Published in final edited form as:

Curr Heart Fail Rep. 2012 September ; 9(3): 211–218. doi:10.1007/s11897-012-0098-4.

Cardiac Side Effects of Anticancer Treatments: New Mechanistic Insights

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Abstract

Damage to heart cells leading to heart failure is a known complication of well-established cancer therapies including anthracycline antibiotics and radiation therapy, and the cardiovascular complications of these therapies has been controlled in large part through dose limitations and modifications of delivery methods. Recent research into the cellular and molecular mechanisms for the cardiovascular effects of these therapies may lead to other cardioprotective strategies that improve effectiveness of cancer treatments. Newer cancer therapies that have been developed based upon specifically targeting oncogene signaling also have been associated with heart failure. Rapid development of a detailed understanding of how these agents cause cardiac dysfunction promises to improve outcomes in cancer patients, as well as stimulate concepts of cardiovascular homeostasis that will likely accelerate development of cardiovascular therapies.

Keywords

Anthracycline; Doxorubicin; Adriamycin; Daunorubicin; Cardiac toxicity; Heart failure; Erbb2; VEGF; Herceptin; Trastuzumab; Cardiac progenitor cell; Cardio-oncology; Sunitinib; Sorafenib; Therapy

Introduction

Cardiovascular diseases, and specifically heart failure, can occur as a consequence of cancer therapy. Despite decades of basic and clinical research, anthracyclines and radiation therapy continue to cause clinically significant heart failure. Recent literature provides a more detailed understanding of how these cytotoxic therapies might cause myocardial damage, and perhaps these observations will translate to changes in clinical management. Newer therapies targeting the ErbB2 oncogene (trastuzumab, lapatinib) and vascular endothelial growth factor (VEGF) angiogenic signaling likewise can induce cardiac dysfunction. There

are some important distinctions one can make between those therapies that induce cytotoxic/genotoxic stress versus those that disrupt cardiovascular homeostasis. Understanding the effects of these agents on the heart and vasculature is improving our knowledge of cardiovascular biology, informing the design of future cancer treatment strategies, and accelerating the development of new treatments for heart failure.

Anthracycline Antibiotics: A Brief Review and Update on Mechanisms of Cardiac Injury

We have recently passed the 50th anniversary of the description of daunorubicin, one of the first anthracycline antibiotic with antitumor activity discovered [1]. Since then, anthracyclines were quickly developed as anticancer therapies that, decades later, continue to be used for the treatment of many hematologic and solid tumor malignancies. In spite of research over these many decades, cardiac toxicity and, importantly, heart failure remain problems that are incompletely understood and limit their use [2•]. The risk of anthracycline-associated heart failure is well known to be a function of cumulative exposure [3]. Clinical and animal research demonstrate that cardiac damage occurs with every exposure, with cumulative damage above a threshold that varies among individuals resulting in cardiac dysfunction and heart failure. Cardiac cells exposed to a single dose of a low concentration of anthracyclines induces myofilament degradation [4] as well as myocyte death [5]. Endomyocardial biopsies of people show ultrastructural changes to the myocardium after a single dose of anthracycline [6, 7], and circulating levels of cardiac troponin demonstrate cardiac myocyte injury after a single dose that correlates with subsequent development of cardiomyopathy [8].

The molecular mechanisms of anthracycline-induced myocyte cell injury, as well as the mode of cell damage and death, are likely multifactorial (Table 1). An established pathway for anthracycline-induced cytotoxicity not specific to cardiac myocytes is the induction of oxidative stress. Anthracycline-induced cell death can be inhibited by anti-oxidants, both in vitro and in vivo (e.g. [5, 9]). Anthracycline compounds are planar molecules that intercalate into nucleic acid chains [10] and disrupt DNA/RNA synthesis and repair [11]. Anthracyclines disrupt DNA in part through interactions with topoisomerase, a critical enzyme for unwinding of the DNA for replication and synthesis [12].

Although cardiac myocytes have low rates of DNA replication, the response to DNA damage appears to play an important role in the myocardial response to anthracyclines. Activation of phosphorylation of histones, with phosphorylation of p53 and induction of p21, well established as DNA damage responses, can be demonstrated in cardiac myocytes exposed to low concentrations of doxorubicin [13]. Mice with genetically ablated p21 are resistant to doxorubicin toxicity [14], although similar experiments with p53 knockout mice have shown mixed results. In some reports, p53 appears to be required for induction of oxidative stress responses, as well as loss of myocytes via apoptosis and autophagy [15, 16], whereas others find that cardiac fibrosis in response to doxorubicin occurs in p53 $-/-$ mice [17]. In addition to nuclear DNA oxidation and damage, anthracyclines are well known to induce mitochondrial dysfunction, with alterations in adenosine triphosphate (ATP) synthesis leading to metabolic stress [18]. Changes in high-energy phosphates induced by anthracyclines occur early after exposure and precede evidence of cardiac contractile dysfunction [19]. It is interesting that some of these mitochondrial effects also may be a function of p53 [15].

Anthracyclines cause disruption of sarcomere structure, with myofilament disorganization and impaired replacement of sarcomeres via a combination of accelerated degradation of myofilaments [20] and desmin [21] as well as transcriptional regulators such as cardiac

ankryn repeat protein (a.k.a. cardiac anthracycline response protein, CARP [22]) and GATA4 [23]. Direct activation of the ubiquitin proteasome system by anthracyclines likely contributes to these events [24]. GATA4 is a zinc finger transcription factor that regulates sarcomere protein expression as well as cell survival signaling that protects against anthracycline cardiotoxicity in mice [25]. It appears that downregulation of GATA4 in response to anthracyclines is mediated by p53 [23]. CARP has a short half-life, and transcriptional activation of CARP is regulated by GATA4 [26•]. Sarcomere synthesis including titin transcription appears to require both GATA4 and CARP. Thus, decreased expression of GATA4 and CARP appear to be key molecular events in anthracycline cardiotoxicity. GATA4 can be induced with common pharmacologic agents such as α -adrenergic agonists, and this appears to protect mice from anthracycline toxicity [25]. Perhaps this is one mechanism by which exercise training acts to protect rodents from anthracycline injury [27]. Further work is necessary to see if this observation translates to clinical cardioprotection from anthracyclines.

Disruption of sarcomeres by anthracyclines appears to begin with degradation of the giant myofilament protein titin [20], an entropic spring that plays an important role in the generation of restoring and passive forces [28, 29]. Titin degradation requires a combination of titin damage by oxidation, as well as activation of Ca^{+2} -dependent proteases calpains [20]. Disruption of myocyte Ca^{+2} handling occurs coincidentally via increased Ca^{+2} leak from the sarcoplasmic reticulum [30] in part through alterations in ryanodine receptor function [31]. The combination of impaired Ca^{+2} handling together with reduced restoring force from titin degradation may account for the observation that impaired relaxation precedes development of systolic dysfunction in the course of treatment with anthracycline-based chemotherapy [32•, 33]. This observation may allow for use of diastolic dysfunction as an early end point for evaluation of interventions designed to prevent anthracycline injury.

Putting these collective findings into a single model of how cardiac myocytes respond to anthracyclines, it appears that genotoxic stress, mitochondrial dysfunction, and oxidation of cellular components lead to activation of protein degradation and suppression of sarcomeric synthesis. Each of these proximal events occurs in part through anthracycline-induced oxidative stress, and this has led to strategies to inhibit oxidative stress. The most successfully developed of these is the iron chelator dexrazoxane, which is in fact cardioprotective [34, 35]. However, this has not been embraced by oncology in part due to the suggestion that dexrazoxane lowers anthracycline anticancer activity. Another concern raised has been effects of antioxidants on drug metabolism, as anthracycline-induced oxidative stress catalyzes the formation of less cytotoxic anthracycline derivatives in myocytes [36]. A wide array of compounds with antioxidant activity has been tested in animal models of anthracycline cardiotoxicity. Given the clinical oncology concern that any of these might limit anthracycline anticancer activity, it would seem appropriate that such research should focus on compounds that themselves have anticancer activity. Going forward, it seems prudent that all such experimental work in animals occur in models of clinically relevant cancer, where cardiac protection can be examined simultaneously with effects on anticancer efficacy.

Other adaptations that determine the degree of cardiotoxicity during anthracycline exposure include cellular activation of drug efflux mechanisms including permeability glycoprotein (p-gp), a 150–180-kDa membrane glycoprotein encoded by the multidrug resistance (MDR) gene that acts as an energy-dependent efflux pump in the ATP-binding cassette transporter family [37, 38]. In the normal heart, MDR1 is expressed at very low levels [39], but is induced in response to anthracycline exposure [40]. Anthracyclines accumulate in cardiac tissue of MDR-1a $-/-$ more than wild-type mice [41]. Studies examining genetic factors that

determine risk for anthracycline cardiotoxicity repeatedly identify variation in members of this family of ATP-binding cassette transporters [42, 43]. Little is known about how the myocardium regulates p-gp expression and activity, and perhaps further studies of this will lead to strategies that limit myocardial uptake of anthracyclines. However, it is well known that several cardiovascular therapeutics (eg, digoxin, verapamil, diltiazem) are substrates for p-gp, and concurrent use of these therapies with anthracyclines theoretically will increase myocardial anthracycline accumulation and toxicity. Hence, we routinely recommend evaluation of the therapeutic regimen of persons with cardiovascular disease anticipating anthracycline-based chemotherapy. Given the emerging evidence that β -adrenergic blockers and angiotensin-converting enzyme inhibitors (none of which are p-gp substrates) can protect from anthracycline cardiotoxicity [44], it seems that these should be the first-line therapies for treatment of hypertension in persons receiving anthracycline chemotherapy.

The most recent insights into anthracycline cardiotoxicity have come from the relatively recent discovery of resident myocardial progenitor cells [45] and the observation that myocardial regeneration does occur at a slow rate [46]. This has led to the concept that anthracycline cardiomyopathy may be in part due to disruption of mechanisms for myocardial renewal. Indeed, anthracyclines appear to have significant toxicity for cardiac progenitor cells, reducing the number [47] as well as accelerating the –aging– of cells in young animals [48••]. The depletion of progenitor cell populations appears to alter tissue architecture with reduced microvasculature, as well as impair the ability of the myocardium to respond to subsequent stress [48••]. It will be interesting to see if the so-called side population of cardiac resident progenitor cells has a similar susceptibility to anthracyclines, given their high expression of one or more ATP-binding cassette transporters such as MDR1 [49]. Whether these findings can be used to develop cardioprotective strategies to recover these cells after anthracycline exposure remains to be seen.

ErbB2-targeted Therapies and Cardiac Dysfunction

Cancer therapies have been developed to specifically target oncogenes including kinases that control cell proliferation and function such as the Homology of Epidermal Growth Factor Receptor 2 (HER2, a.k.a. ErbB2), which is overexpressed in ~20 %–30 % of breast and other epithelial derived tumors (eg, [50]). Trastuzumab is a humanized monoclonal antibody that targets ErbB2 and slows the progression of otherwise very aggressive breast cancers in preclinical models. The ErbB2 receptor has diverse functions in many tissues including the heart [51]. In the pivotal clinical trials leading to approval of trastuzumab for treatment of ErbB2-positive breast cancer, trastuzumab was tested alone or in combination with anthracyclines [52]. While trastuzumab prolonged disease-free survival for study participants, there was an associated increased incidence of systolic dysfunction and heart failure [52]. Since that observation, there has been considerable effort applied to understanding this effect.

The importance of ErbB signaling in the heart was first recognized when ErbB2, ErbB4, and neuregulin (NRG)-1–null mice all were noted to have prenatal arrest of development with failure of cardiac development in utero [53–56]. In vitro work established that cardiac myocytes in the adult heart express both ErbB2 as well as ErbB4 receptors, and stimulation of these with the endothelial cell–derived neuregulin-1 activate cell growth and survival effects [57]. Conditional deletion of ErbB2 in the adult heart survive to adulthood but develop dilated cardiomyopathy, with increased mortality and susceptibility to anthracyclines [58, 59]. Hence, ErbB2 expression and activity appears necessary for maintenance of cardiac function in the adult heart.

Experimental work in vitro has examined whether anti-bodies to ErbB2 alter myocyte responses to anthracyclines. Studies examining effects of anti-ErbB2 on anthracycline-induced myocyte death have given mixed results in vitro [60–62]. Direct use of trastuzumab in rodents to examine this hypothesis in vivo has been limited by the poor affinity of trastuzumab for rodent ErbB2. While one group of investigators have reported pro-apoptotic effects of trastuzumab in rodents [63], these investigators never demonstrated direct binding of trastuzumab to rodent ErbB2, and did not utilize appropriate control antibodies to rule out effects of using humanized antibodies in rodents. At this point, it is still unclear whether trastuzumab-associated cardiac dysfunction is a result of increased myocyte cell death.

Since the initial observations reported from the pivotal trials leading to the approval of trastuzumab for the treatment of breast cancer, prospective observations in persons developing trastuzumab-associated cardiac dysfunction suggest that this is often reversible [64]. Given the limited regenerative capacity of the heart, this finding would not support the concept that trastuzumab accelerates myocyte cell death as a primary mechanism for induction of cardiac contractile dysfunction. Alternative mechanisms include effects of trastuzumab on regulation of myofilament turnover as well as myocyte interactions with other cells and matrix to regulate myocardial contractility. In rat myocytes, treatment with anti-erbB2 augments anthracycline-induced myofilament disarray [4]. Independent of anthracyclines, anti-ErbB2 suppresses neuregulin activation of src/focal adhesion kinase and focal adhesion complex formation [65]. ErbB2 signaling is also involved in the modulation of cardiac contractility. In isolated cells, activation of ErbB2 decreases diastolic calcium and attenuates doxorubicin-dependent alteration of calcium amplitude and sarco/endoplasmic reticulum Ca^{2+} -ATPase (SERCA) levels [66].

ErbB2 is expressed in endothelial cells in the heart and vasculature, where it transduces an angiogenic signal [67]. An antiangiogenic effect of trastuzumab has been proposed both as a potential mechanism for the beneficial effects of trastuzumab as well as the detrimental effect on cardiac function [68]. Likewise, bone marrow-derived endothelial progenitor cells, which have been implicated in cardiac repair after injury [69], express ErbB2 receptors [70]. The possible role that these cells play in trastuzumab-associated cardiac dysfunction remains to be examined in a clinical setting.

Lastly, antibody-directed cellular cytotoxicity (ADCC) is another alternative mechanism of cardiac injury. The Fc fraction used to humanize the ErbB2 antibody recruits host immune cells, mediating a cytotoxic response against ErbB2-overexpressing cells. In cells with normal ErbB2 receptor expression, there is potential for immunemediated cytotoxicity augmenting cardiac dysfunction [71]. Radiolabeled trastuzumab has been used to demonstrate ErbB2 expression in the myocardium by noninvasive imaging [72], and this is increased in the myocardium of patients being treated for cancer [73]. Combining this method of myocardial trastuzumab binding with strategies to detect tissue inflammation in persons with trastuzumab-associated cardiac dysfunction would help address the ADCC hypothesis.

Unlike trastuzumab, lapatinib is a small-molecule dual inhibitor of ErbB2 and epidermal growth factor receptor (EGFR, a.k.a. erbB1 EGFR), which appears to have less effect on cardiac function. Lapatinib binds reversibly to the intracellular ATP-binding site of the kinase, blocking phosphorylation of the receptor and inhibiting intracellular signaling (Ras/Raf MAPKs and the PI3K/Akt), and in cancer cells increases apoptosis and inhibits proliferation. Inhibition of the ErbB2 receptor with such tyrosine kinase inhibitors in cardiac myocytes disrupts myofilament homeostasis, similar to that induced by anti-ErbB2 antibodies [74]. To date, lapatinib use has been associated with lower rates of adverse

cardiac events than trastuzumab [75]. The low rate of cardiac dysfunction may reflect the highly selected group of patients that were enrolled into the lapatinib trials, with exclusion of those with any degree of myocardial stress or dysfunction. Other possible explanations include lapatinib-induced activation of cardioprotective pathways, though to date this has only been demonstrated in a cell line that poorly represents an adult cardiac myocyte [76].

Several cancers therapies for pancreatic cancer, non-small cell lung cancer, colorectal cancer, and squamous cell cancer target EGFR (a.k.a. erbB1; erlotinib, gefitinib, cetuximab, and panitumumab). While EGFR is involved in myocardial development and regulation of myocyte function, clinical studies with EGFR monoclonal antibodies or tyrosine kinase inhibitors have not been associated with cardiac dysfunction. These data are in accordance with in vitro experiments with an ErbB1-specific inhibitor, where there was no observable effect on myofibrillar structure, cell death, or cardiac contractility [74].

It will be interesting to see how this field evolves with the development of other ErbB-targeted therapies such as pan- Her (pan-erbB) inhibitors, which bind irreversibly to ErbB family of tyrosine kinase receptors [77]. The early clinical studies with the first of these, canertinib, have shown some evidence of efficacy but with high rates of adverse events, though cardiotoxicity has not been reported [78]. As trial entry criteria and clinical use broaden to include patients with known cardiovascular disease, the basic science of ErbB receptor signaling and its importance in the maintenance of the heart and response to injury would suggest the need for continued scrutiny and vigilance in monitoring potential cardiotoxic off-target effects of these agents.

The attention that these developments in cancer therapy have put on cardiac erbB signaling has accelerated development of neuregulin as a possible therapy for heart failure [79]. Recombinant NRG improves cardiac function and survival in several animal models of systolic heart failure, and this has led to early phase clinical trials that are ongoing. There are obvious concerns that NRG may promote tumor cell growth and survival. However, NRG has tumor suppressor effects as well [80]. Collaboration between disciplines will be important as this clinical research proceeds.

Angiogenesis Inhibitors and Cardiac Contractile Dysfunction

Angiogenesis is now an established target for cancer therapy [81], but produces systemic cardiovascular effects, causing hypertension, myocardial infarction, thrombosis, and heart failure. Hypertension is a well-recognized effect of VEGF-targeted cancer therapies [82, 83] that is often corrected with antihypertension medications. Heart failure is a less common side effect of specific VEGF-targeted therapies. Heart maintenance and adaptation to changes in demand, as in other organs, is a carefully orchestrated change in tissue mass that balances maintenance and growth of individual myocytes with micro- and macrovascular growth through paracrine signaling. This has been demonstrated with experimental models such as when angiogenesis is specifically inhibited with adenoviral overexpression of soluble VEGF receptor, and the adaptation of the heart to pressure overload is prevented with development of heart failure [84]. Anti- VEGF therapies have been shown to accelerate cardiac myocyte apoptosis in the presence of hypertension [85]. This may be augmented in patients with prior chemotherapy exposure, as there is evidence that many cancer therapies including anthracyclines cause vascular damage and leave the heart with an impaired paracrine reserve. As discussed above, this may explain the inability of the anthracycline-exposed heart to adapt to stimuli for physiological growth [48]. Hence, it should not be surprising that the anticancer treatments targeting angiogenesis can induce cardiac contractive dysfunction.

Multi-tyrosine kinase inhibitors that were selected for effects on angiogenesis also have been developed, and appear to have a greater tendency to promote development of heart failure perhaps due to the broader effects of these compounds. Sunitinib is a multitargeted tyrosine kinase inhibitor that targets VEGF receptors, platelet-derived growth factor receptors (PDGFRs), c-kit (stem cell factor), colony stimulating factor-1, and RET gene, which was FDA approved to extend survival in gastrointestinal stromal tumors (GIST) and renal-cell carcinoma [86, 87]. Cardiac events (myocardial infarction, heart failure, and cardiovascular death) were observed in 11 % of GIST tumor patients who were treated with sunitinib [88]. Similar rates of events have been seen with the multi-tyrosine kinase inhibitor sorafenib [89]. Rodents demonstrate sensitivity to sunitinib, with mitochondrial dysfunction and cardiomyocyte apoptosis and cardiac contractile dysfunction [88]. The mechanism of cardiotoxicity is not well understood, but inhibition of 5'-adenosine monophosphate-activated protein kinase (AMPK) and PDGFR by sunitinib provide possible explanations [90, 91••]. AMPK is a well-studied regulator of metabolism that is critical for regulation of myocardial response to pressure overload and ischemic injury [92]. Cardiac myocytes and endothelial cells ubiquitously express PDGFRs, and PDGF signaling is a component of paracrine regulation of endothelial cell-myocyte interactions that regulate response to pressure overload [91••]. Further clinical work is necessary to develop a better mechanistic concept, prognostic understanding, and risk stratification of patients undergoing treatment with sunitinib.

Conclusions

In this brief review, we have focused on providing an update of recent studies that help elucidate the mechanisms for cardiac dysfunction induced by some cancer therapies. Discoveries of mechanisms for how tumor cells escape programmed cell death inherent to the turnover of cells in normal tissues has led to an expanding array of strategies for the development of novel therapies to treat cancer. Non-cancer cells, including those in the cardiovascular system, are regulated by these same pathways [93]. As these potential therapies move forward with clinical development, it will be important that the cardiovascular clinical and research communities not only stay current with these developments, but fully engage in collaborative work with the oncology research and clinical communities.

Acknowledgments

This work was supported by grants HL068144 from the National Institutes of Health to Dr. Douglas Sawyer, an Established Investigator Award to Dr. Douglas Sawyer, and a pilot project from the Breast Cancer Specialized Program of Research Excellence (SPORE) grant P50CA98131.

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Table 1

Summary of experimental effects of anticancer therapies on cardiovascular tissue

Anticancer therapy	Cardiac side effects
Anthracyclines	Produce oxidative stress
	Disrupt DNA/RNA synthesis and repair
	Induce mitochondrial dysfunction
	Accelerate degradation of myofilaments, desmin, and titin
	Impair calcium handling
	Alter drug efflux pumps
	Reduce cardiac progenitors cells
ErbB2-targeted therapies	Inhibit pro-survival intracellular signaling
	Augment anthracycline-induced myofilament disarray
	Inhibit ErbB-regulated angiogenesis
	Produce antibody-directed cellular cytotoxicity (monoclonal ErbB2-targeted therapies)
VEGF-targeted therapies	Inhibit cardiovascular repair and vascular growth
Therapies that inhibit PDGFR	Impair response to pressure overload
Therapies that inhibit AMPK	Disrupt metabolic response to ischemic injury

ErbB2 Homology of Epidermal Growth Factor Receptor 2; *VEGF* vascular endothelial growth factor; *PDGFR* platelet-derived growth factor receptor; *AMPK* 5' adenosine monophosphate-activated protein kinase