation approved in Europe; Teva Pharma B.V., Essex, UK) were highly active against tumors and generally less cardiotoxic than standard doxorubicin.<sup>137</sup> A recent review of 2 randomized controlled trials (including 521 patients) concluded that both clinical HF and subclinical cardiac dysfunction were less common in patients treated with liposomal-encapsulated doxorubicin than with a nonliposomal formulation.<sup>138</sup> Both the increased cost of liposomal agents and the increased risk of hand-foot syndrome (also known as palmar plantar erythrodysesthesia) limit the broad use of these agents.<sup>139</sup>

Recent prospective studies have investigated the prophylactic role of ACE inhibitors and BB as cardioprotective agents. In a prospective trial, 90 patients with acute leukemia undergoing treatment with anthracycline-based chemotherapy were randomized to start enalapril and carvedilol versus placebo (OVERCOME [Prevention of Left Ventricular Dysfunction With Enalapril and Carvedilol in Patients Submitted to Intensive Chemotherapy for the Treatment of Malignant Hemopathies] trial).<sup>140</sup> The OVERCOME trial demonstrated that prophylactic use of enalapril and carvedilol stabilized LVEF in comparison to the control group at 6 months, albeit a small absolute difference ( $-3.1$  by echocardiography;  $P=0.09$ ). A recent meta-analysis identified 4 published small randomized studies (18–45 patients with breast cancer) evaluating the possible cardioprotective role for BB and angiotensin antagonists in patients undergoing anthracycline-based chemotherapy.<sup>141</sup> BBs and ACE inhibitors were associated with better LVEF preservation, especially in patients treated with higher cumulative doses of anthracyclines.<sup>141</sup> The PRADA trial (Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy) was a randomized, placebo-controlled, double-blind study to determine whether angiotensin receptor blocker (candesartan) or BB (metoprolol) alone or in combination may prevent the development of LV dysfunction in patients on standard adjuvant treatment for early breast cancer.<sup>142</sup> The results from the  $2 \times 2$  factorial design study involving 120 patients were presented at the 2015 American Heart Association meeting. The primary outcome, decline in LVEF from baseline to end of the study, was  $-0.8\%$  in the candesartan group versus  $-2.6\%$  in the placebo group ( $P=0.026$  for between-group difference). The authors concluded that candesartan protected against an early

decline in LVEF associated with adjunct therapy for breast cancer; however, metoprolol showed no cardioprotective effect over placebo. The critics suggest the authors should have used carvedilol and considered a unified definition of cardiotoxicity to improve the generalizability of the study. Despite the criticism, the PRADA study garners much impact as one of the largest prospective studies in the cardio-oncology field, examining role of a cardioprotective regimen in breast cancer patients. Until recently, many of the studies in the cardio-oncology were retrospective or observational in nature. As the field continues to evolve, larger prospective, multicenter, randomized trials will add to our knowledge on how to prevent cardiotoxicity with specific chemotherapies. Until then, various forms of chemotherapy-induced cardiomyopathy will continue to be treated with standard HF therapy, appropriate risk factor modification, and cardiovascular screening that is in line with current guidelines and the major oncology clinical trials.

### Conclusions

As targeted cancer therapies continue to emerge, the cardio-oncology community needs to stay focused on the analogous mechanism of action in both tumors and cardiovascular system to anticipate issues related to cardiotoxicity. An enhanced understanding of the mechanisms of cardiotoxicity related to chemotherapy and radiation may lead to improved cardioprotective therapies. Additionally, larger prospective studies are needed to solidify guidelines on appropriate monitoring, prevention, and treatment of cancer-related cardiac conditions.

### Disclosures

None.

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