

Cancer Therapy–Induced Cardiotoxicity: Basic Mechanisms and Potential Cardioprotective Therapies

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Case Presentation

The patient is a 63-year-old man with a history of well-controlled hypertension who is diagnosed with diffuse large B-cell lymphoma and treated with a doxorubicin-containing chemotherapy regimen. During therapy, he is continued on hydrochlorothiazide for his hypertension. Three months later, he complains of dyspnea on exertion and mild lower extremity edema. A transthoracic echocardiogram reveals a moderately reduced left ventricular ejection fraction (LVEF), which is new compared with a study performed before he underwent chemotherapy.

1. What are the mechanisms of cardiotoxicity due to cancer therapies?
2. What basic and clinical data are there to support the use of particular medications to treat cardiotoxicity in the oncology patient?

Life expectancy after the diagnosis and treatment of cancer has increased significantly in the past 2 decades,¹ uncovering the unintended consequences of cancer therapy on the cardiovascular system and leading to accelerated cardiovascular disease in patients treated with a wide variety of antitumor agents.^{2–6} Given the high prevalence of cardiovascular disease and associated risk factors in the general population, patients may have compromised reserve before

starting chemotherapy.^{7,8} Furthermore, patients treated with cardiotoxic cancer therapies often develop multiple risk factors such as hypertension, obesity, dyslipidemia, and metabolic syndrome, further worsening cardiovascular reserve and increasing the likelihood of subsequent cardiotoxicity.⁹

Cancer therapy–induced cardiotoxicity is due to a combination of “on-target” and “off-target” effects. These effects result from redundancy in essential signaling cascades that promote undesired cancer cell proliferation but also protect cardiomyocyte and endothelial cells, especially in response to stress. Effective therapies for treating cancer therapy–induced cardiotoxicity need to either exploit tissue-specific differences between cancerous tissues and the cardiomyocyte/cardiac endothelium or, more specifically, affect the cardiotoxic mechanisms without disrupting antitumor pathways. In this review, we focus on 3 classes of commonly used agents (anthracyclines, the ErbB2 inhibitor trastuzumab, and the vascular endothelial growth factor [VEGF] signaling pathway inhibitors sunitinib and sorafenib), which have established cardiotoxicity. For each class of agents, we first provide a broad overview of the leading hypotheses regarding the mechanisms of cardiotoxicity, noting the uncertainty and relevant controversies in the field. We then review the basic and clinical data to support use of specific therapies in the treatment of cancer therapy–induced cardiotoxicity, noting areas where further research is needed.

Cardiotoxicity Due to Anthracyclines: Mechanisms and Potential Therapeutics

Anthracyclines are likely the most frequently cited and well-studied class of cardiotoxic anticancer agents, and although they are effective, their use is limited by dose-dependent toxicity.^{10,11} Retrospective analyses from clinical trials in adults suggest that the incidence of congestive heart failure (HF) due to doxorubicin was 1.7% at a cumulative dose of 300 mg/m², 4.7% at 400 mg/m², 15.7% at 500 mg/m², and 48% at 650 mg/m².¹⁰

Anthracyclines target topoisomerase II (Top2), binding to both DNA and Top2 to form complexes that trigger cell death.

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There are multiple proposed mechanisms of anthracycline-induced cardiotoxicity; however, the most widely cited and accepted mechanism is the formation of reactive oxygen species (ROS) leading to oxidative stress.^{6,12–15} The generation of ROS occurs via multiple pathways. Anthracyclines enter cells and the quinone moiety undergoes redox cycling, generating free radicals by an enzymatic pathway via the mitochondrial respiratory chain and via a nonenzymatic pathway involving direct interactions between anthracyclines and intracellular iron.¹² This results in impaired mitochondrial function, cellular membrane damage, and cytotoxicity.^{6,14} Toxic hydroxyl radicals from anthracycline–iron complexes act as cytotoxic messengers. The enzyme nitric oxide synthase also plays a role in the generation of anthracycline-mediated reactive nitrogen species and worsens nitrosative stress.¹³

Recent data suggest that the formation of ROS also occurs via the isozyme Top2 β in cardiomyocytes.¹⁶ Both Top2 α , which is overexpressed in proliferating cancerous tissues, and Top2 β , which is expressed in adult mammalian cardiomyocytes, are targets of anthracyclines. After doxorubicin exposure, cardiomyocytes from wild-type mice exhibited significant abnormalities in the *p53* tumor suppressor gene, β -adrenergic signaling, and apoptotic pathways. In contrast, cardiomyocytes from a cardiomyocyte-specific Top2 β knockout mouse (Top2 $\beta^{\Delta/\Delta}$) exhibited markedly fewer changes. With prolonged doxorubicin exposure, wild-type cardiomyocytes, again in comparison to Top2 $\beta^{\Delta/\Delta}$ cardiomyocytes, showed worse alterations in the expression of genes that regulate mitochondrial function, biogenesis, and oxidative phosphorylation, including downregulation of peroxisome proliferator-activated receptor γ coactivator-1 α and -1 β . Peroxisome proliferator-activated receptor γ coactivator-1 α is an established and critical regulator of oxidative metabolism and is abundantly expressed in the heart^{17,18}; it may play a role in the pathogenesis of HF.^{19,20}

Other mechanisms that affect the Top2–DNA complex may also play a role in anthracycline-mediated cytotoxicity. The GTPase Rac1 is an essential regulator of DNA damage seen after Top2 inhibition by anthracyclines.^{21–23} Rac1 is also a subunit of NADPH oxidase and is necessary for its activation and ROS generation. In an animal model of doxorubicin-induced cardiotoxicity, cardiomyocyte-specific Rac1 deletion led to reduced ROS formation, attenuated apoptosis, and improved myocardial function.²¹ Anthracyclines may also affect the population of cardiac progenitor cells, which leads to an impaired response to pathologic stress and injury repair. Data from animal models have shown that exposure to doxorubicin leads to a decrease in c-Kit⁺ cardiac progenitor cells, and exposure to doxorubicin impaired *in vitro* proliferation of c-Kit⁺ cardiac progenitor cells.^{24,25}

Anthracycline therapy may also lead to impaired diastolic relaxation via calpain-dependent titin proteolysis and increased intracellular calcium due to impaired sequestra-

tion.^{26,27} It is unclear whether these effects are ROS dependent or independent, but titin proteolysis may result in myofilament instability and degradation, cardiomyocyte cell death, and subsequent abnormalities in diastolic function.²⁶

Additional data have suggested that anthracycline therapy renders cardiomyocytes more susceptible to alterations in neuregulin-1 (NRG-1) and ErbB signaling and subsequent prosurvival pathways, mediated by phosphoinositide 3-kinase, the serine/threonine-specific protein kinase Akt, mitogen-activated protein kinase, and extracellular signal-regulated kinase (ERK) 1/2 signaling cascades. Administration of NRG-1 is known to be cardioprotective in the setting of anthracycline-induced cardiotoxicity and, conversely, NRG-1 heterozygotes have decreased survival and cardiac function with doxorubicin exposure compared with wild types.^{28–32} In animal models, acute treatment with doxorubicin led to decreased ErbB4, partially mediated by microRNA-146a-induced degradation, but no change in ErbB2 expression.³³ However, in another *in vivo* murine study, ErbB2 expression was increased after long-term doxorubicin treatment.³⁴ The explanation behind the observed discordance in ErbB2 and ErbB4 receptor expression in models of anthracycline cardiotoxicity is not clear but may be related to the duration of cardiomyopathy and stage of compensation, or potentially the involvement of other inhibitors or activators of ErbB receptor expression.

In summary, there is basic evidence to support the following key mechanisms in anthracycline-induced cardiotoxicity: formation of ROS and increased oxidative stress via multiple pathways including redox cycling of the quinone moiety of doxorubicin, the formation of anthracycline–iron complexes, downstream effects of Top2 β inhibition, and Rac1 signaling; impaired calcium signaling and intracellular sequestration affecting myocardial relaxation; negative effects on cardiac progenitor cells; and impairment of prosurvival signaling pathways via NRG-1 and ErbB inhibition (Figure 1A).

In the following sections, we detail the potential rationale for both existing and novel therapies that may attenuate the observed cardiotoxicities of anthracyclines in the context of these mechanisms (Table 1, Figure 1B). When available, we also present human level data to support the effects of these interventions.

Evidence for Dexrazoxane or Statin Therapy to Reduce Oxidative Stress and Inhibit Top2 β and Rac1 Signaling

Dexrazoxane (ICRF-187), the only US Food and Drug Administration–approved drug for the prevention of anthracycline-related cardiotoxicity, acts by chelating redox-active iron, thereby preventing the formation of anthracycline–iron complexes and subsequent ROS formation.¹⁴ Other iron chelators, however, have not shown a benefit after anthracycline treat-

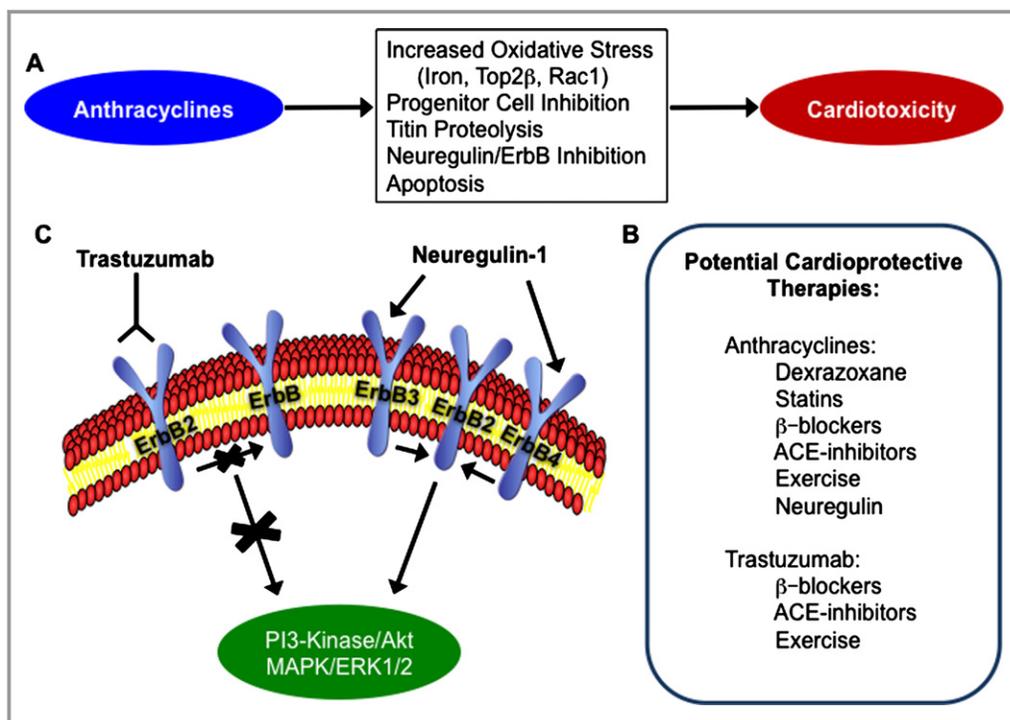


Figure 1. Proposed mechanisms and potential cardioprotective therapies for cardiotoxicity due to anthracyclines and ErbB inhibitors. A, Mechanisms of anthracycline-induced cardiotoxicity. B, Potential cardioprotective therapies target the described mechanisms of cardiotoxicity. C, Mechanisms of ErbB inhibitor-induced cardiotoxicity by trastuzumab. ACE indicates angiotensin-converting enzyme; ERK1/2, extracellular signal-regulated kinase 1/2; MAPK, mitogen-activated protein kinase; NRG-1, neuregulin-1; PI3K, phosphoinositide 3-kinase; Top2 β , topoisomerase II β .

ment, leading to the hypothesis that dexrazoxane acts via additional mechanisms.¹⁴ Interestingly, in cardiomyocytes, dexrazoxane inhibits formation of drug-induced Top2 α - and Top2 β -DNA cleavage complexes, reducing anthracycline-induced DNA damage.³⁵ However, this concomitant inhibition of Top2 α cleavage complexes has generated some concern that dexrazoxane may render anthracyclines ineffective against cancer cells, and clinical trial data remain controversial.

Overall, data from several human clinical studies suggest that dexrazoxane is cardioprotective in the setting of anthracycline therapy. In a recent Cochrane meta-analysis, dexrazoxane use in the setting of anthracycline therapy was associated with a decreased risk of clinical HF (relative risk 0.18, CI 0.1 to 0.32, $P < 0.001$).³⁶ However, there was no effect on overall survival. Despite data suggesting cardioprotection after dexrazoxane treatment, in our experience, it is used with less frequency, possibly secondary to concerns regarding the potential interference by dexrazoxane on the antitumor effects of doxorubicin and the potential for an increase in secondary leukemias. However, in the referenced Cochrane review, there was no difference in oncologic response, and the only adverse effect associated with dexrazoxane was an increased risk of leukopenia at nadir but not at time of recovery.³⁶

Other medications that have antioxidant properties may also be effective therapies for anthracycline-induced cardiotoxicity. HMG-CoA reductase inhibitors, or statins, have been shown to have pleiotropic effects including antioxidant and anti-inflammatory properties. In vitro studies have shown that lovastatin reduced doxorubicin-induced cardiomyocyte cell death³⁷ and reduced Top2 β -mediated DNA damage, thought to be due to impaired Rac1 signaling.³⁸ As noted, Rac1 inhibition has been shown to attenuate doxorubicin-induced cardiotoxicity. In animal studies, lovastatin attenuated troponin I elevation and cardiac fibrosis after exposure to doxorubicin,³⁸ and mice treated with fluvastatin had an attenuation of left ventricular (LV) dysfunction after doxorubicin exposure, postulated to be due to antioxidant and anti-inflammatory mechanisms.³⁹ Interestingly, lovastatin may potentiate the antitumor effects of doxorubicin in vitro and in vivo in human fibrosarcoma cells.³⁸

Data regarding statin therapy for anthracycline-induced cardiotoxicity in humans are more limited. In a retrospective observational study of 201 breast cancer patients treated with anthracyclines, concomitant statin use for other indications in 64 patients was associated with a reduced risk of HF hospitalization compared with propensity-matched controls (hazard ratio 0.3, 95% CI 0.1 to 0.9, $P < 0.03$).⁴⁰ Other small studies of atorvastatin use (40 mg/day) in the setting of

Table 1. Potential Cardioprotective Strategies in Cancer Therapy Cardiotoxicity

Class of Cancer Therapy	Potential Cardioprotective Therapies	Hypothesized Biologic Mechanisms of Action	Available Evidence
Anthracyclines	Dexrazoxane	<ul style="list-style-type: none"> Decreased ROS formation via prevention of anthracycline–iron complex formation Reduced anthracycline-induced DNA damage via inhibition of Top2–DNA cleavage complexes 	<ul style="list-style-type: none"> In vitro and in vivo animal studies Randomized clinical trials Meta-analyses
	HMG-CoA reductase inhibitors	<ul style="list-style-type: none"> Reduced cell death and Top2β-mediated DNA damage via Rac1 inhibition 	<ul style="list-style-type: none"> In vitro and in vivo animal studies Retrospective clinical studies and small randomized clinical trial
	β -Blockers	<ul style="list-style-type: none"> Increased prosurvival signaling via recruitment of β-arrestin and transactivation of EGFR Mitigation of oxidative stress Enhanced lusitropy 	<ul style="list-style-type: none"> Small randomized clinical trials, including combination ACE inhibitor and β-blocker therapy
	ACE inhibitors	<ul style="list-style-type: none"> Attenuated oxidative stress and interstitial fibrosis Improved intracellular calcium handling Improved cardiomyocyte metabolism Improved mitochondrial function 	<ul style="list-style-type: none"> Randomized clinical trials, including combination ACE-inhibitor and β-blocker therapy
	Exercise training	<ul style="list-style-type: none"> Decreased ROS formation Reduced pro-apoptotic signaling Improved calcium handling Improved myocardial energetics via augmented AMPK activity 	<ul style="list-style-type: none"> In vivo animal studies
	Bivalent neuregulin	<ul style="list-style-type: none"> Biased ErbB signaling 	<ul style="list-style-type: none"> In vitro and in vivo animal studies from single laboratory
Trastuzumab	ACE inhibitors	<ul style="list-style-type: none"> Decreased angiotensin-induced blockade of NRG-1/ErbB pathway 	<ul style="list-style-type: none"> Retrospective clinical studies (in combination with β-blockers)
	β -Blockers	<ul style="list-style-type: none"> Increased prosurvival signaling via recruitment of β-arrestin and transactivation of EGFR 	<ul style="list-style-type: none"> Retrospective clinical studies (one in combination with ACE inhibitors)
	Exercise	<ul style="list-style-type: none"> Enhanced NRG-1/ErbB signaling Increased myocardial Akt Inhibition of TGF-β signaling 	<ul style="list-style-type: none"> Small, single group study with failure to demonstrate an attenuation of trastuzumab-induced LV dilation
Sunitinib	Thalidomide	<ul style="list-style-type: none"> Improved pericyte function via PDGFR signaling 	<ul style="list-style-type: none"> In vivo animal studies from single laboratory
	AMPK activators	<ul style="list-style-type: none"> Restoration of favorable myocardial energetics 	<ul style="list-style-type: none"> Controversial in vitro and in vivo data

ROS indicates reactive oxygen species; Top2, topoisomerase-II; EGFR, epidermal growth factor receptor; ACE, angiotensin-converting enzyme; NRG-1, neuregulin-1; TGF, transforming growth factor; LV, left ventricular; PDGFR, platelet-derived growth factor receptor; AMPK, AMP-activated protein kinase.

anthracycline therapy demonstrated a decrease in high-sensitivity C-reactive protein levels and maintenance of cardiac function, compared with controls.⁴¹ Interestingly, human level data also suggest that statins have potential antitumor effects via other mechanisms.^{42,43} Further clinical data are necessary to verify these findings.

β -Blocker Therapy May Attenuate Anthracycline-Induced Cardiotoxicity via Several Mechanisms

Inhibitors of β -adrenergic signaling reduce mortality in patients with systolic HF, and there is growing use for these agents in mitigating anthracycline cardiotoxicity.⁴⁴ Although the exact mechanisms of cardioprotection with β -blockers remain to be delineated, we hypothesize that there are a number of key effects. Certain β -blockers (carvedilol, nebiv-

lol, alprenolol) inhibit β -adrenergic receptor–mediated G protein–coupled receptor signaling while preserving β -adrenergic receptor recruitment of β -arrestin and transactivation of ErbB1 (or epidermal growth factor receptor).^{45,46} Beta-arrestin is cardioprotective under long-term catecholamine stimulation, and activation of prosurvival signaling via the ErbB receptor pathway and related downstream mediators has been associated with an attenuation of anthracycline-induced cardiotoxicity, as noted here earlier. Carvedilol, specifically, has also been shown in animal models to mitigate oxidative stress in a variety of pathologic states including ischemia–reperfusion injury⁴⁷ and dilated cardiomyopathy.⁴⁸ Carvedilol also prevents doxorubicin-induced mitochondrial respiration alterations and changes in mitochondrial calcium loading capacity.⁴⁹ As noted previously, anthracycline therapy may lead to impaired diastolic relaxation via titin proteolysis and

impaired intracellular calcium sequestration.^{26,27} β -Blockade prevents myocardial calcium overload and results in enhanced lusitropy,⁵⁰ providing further potential mechanistic rationale toward the favorable effects of this therapy.

Randomized, clinical trial data demonstrating the beneficial effects of β -blockers for anthracycline cardiotoxicity are more limited. In a small, randomized placebo-controlled study, patients treated with carvedilol at anthracycline initiation showed attenuation of the decline in LVEF observed in the placebo group at 6 months⁵¹ and attenuated alterations in diastolic function. In another small, randomized placebo-controlled study by the same group of investigators, patients with breast cancer were randomized to nebivolol or placebo to be initiated 7 days before anthracycline-based chemotherapy and continued for 6 months. Compared with controls (n=18), patients treated with nebivolol (n=27) had attenuation of LVEF decline at 6 months.⁵² Recent data from the OVERCOME (prevention of left Ventricular dysfunction with Enalapril and carvedilol in patients submitted to intensive Chemotherapy for the treatment of Malignant Hemopathies) trial have also shown that β -blocker therapy, in combination with angiotensin-converting enzyme (ACE) inhibitor therapy, may be beneficial in preventing anthracycline-induced cardiotoxicity, with treated patients demonstrating less significant changes in LVEF and a lower incidence of death or HF compared with placebo.⁵³ The role of prophylactic β -blocker and angiotensin receptor blocker therapy is also under active investigation in patients undergoing epirubicin therapy in the PRADA (Prevention of Cardiac Dysfunction during Adjuvant breast cancer therapy) study.⁵⁴

ACE Inhibitor Therapy May Be Cardioprotective in Patients at Increased Risk of Anthracycline-Associated Cardiotoxicity

Multiple animal studies have shown a beneficial effect of ACE inhibitor therapy on anthracycline-induced cardiotoxicity.^{55–58} Possible key mechanisms supporting the benefit of ACE inhibition in chemotherapy-induced cardiotoxicity include a reduction in interstitial fibrosis,^{59,60} attenuation of oxidative stress,^{55,57} improved intracellular calcium handling,⁶¹ and alterations in gene expression that affect cardiomyocyte metabolism and mitochondrial function.⁶²

In addition to the OVERCOME trial, there is a fair amount of human-level data to support the role of ACE inhibitors in the prevention and treatment of anthracycline-induced cardiotoxicity, although sample sizes in each of these studies are small. In a study focused on the effect of enalapril alone, 114 patients with a baseline normal LVEF but an elevated troponin I level within 72 hours after high-dose anthracycline administration were randomized to enalapril or placebo after completion of chemotherapy and followed for 12 months.⁶³ Interestingly, 43% of control subjects and none of the ACE inhibitor-treated

patients met the primary end point (decrease in LVEF of >10%). Additionally, there were 30 cardiac events in the control patients and only 1 cardiac event in ACE inhibitor-treated patients.

In another observational study by the same group of investigators, patients with an LVEF \leq 45% attributed to anthracycline cardiotoxicity were treated with enalapril with the addition of carvedilol as tolerated.⁶⁴ Normalization of LVEF was achieved in 42% of patients, who were deemed “responders.” Patients who had a shorter time to the initiation of ACE inhibitors and β -blockers after completing chemotherapy were more likely to be responders. No response was observed in patients in whom therapy was initiated >6 months after completion of chemotherapy. These findings suggest that the prompt institution of these medications is important in the recovery of LVEF. However, this study was not randomized and it is unclear if any of these patients might have improved over time without specific pharmacologic intervention.

Nonpharmacologic Therapy: Exercise Training May Reduce Cardiotoxicity After Anthracycline Therapy

Aerobic exercise has been shown in multiple studies to attenuate doxorubicin-induced cardiotoxicity in animal models, with purported mechanisms including decreased ROS formation, reduced activation of proapoptotic signaling, increased GATA-4 expression leading to preservation of cardiomyocyte proliferation, improved calcium handling potentially via modulation of calpain activation, and activation of the AMP-activated protein kinase (AMPK) pathway, which results in improved myocardial energetics.⁶⁵ While, at the time of this review, there are no published clinical studies to evaluate exercise therapy as a specific treatment to rescue anthracycline-induced cardiomyopathy, data suggest that long-term exercise could improve impaired angiogenesis and alterations in cellular metabolism seen after anthracycline chemotherapy.⁶⁶ Exercise therapy has been noted to decrease all-cause mortality in the oncologic patient population; however, studies are needed to specifically define the effect of exercise on cardiotoxicity in this population, and some of these trials are under way (www.clinicaltrials.gov, NCT01943695).⁶⁷

NRG-1 Signaling via the ErbB Receptor Family as a Cardioprotective Stress Response: Role for Biased ErbB Signaling to Mitigate Anthracycline Cardiotoxicity

Activation of the ErbB receptor family using the recombinant ligand NRG-1 is currently being studied in early phase clinical trials as a therapy for chronic systolic HF. The administration of this recombinant protein to cancer patients might raise

theoretical concerns over increased proliferation of neoplastic cells. However, recent studies have reported novel methodologies to exploit differences in ErbB expression between neoplastic cells (primarily ErbB2/3) and cardiomyocytes (primarily ErbB2/4),⁶⁸ and create opportunities for controlled signaling activation to create the desired prosurvival effects in cardiomyocytes while avoiding the known neoplastic consequences of this cascade. A recent study describing a cleverly engineered bivalent neuregulin demonstrated signaling toward ErbB3 homotypic interactions in cancer cells, and ErbB4 homotypic interactions in cardiomyocytes, with preservation of some degree of ErbB2 phosphorylation and the Akt and ERK signaling cascades.⁶⁹ Bivalent neuregulin did not interfere with doxorubicin-mediated antitumor effects *in vitro* but did protect against doxorubicin cardiotoxicity *in vitro* and *in vivo*. However, bivalent neuregulin stimulation of isolated cardiomyocytes still led to a modest degree of ErbB2 phosphorylation, raising some potential uncertainty about its use in patients with ErbB2 malignancies.

Cardiotoxicity Due to ErbB2/HER2 Inhibitors: Mechanisms and Potential Therapeutics

ErbB2 is an important mediator of unregulated cell growth and proliferation in many types of cancer and is most notably overexpressed in ErbB2/HER2-positive breast cancer.⁷⁰ Inhibition of the ErbB2 receptor forms the basis of ErbB2 therapeutics.⁷¹ Although there was hope that targeted cancer therapeutics would spare patients of the morbidity associated with cancer therapy, patients treated with the humanized anti-ErbB2 monoclonal antibody trastuzumab were found to be at increased risk of cardiotoxicity, worsened when treated with concomitant or sequential anthracycline chemotherapy.^{72–75}

In one of the first clinical trials demonstrating trastuzumab's efficacy against HER2/ErbB2-overexpressing metastatic breast cancer, cardiotoxicity was noted in 27% of patients receiving trastuzumab concurrently with anthracycline therapy and 13% of patients receiving paclitaxel and trastuzumab.⁷¹ A subsequent meta-analysis of adjuvant trastuzumab therapy in ErbB2/HER2-positive breast cancer patients noted the likelihood of cardiotoxicity was nearly 2.5-fold higher after trastuzumab therapy.⁷⁵

As noted in the previous section, the ErbB family of receptors plays a pivotal role in cardioprotection in the setting of pathologic stressors including anthracycline-induced cardiotoxicity. Importantly, trastuzumab alone has proved to cause cardiac dysfunction, even in the absence of anthracycline therapy. Trastuzumab binds to the extracellular domain of ErbB2/HER2 and leads to reduced ErbB2 signaling via several mechanisms. In tumor cells, trastuzumab results in the inhibition of receptor dimerization, downregulation of ErbB2 from the cell surface membrane, blockade of proteo-

lytic cleavage of ErbB2, antibody-dependent cell-mediated cytotoxicity, and enhanced ubiquitination and degradation of the ErbB2 receptor.^{76,77}

It is widely speculated that the cardiac dysfunction observed with this agent is a direct consequence of ErbB2 inhibition in cardiomyocytes, but this remains to be unequivocally proven. Heterodimerization of ErbB2/ErbB4 on binding of the receptor's ligand NRG-1 to ErbB4 activates a powerful cell survival pathway that is an important regulator of cellular growth and proliferation in the setting of pathologic stress. Mice with a cardiac-specific deletion of ErbB2 develop dilated cardiomyopathy^{78,79} and demonstrate exaggerated systolic dysfunction after pressure overload compared with wild-type mice.⁷⁸ ErbB2 and ErbB4 expression is preserved during compensated hypertrophy but declines in the early stages of systolic dysfunction in mice subjected to pressure overload.⁸⁰ Data from explanted failing human hearts show conflicting results regarding increased versus decreased expression of ErbB2 and ErbB4 at the time of ventricular assist device explant but are consistent in demonstrating increased expression after ventricular unloading.^{81,82} Overall, these findings suggest that perturbations in ErbB receptor signaling are important in the maintenance of myocardial function.

In the subsequent sections, we review the limited data that may support the current practice of conventional therapies such as ACE inhibitors and β -blockers to treat cardiotoxicity, and we postulate therapies that may be effective based on what we know about the pathophysiology of cardiotoxicity due to ErbB2 inhibitors (Figure 1B and 1C).

ACE Inhibitors May Exert Beneficial Effects via Modulation of the Neuregulin/ErbB System

As noted, there are multiple potential mechanisms for the efficacy of ACE inhibition in anthracycline cardiotoxicity that may be specific to anthracycline-induced cardiac injury as well as, more generally, to cardiac repair with any type of injury. A similar paradigm exists for the efficacy of ACE inhibitors with trastuzumab-induced cardiac dysfunction. Angiotensin is a potent downregulator of the actions of the NRG-1/ErbB system,⁸³ making it tempting to speculate that the beneficial effects of ACE inhibition may be related to this effect. Whether angiotensin receptor blockers also have a beneficial effect in preventing trastuzumab cardiotoxicity remains unknown, but this is an area of active investigation (NCT00459771, www.clinicaltrials.gov).

β -Blockers May Promote Prosurvival ERK Signaling After ErbB2 Inhibition

Certain β -blockers (carvedilol, alprenolol, nebivolol) activate the ErbB-mediated prosurvival mitogen-activated protein

kinase/ERK1/2 pathway via recruitment of β -arrestin and activation of ErbB1, as discussed previously.^{45,46} There are nonrandomized data that suggest the combination of ACE inhibitors and carvedilol is beneficial for the recovery of LVEF in patients rechallenged with trastuzumab after initially experiencing cardiotoxicity with this agent.⁸⁴ Furthermore, in a retrospective study of patients treated with trastuzumab, dual therapy with ACE inhibitors and β -blockers was associated with LVEF recovery at 12 months.⁸⁵ However, large, placebo-controlled randomized clinical trials are warranted to determine the timing of initiation of these medications and the patients most likely to benefit from their use. There are a number of studies under way investigating the utility of pharmacologic prophylaxis with β -blockers in the setting of trastuzumab use, including Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research Trial⁸⁶ and NCT0100818 (www.clinicaltrials.gov).

Exercise Is Not Yet Established as a Means of Preventing Trastuzumab-Induced LV Remodeling

Proposed mechanisms by which exercise may attenuate trastuzumab-induced cardiac dysfunction have been recently summarized in another recent review but include potentially augmentation of NRG/ErbB signaling, increases in myocardial Akt, and inhibition of transforming growth factor- β signaling.⁸⁷ In contrast to the encouraging data on anthracycline cardiotoxicity,⁶⁵ more limited data in patients treated with trastuzumab have not yet found exercise training to be effective in preventing adverse LV remodeling. A small, single-group study of 17 patients undergoing standardized aerobic training during the first 4 months of trastuzumab therapy revealed an increase in resting LV volumes and a decrease in LVEF after 4 months of trastuzumab, although the sample size, short duration of exercise, and brief follow-up may have substantially limited the ability to detect significant differences.⁸⁸ Human studies in the noncancer population have demonstrated changes in ErbB with exercise and associations between NRG-1 and cardiopulmonary fitness.^{89,90} The direct relevance of these studies to trastuzumab and utility of exercise for cardioprotection remains unknown, and further studies are warranted.

Cardiotoxicity Due to VEGF Signaling Pathway Tyrosine Kinase Inhibitors: Mechanisms Related to Sorafenib and Sunitinib and Potential Therapeutics

Tyrosine kinase inhibitors act primarily by competitively binding to and inhibiting the ATP binding pocket, which is

conserved across the >500 kinases that are expressed in humans.⁹¹ The VEGF signaling pathway inhibitors (VSPIs), such as sorafenib and sunitinib, target the vascular endothelial growth factor receptor (VEGFR) and the platelet-derived growth factor receptor (PDGFR) families. Although they are effective anticancer therapies, their use is sometimes limited by hypertension and LV dysfunction.^{92–96} The most frequently noted cardiotoxicity due to VSPIs is hypertension, with an incidence of 19% to 47%.^{93,97,98} Cardiac dysfunction, manifested as HF or asymptomatic declines in LVEF, has also been noted; the incidence of HF is estimated to be 4% to 8%, while the incidence of asymptomatic LVEF decline is even higher, up to 28% for LVEF declines $\geq 10\%$.^{93,99}

The cardiovascular toxicity caused by the VSPIs is due to on-target effects and off-target effects via inhibition of several other kinases important in the maintenance of cardiovascular function. Here, we focus on the 2 VSPIs most studied for their cardiotoxic effects: sorafenib and sunitinib. Sorafenib acts primarily through its inhibition of VEGFR2, PDGFR, rapidly accelerated fibrosarcoma (RAF-1) and proto-oncogene B-Raf, fms-like tyrosine kinase-3, and c-Kit.¹⁰⁰ Sunitinib acts primarily through its inhibition of VEGFR, PDGFR, c-Kit, and fms-like tyrosine kinase-3.¹⁰¹ The 2 therapies share many of the same mechanisms of cardiotoxicity, although sorafenib may have additional effects through inhibition of the RAF family of kinases.

While the focus of this review is cancer therapy-induced cardiac dysfunction, we devote a portion of this discussion to the hypertension commonly observed with these VEGF signaling pathway inhibitors, given its potential role in the pathogenesis of subsequent LV dysfunction. Mechanisms of hypertension due to VSPIs have been reviewed recently¹⁰² and include decreased nitric oxide signaling, possibly increased endothelin-1 production, and capillary rarefaction in the endothelium, which may worsen ventricular-vascular coupling. Another mechanism of hypertension may be related to the VEGF-mediated suppression of nephrin, which is important for the maintenance of the glomerular slit diaphragm and may contribute to the proteinuria seen with this class of tyrosine kinase inhibitors.¹⁰³

Both sorafenib and sunitinib inhibit VEGF, which is a downstream target of hypoxia-inducible factor-1 α . The VEGF pathway is a critical stress-induced cardioprotective mechanism.^{104–106} Blockade of VEGF-VEGFR signaling in mice subjected to pressure overload led to a reduction in capillary density, impaired compensatory hypertrophy, LV dilatation, and contractile dysfunction.^{104,105} In animal models of nonischemic cardiomyopathy, overexpression of VEGF led to attenuation of apoptosis and proapoptotic signaling pathways and delayed progression to HF after tachypacing.¹⁰⁷ These data suggest that inhibition of VEGF may impair myocardial function, especially in the setting of pathologic stress, such as

increased afterload or hypertension. Furthermore, exposure to sunitinib in animal models led to increased expression of genes involved in the hypoxia response, including cardiac prolyl hydroxylase domain-containing protein 3), which is important in the regulation of hypoxia-inducible factor-1 α .¹⁰⁸ Intriguing hypotheses have suggested that chronic dysregulated activation of the hypoxia response genes, specifically hypoxia-inducible factor-1 α , results in myocardial dysfunction.^{6,109} However, this remains speculative to date, and this hypothesis needs to be more definitively tested.

Sunitinib and sorafenib are also known to inhibit PDGFR, which plays a critical role in cell survival and cardioprotection in the setting of pathologic stress. In animal models, PDGFR- β is upregulated after pressure overload stress, and mice with cardiac-specific deletion of PDGFR- β exposed to marked increases in afterload after transaortic constriction sustained greater LV dilation, worsened cardiac function, and pulmonary congestion compared with controls.¹¹⁰ The PDGFR- β knockout mice also show impaired activation of prosurvival signaling pathways, and increased apoptosis after pressure overload, and decreased expression of pro-angiogenic genes.¹¹⁰ Although PDGFR inhibition is known to impair angiogenesis, recent data have suggested a novel mechanism for sunitinib-induced cardiotoxicity related to this pathway. In vivo, sunitinib treatment led to coronary microvascular dysfunction, postulated to be due to loss of pericytes.¹⁰⁸ PDGFR inhibition impairs the growth and survival of pericytes, a type of cell that is closely associated with the microvasculature of some tissues and supports microvascular function.^{111,112} Although it is unclear exactly how pericytes support coronary microvascular function, pericytes are known to regulate the blood–brain barrier and loss of pericytes leads to increased vascular permeability.¹¹³

Due to the conserved ATP binding domain, in vitro studies have shown that sorafenib inhibits ≥ 15 kinases, while sunitinib inhibits >30 kinases.¹¹⁴ By inhibiting multiple kinases, sorafenib and sunitinib affect several other fundamental cardiovascular signaling pathways. Both sunitinib and sorafenib are known to inhibit the stem cell growth factor receptor known as c-Kit or CD117, which is expressed by precursors for hematopoietic stem cells and endothelial progenitor cells and is important for mobilization of these cells to sites of injury.¹¹⁵ Reduced c-Kit kinase activity impairs injury repair after myocardial infarction, thought to be secondary to disrupted recruitment of progenitor cells to the site of injury.^{116,117}

In the case of sorafenib, inhibition of prosurvival ERK signaling via proto-oncogene B-Raf inhibition may also play a role in development of cardiotoxicity. As discussed previously, prosurvival ERK signaling is important for cardioprotection, especially in the setting of increased stress. Because VEGF signaling pathway inhibitors result in impaired angiogenesis

and increased afterload, the cardiomyocyte may be even more reliant on the cardioprotective ERK pathway. Indeed, sorafenib induces cardiomyocyte apoptosis in vitro, and this effect appears to be mediated by RAF inhibition and decreased ERK signaling.¹¹⁸ RAF kinases also inhibit apoptosis via protein–protein interactions with apoptosis signal-regulating kinase 1, while genetic deletion of RAF leads to cardiomyopathy that can be rescued by apoptosis signal-regulating kinase 1 inhibition.^{119,120} Although the direct effects of sorafenib treatment on apoptosis signal-regulating kinase 1 are unclear, animal models suggest that the kinase activity of RAF is pivotal in the setting of pressure overload stress.¹²¹

Sunitinib therapy has been shown in multiple studies to compromise myocyte energy homeostasis¹⁰¹ and inhibit the compensatory upregulation of AMPK, which is critical in maintaining favorable myocardial energetics.^{122,123} Sunitinib inhibits AMPK activity in mice, and in cardiomyocyte culture, restoration of AMPK activity reduced cell death.¹²³ However, intracellular ATP was not affected in one study while it was decreased in another study.^{122,123} The controversies regarding these data and the translation of these findings to humans need to be further delineated.

In summary, there is basic evidence to support the following mechanisms in sorafenib- and sunitinib-induced cardiotoxicity: inhibition of angiogenic growth factors, inhibition of PDGFR signaling, impaired prosurvival signaling, inhibition of c-Kit signaling, and alterations in AMPK activity resulting in energy compromise and mitochondrial dysfunction (Figure 2A). The precise role of hypertension and worsening afterload in the development of subsequent LV dysfunction remains unclear, although multiple basic studies suggest a worsening of cardiac function with sunitinib that occurs primarily in the setting of pressure overload. Potential therapeutics to attenuate sorafenib- and sunitinib-induced hypertension and cardiac dysfunction, in the context of their purported mechanisms, are further discussed next (Figure 2B).

Hypertension Due to VEGF Signaling Pathway Inhibitors: Current Management Considerations

As noted, proposed mechanisms of hypertension due to VSPIs include decreased nitric oxide signaling, increased endothelin-1 production, and capillary rarefaction. The clinical evaluation of hypertension has typically occurred via multiple potential grading systems, including those provided by the Joint National Committee, the European Society of Hypertension and Cardiology, and the Common Terminology Criteria of Adverse Events criteria, although a uniform grading system is clearly important. Principles for the management of hypertension secondary to VSPIs have been published.^{124,125} Consensus guidelines would suggest a careful assessment of cardiovascular risk factors at baseline, judicious blood

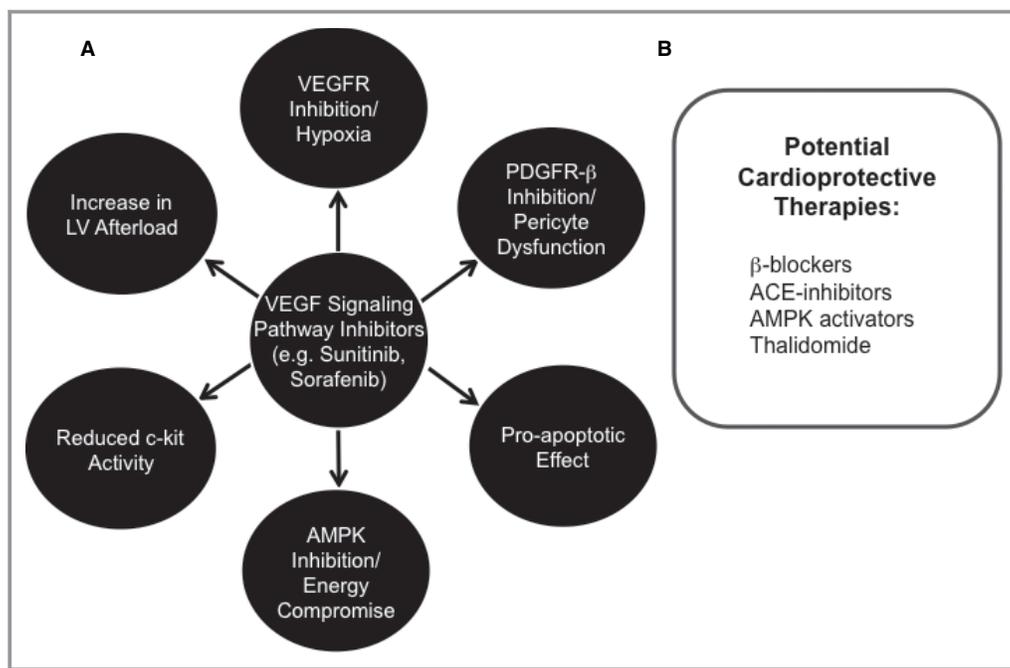


Figure 2. Proposed mechanisms of cardiotoxicity due to VEGF signaling pathway inhibitors sunitinib and sorafenib. A, Sunitinib- and sorafenib-induced cardiotoxicity are secondary to multiple potential mechanisms. B, These effects are attenuated by potential cardioprotective therapies. ACE indicates angiotensin-converting enzyme; AMPK, AMP-activated protein kinase; LV, left ventricle; PDGFR- β , platelet-derived growth factor- β ; VEGF, vascular endothelial growth factor.

pressure monitoring, and pharmacologic management as per established guidelines set forth via Joint National Committee guidelines, the European Society of Hypertension and Cardiology, and representatives of a National Cancer Institute task force.^{125,126} Blood pressure lowering should be individualized, but commonly prescribed agents include ACE inhibitors and angiotensin receptor blockers (with caution regarding their use in patients with significant renal impairment), β -blockers, dihydropyridine calcium channel blockers, and diuretics. Nondihydropyridine calcium channel blockers are contraindicated given the common interactions with VEGF signaling pathway inhibitors and the *CYP3A4* pathway. There are case reports of the efficacy of long-acting nitrates in 2 patients who were treated with antiangiogenic cancer therapies and remained hypertensive after treatment with an ACE inhibitor and calcium channel blocker.¹²⁷ There have been no large-scale randomized clinical studies to evaluate the most effective therapy to treat hypertension due to VSPi; therefore, any purported benefit of a particular class of antihypertensives is speculative at this time. Given the hypothesized role of decreased nitric oxide signaling in the pathogenesis of hypertension with these agents, nitrates may be a mechanistically relevant class of drugs to use. Additionally, the β 1-selective adrenergic receptor antagonist nebivolol may enhance nitric oxide signaling, suggesting its therapeutic potential in this population.^{128–130}

Disruption of Mitochondrial Function and Myocardial Energetics: Role for ACE Inhibitors, β -Blockers, and AMP Kinase Activation

As noted, impaired myocardial energetics may contribute to sunitinib-induced cardiac dysfunction, generating the hypothesis that agents that promote favorable myocardial energetics could be beneficial. The introduction of a constitutively active AMPK into cardiomyocytes resulted in partial resistance of these cells to sunitinib-induced apoptosis,¹²³ suggesting that agents that augment AMPK activity may attenuate sunitinib-induced cardiotoxicity.

Conventional therapies for HF—ACE inhibitors and β -blockers—have been shown to improve myocardial energetics as part of their cardioprotective effects.^{131,132} Agents like metformin may have properties augmenting AMPK activity,^{133,134} and treatment with metformin has been shown in animal models to prevent LV dysfunction after various pathologic stressors such as myocardial infarction, chronic tachycardia, and chronic hypertension.^{135–138} Although one in vitro study specific to sunitinib cardiotoxicity did not show a beneficial effect of metformin,¹²² the translation of these findings to humans remains unknown. Certainly, further studies are indicated to assess the ability of metformin to augment AMPK activity and therefore attenuate sunitinib-induced cardiotoxicity.

PDGFR-Induced Coronary Microvascular Dysfunction via Depletion of Pericytes: Role for Thalidomide in Sunitinib-Induced Cardiotoxicity

Recent data in patients with hereditary hemorrhagic telangiectasia have shown that thalidomide reduced epistaxis via increased PDGFR signaling and vessel maturation and increased pericyte proliferation and recruitment.¹³⁹ Addition of thalidomide to sunitinib therapy in a xenograft model of human renal cell carcinoma did not impair antitumor activity compared with sunitinib alone.¹⁰⁸ Thalidomide did, however, attenuate cardiotoxicity after sunitinib treatment in vivo.¹⁰⁸ To date, there have not been any human-level data to test this hypothesis in sunitinib-treated patients.

Sorafenib Inhibits RAF Family Kinases Leading to Impaired Prosurvival Signaling: Role for Increased ERK Activity by β -Blockers and Potential Detrimental Effects by α -Blockers

As discussed previously here, sorafenib may impair pro-survival ERK signaling via RAF inhibition, leading to increased susceptibility to pathologic stress. Interestingly, the α -adrenergic agonist phenylephrine has been shown to markedly reduce sorafenib-induced cell death via downstream ERK activation. Furthermore, the α -adrenergic receptor antagonist prazosin worsened sorafenib-induced LV dysfunction in vivo.¹¹⁸ This suggests that α -adrenergic receptor antagonists should not be used in conjunction with sorafenib. Although long-term treatment with α -adrenergic agonists, such as phenylephrine, is not standard in the management of cardiomyopathy, these data do suggest that the certain β -blockers that enhance ERK activity via recruitment of β -arrestin^{45,46} may have a role in the treatment of sorafenib-induced cardiotoxicity.

Summary

Mechanisms of cancer therapy-induced cardiotoxicity include a combination of on-target effects on signaling cascades essential to both cancer progression and normal cardiac function and off-target effects due to nonselective actions. Effective therapies to treat cancer and cancer therapy-induced cardiotoxicity must either take advantage of tissue-specific differences or affect the downstream mediators of toxicity, and there are active studies under way to develop new targeted therapies.^{140,141} Other effective therapies for cardioprotection include typical pharmacologic therapies used in cardiovascular disease that promote increased cardiac reserve and reverse remodeling under the stress of cancer therapy. Most of the data regarding mechanisms of cardiotoxicity due to cancer therapy have been obtained from

animal models of this disease process; therefore, further studies to improve our understanding of the relevance of these pathways in humans are necessary.

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