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Mechanisms of Anthracycline Cardiotoxicity and Strategies to Decrease Cardiac Damage

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Abstract

Anthracyclines are common chemotherapeutic agents used to treat many different types of cancer. Unfortunately, the use of anthracyclines is limited by their cardiotoxic effects, which may become manifest as late as 20 years from initial exposure. Studies in cells and animals suggest that the mechanism of anthracycline-induced cardiotoxicity (AIC) is multifactorial. Anthracyclines induce multiple forms of cellular injury by free radical production. In addition, anthracyclines alter nucleic acid biology by intercalation into DNA and modulate intracellular signaling, leading to cell death and the disruption of homeostatic processes such as sarcomere maintenance. In an effort to decrease AIC, many strategies have been tested, but no specific therapies are universally acknowledged to prevent or treat anthracycline-induced cardiac dysfunction. Newer imaging modalities and cardiac biomarkers may be useful in improving early detection of cardiac injury and dysfunction. As long as there is no cardiac-specific therapy for AIC, evidence suggests that high-risk patients will benefit from prophylactic treatment with neurohormonal blockade by angiotensin-converting enzyme inhibitors and beta-adrenergic receptor blockers.

Keywords

Anthracycline; Adriamycin; Doxorubicin; Daunorubicin; Heart failure; Congestive heart failure; Cardiomyopathy; Cardiac dysfunction; Pathophysiology; Myocyte biology; Cell death; Oxidative stress; Echocardiography; B-type natriuretic peptide; Troponin; Titin; GATA4; Sarcopenia

Introduction

Anthracyclines are effective agents used commonly to treat hematologic malignancies (leukemias, lymphomas) and solid-tumor malignancies (carcinomas, sarcomas). The broad use of anthracyclines for over 40 years has dramatically improved cancer survival statistics. For example, children with leukemia prior to the 1960s had an overall 5-year survival of 30%. With the increased use of anthracycline-based chemotherapy and early detection, 5-year survival in children is now 80% [1]. Unfortunately, though mortality rates decrease with anthracyclines, life-altering cardiac sequelae from anthracyclines remain a problem,

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with a range of 5% to 23% of patients developing late-onset heart failure secondary to anthracycline-induced cardiotoxicity (AIC) [2, 3•].

Cardiotoxic effects of anthracyclines range in severity and are classified by time of onset as *acute*, occurring during or immediately after infusion; *early*, occurring within 1 year of exposure; and *late*, occurring 1 to 20 years after initial exposure [4•]. Acute AIC is a reversible process manifesting itself by disturbances in electrical conduction (QT prolongation, nonspecific T-wave changes) and arrhythmias [4•]. In contrast, both early and late AIC manifest as decreased left ventricular (LV) function, diminished exercise capacity, and progressive heart failure symptoms. The risk for early and late AIC is a function of cumulative anthracycline exposure [5]. At a cumulative dose of 400 mg/m², there is a 5% risk of developing heart failure, which increases to 25% at 700 mg/m² [5]. An empiric cutoff of 500 mg/m² has been suggested to minimize cardiotoxic effects of doxorubicin-induced cardiomyopathy. If patients have other predisposing risk factors for AIC such as older age (>65 years), prior cardiac pathology (hypertension, LV hypertrophy, coronary artery disease), diabetes, or prior radiation exposure, the recommended total cumulative exposure is decreased to 450 mg/m². Even at low cumulative doses, however, such as standard-dose therapy for breast cancer, 5% of patients will have evidence of AIC [6]. Thus, every exposure to an anthracycline carries some risk of inducing cardiac dysfunction.

Mechanisms of Anthracycline-Induced Cardiotoxicity

The mechanism and pathogenesis of AIC remain controversial and poorly understood. Typical pathologic changes in the heart include vacuolar degeneration of the sarcoplasmic reticulum, swelling and disruption of the mitochondria, and myofilament degeneration [7]. There is also evidence of myocyte loss. Pathologic evidence includes early studies showing chromatin condensation, as can be seen in apoptotic cells in the myocardium of anthracycline-treated patients [8]. Animal studies have shown similar findings [9]. In addition, cell death likely occurs by necrosis. Elevation of serum troponin is observed in patients treated with anthracyclines, consistent with the induction of cell death [10]. Endothelial cells and progenitor cell populations in the heart are also susceptible to anthracycline-induced cell death. Thus one explanation for AIC is that myocytes are lost with every exposure, and the pool of endogenous reparative cells diminishes, predisposing the heart to inadequate healing.

The molecular mechanisms of myocyte injury are likely to be multifactorial. A commonly cited pathway involves anthracycline-induced generation of reactive oxygen species (ROS). There is evidence that anthracyclines catalyze the formation of intracellular oxygen radicals through at least two pathways. In the nonenzymatic pathway, anthracyclines may directly react with ferric iron (Fe³⁺), leading to free radical and alcohol adducts [11]. Within the enzymatic pathway, anthracycline interacts with the mitochondrial respiratory chain and other cytochrome-containing enzymes, producing ROS [11]. In the enzymatic pathway, a key molecular factor may be the affinity of anthracyclines for cardiolipin, a phospholipid located within the inner mitochondrial membrane at the site of the respiratory chain [12]. Anthracycline-associated cardiolipin is reduced by NADH, drawing an electron away from the mitochondrial respiratory chain and subsequently reducing oxygen to form a superoxide

anion radical. Free radicals formed by any of the mechanisms go on to damage multiple cellular components, including lipids of the cell membrane, proteins, and nucleic acids. In isolated cells, ROS are mechanistic in anthracycline-induced cell death [13]. Mice that overexpress manganese superoxide dismutase appear protected from mitochondrial damage and have decreased markers of myocyte cell death [14].

Although free radical generation leading to direct oxidative damage to cellular components remains a common postulated mechanism of AIC, there are alternative proposed mechanisms that probably contribute to cardiac dysfunction. Anthracycline compounds have a planar structure, which intercalates into the DNA through noncovalent interaction, preventing further DNA and RNA synthesis and likely contributing to the death of myocytes and mitochondrial mutations [15]. Anthracyclines disrupt DNA by poisoning topoisomerase, a critical enzyme for unwinding of the DNA for replication and synthesis, thereby causing growth arrest and programmed cell death [15].

Cellular oxidative stress activates an array of kinase pathways that modulate myocyte fate and response to anthracyclines. Mitogen-activated protein kinases (MAPKs) and stress-activated protein kinases (SAPKs) are important intracellular signal transduction intermediates, which regulate cellular responses to stimuli by regulating gene expression, survival pathways, proliferation, and growth. Anthracyclines activate the MAPK/ERK (extracellular signal-regulated kinase) pathway via oxidant stress, and this appears to regulate cell survival [16]. In addition, anthracyclines may alter the ability of a myocyte to regulate prosurvival signaling. The PI3K/Akt pathway is activated in the heart in response to many different growth factors, including neuregulin, insulinlike growth factor-1 (IGF-1), and interleukins [17, 18]. In vitro studies show that PI3K/Akt protects against anthracycline-induced apoptosis [18]. There is some evidence that the activity of these and other myocytoprotective pathways is reduced in the injured heart [19], thereby increasing the susceptibility of myocytes to further anthracycline exposure. This may be one mechanism to explain persistent ventricular remodeling late after anthracycline exposure, as well as the increased susceptibility of the heart to cumulative anthracycline exposure.

Clinically significant cardiac toxicity from anthracyclines is unpredictable in individuals, even with similar cumulative doses and clinical conditions. Because of the wide variation in individual cardiac toxicity from anthracyclines, a few groups have looked at potential genetic modulators of this sensitivity [20, 21]. Wojnowski et al. [21] carried out a nested case-control study of adult patients enrolled in a prospective randomized clinical trial of anthracycline-containing treatment regimens for non-Hodgkin's lymphoma. They examined 175 single-nucleotide polymorphisms (SNPs) in 73 genes with a biologically plausible role in anthracycline cardiotoxicity and found associations of either acute or chronic cardiotoxicity with six SNPs in five genes: *CYBA*, *RAC2*, *NCF4*, *MRP1*, or *MRP2*. The first three genes are all components of the NADPH oxidase complex and the other two genes are members of the family of adenosine triphosphatase (ATP)-binding cassette transporters (multi-drug resistance proteins, MDR) that confer resistance to a range of chemotherapeutic agents [21, 22]. MDR is a pump that lowers the intracellular concentration of anthracyclines, and presumably genetic variations that reduce its expression or activity increase the risk for AIC. Mice with inactivating mutations of components of the NADPH oxidase complex are

protected from AIC. Thus it would appear that variants in NADPH oxidase that increase enzyme activity would increase the risk for AIC.

Another mechanism contributing to AIC is the disruption of sarcomere maintenance. Anthracycline exposure in animal models leads to the downregulation of important transcriptional factors necessary for cardiac sarcomere synthesis. GATA4 is a zinc finger transcriptional factor involved in regulating sarcomere protein expression and in cell survival signaling. Myocardial GATA4 regulates cardiac-specific and anti-apoptotic genes [23, 24]. Several GATA4 regulated genes, including cardiac Adriamycin-responsive protein (CARP) [25], alpha-myosin heavy chain [26], and atrial natriuretic peptide (ANP) [27], are suppressed by anthracycline exposure. Thus downregulation of GATA4 by anthracyclines suppresses the ability of cardiac myocytes to synthesize new protein.

Direct effects of anthracyclines on sarcomere protein stability also contribute to the disruption of sarcomere maintenance, and thus to myocardial dysfunction. Titin is a large myofilament protein important for modulation of sarcomere restoration and passive elastic forces [28]. Titin is degraded early after anthracycline exposure via a calpain-dependent mechanism. This response predisposes isolated cardiac myocytes to necrotic cell death [29]. Independent of anthracyclines, it is established that titin disruption leads to the development of a cardiomyopathy [28]. Thus the disruption of sarcomere proteins and the suppression of sarcomere synthesis probably contribute to the cardiac sarcopenia observed clinically after anthracycline exposure.

There is increasing evidence that progenitor cell populations derived from the bone marrow and those within the heart are affected by anthracycline, and that this contributes to the late cardiotoxicity observed [30]. Huang et al. [31] demonstrated in a juvenile mouse experiment that doxorubicin exposure decreased the number of cardiac progenitor cells and altered vascular growth. This effect was associated with a maladaptive response to physiologic stresses (exercise) and pathologic stresses (ischemia) in treated mice, with impaired adaptive growth and accelerated heart failure. The mice exposed to doxorubicin had decreased numbers of cardiac progenitor cells (c-kit⁺ cells) and reduced neovascularization in response to stress [31]. These studies suggest that anthracycline exposure alters the endogenous adaptive reserve of the heart, and they provide an interesting paradigm for the mechanism of AIC, which warrants further investigation.

Oncology-Based Methods to Decrease Cardiotoxicity

Attention to the cardiotoxicity of anthracyclines has led to changes in cancer treatment protocols over the years. These have included limiting the cumulative anthracycline exposure, changing the rate of administration, altering the formulation, and exploring whether some anthracyclines are less cardiotoxic than others. Limiting peak concentrations has been examined either by changing the rate of infusion or by encapsulating anthracyclines in liposomal microparticles. Evidence that lowering peak concentrations by lowering the rate of infusion reduces the risk of anthracycline cardiotoxicity is mixed. In a large meta-analysis of adult solid tumors treated with anthracyclines, a longer infusion (>6 hours) lowered the rates of clinical heart failure as compared with shorter-duration infusions

of equivalent doses [31]. In a large study, however, a 48-hour infusion showed no cardioprotective benefit in high-risk children with leukemia, compared with a bolus infusion administered in less than 1 hour: subclinical cardiotoxicity occurred at similar rates in both treatment groups [32].

Liposomal encapsulated drugs appear to preferentially distribute to tumors because of vascular permeability changes 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; Centocor Ortho Biotech, Horsham, PA) and Myocet (nonpegylated formulation; Sopherion Therapeutics, Princeton, NJ) are two agents that have been used in phase 2 studies of metastatic breast cancer; they were highly active against tumor and less cardiotoxic than doxorubicin alone [33]. A recent review of two randomized controlled trials (521 patients) concluded that both clinical heart failure and subclinical cardiac dysfunction were less common in patients treated with liposomal encapsulated doxorubicin than with a nonliposomal formulation [34].

Other agents such as an iron chelator, dexrazoxane, are used to reduce AIC by decreasing anthracycline-induced free radical formation. There is some concern that dexrazoxane contributes to more adverse effects and potentially limits the tumor response. A systematic review of the Cochrane database analyzed nine randomized controlled trials in which dexrazoxane was implemented with anthracyclines [35]. The meta-analysis showed a statistically significant benefit in favor of dexrazoxane for decreased occurrence of heart failure and cardiac dysfunction. There was no detectable difference in tumor response rates, but dexrazoxane was associated with lower white blood cell counts [35]. The authors of this analysis recommend that dexrazoxane be reserved for patients who are at increased risk of cardiac damage.

Detecting and Monitoring Anthracycline Cardiotoxicity: What Does Modern Cardiology Have to Offer?

Despite the long-standing history of cardiotoxicity from anthracyclines, there are no consensus guidelines for monitoring cardiac function in adults undergoing chemotherapy. Cardiac function is traditionally monitored serially during anthracycline treatment by cardiac echocardiography (echo) or radionuclide ventriculography (RVG). Although both methods detect significant changes in LV function, they are somewhat insensitive in detecting early signs of cardiac stress, myocardial injury, and changes in myocardial compliance. Novel echo imaging techniques are being evaluated to determine if early changes in cardiac compliance and diastolic filling predict the late development of systolic dysfunction [36].

Using tissue Doppler imaging, it is possible to extract parameters such as velocity, deformation (strain), and deformation rate (strain rate), representing a new approach to the assessment of LV function. Small studies examining tissue Doppler and strain rate imaging appear promising in detecting subclinical changes in cardiac performance before changes in ventricular ejection fraction are evident, but much larger studies with longer follow-up are needed [36, 37]. The advantages of these techniques are that they do not require a separate

examination, and the technology is available on most current machines. The disadvantage is that data analysis currently is off-line, very time-consuming, and dependent on “above-average” acoustic windows.

Real-time three-dimensional echocardiography also is being explored as a new modality to serially monitor cardiac function; it correlates with standard RVG and two-dimensional echo [38]. A few small studies have examined the utility of cardiac MRI with delayed gadolinium enhancement in identifying AIC and trastuzumab-induced cardiotoxicity. Larger trials are needed to determine whether delayed enhancement is an adequate technique to detect acute or late-onset myocardial dysfunction in anthracycline-treated patients.

Many small studies have investigated the utility of cardiac biomarkers that may predict and monitor cardiac injury (troponin, myoglobin) or volume changes (natriuretic peptides) during anthracycline cycles [39]. Natriuretic peptides are altered during chemotherapy and correlate with reductions in LV ejection fraction [40•]. Similarly, cardiac troponin has been reported to have some prognostic value for risk stratification of patients during anthracycline treatment [3•]. A large, prospective, multicenter trial is necessary to definitively examine these strategies and determine whether biomarker-based risk stratification can improve overall outcome for patients requiring anthracycline-based cancer therapy.

Treatment for Anthracycline-Induced Cardiomyopathy

Despite efforts to detect early cardiac dysfunction in anthracycline-treated patients, many will experience symptomatic and asymptomatic heart failure. Cancer survivors who develop late AIC with New York Heart Association (NYHA) class III–IV heart failure have a poor prognosis, with a 1-year mortality of 40% and 2-year mortality of 60% [41]. At present, there is no specific treatment for AIC, and the clinical approach is based on standard therapy for systolic heart failure. Some small clinical trials in patients with AIC help to support the use of specific neurohormonal blockers (Table 1).

Angiotensin-converting enzyme (ACE) inhibitors block the neurohormonal conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. In general, ACE inhibitors reduce afterload on the heart and potentially alter cardiac remodeling and fibrosis. Early studies treated 135 long-term survivors of pediatric cancer with an ACE inhibitor (enalapril) versus placebo in a randomized, controlled trial, which demonstrated that the enalapril-treated group had less LV systolic wall stress [42]. However myocardial remodeling did continue in this group.

Beta-blockers are a standard therapy in the treatment of chronic heart failure, in which they alter remodeling and reduce mortality. One of the mechanisms of action of beta-blockers in heart failure is the reduction or reversal of catecholamine-induced myocardial remodeling [43]. In a recent study, Cardinale et al. [3•] treated 201 patients identified with AIC (LV ejection fraction < 45%) with the ACE inhibitor enalapril and the beta-blocker carvedilol for an average of 36 months. Eighty-five patients (42%) had normalization of the ejection fraction and were considered to be responders; 26 patients (13%) had improved ejection fraction and were considered partial responders; and 90 patients (45%) were nonresponders.

Predictors for improved LV recovery were low NYHA class and the beginning of treatment within 4 months after the end of chemotherapy.

It is worth noting that neurohormonal blockade may also help to prevent AIC. For example, in a small study of 50 patients undergoing anthracycline treatment, patients were randomized to prophylactic treatment with carvedilol (12.5 mg once daily) versus placebo [44]. After 6 months, there was small but statistically significant difference in the ejection fraction in the control group (from 68.9% to 52.3%; $P<0.001$) but not in the carvedilol-treated group (from 70.5% to 69.7%; $P=0.3$). Though this study is small, it highlights the idea of using conventional heart failure treatment to prevent cardiac dysfunction during cardiotoxic chemotherapy. This study using a beta-blocker and similar studies with ACE inhibitors support the use of these classes of antihypertensives in all patients with any degree of hypertension who are undergoing anthracycline-based chemotherapy [45].

Emerging Cardioprotective Strategies

Research continues to identify new strategies for cardioprotection (Table 2). Riad et al. [46] examined in mice whether pretreatment with statins attenuated the cardiotoxic effects of doxorubicin. The authors postulated that statins might prevent AIC by means of anti-inflammatory and anti-oxidative effects. Pretreatment with fluvastatin in the doxorubicin-treated mice improved LV hemodynamics, decreased the expression of inflammatory cytokines, and increased mitochondrial expression of anti-oxidative enzymes, including superoxide dismutase [46]. The dose of fluvastatin used in this animal model was much higher than the dose needed to lower cholesterol, but the notion that statins may be an additional prophylactic agent is intriguing and warrants testing in a prospective randomized trial of anthracycline-treated patients.

Erythropoietin is a hormone often administered to patients to stimulate production and maturation of red blood cells. Based on other studies showing that erythropoietin prevented the apoptosis of neurons, vascular endothelial cells, and cardiomyocytes, Kim et al. hypothesized that this treatment may have a chemoprotective effect [47]. In a preclinical study, they administered erythropoietin to mice 4 days prior to treatment with doxorubicin. These researchers found that erythropoietin treatment in doxorubicin-treated mice decreased ventricular myocyte apoptosis and DNA fragmentation. They proposed that the cardioprotective effects occurred through the PI3K-Akt prosurvival cell-signaling pathway. Recently, however, there has been some concern that erythropoietin supplementation in the setting of anemia may alter tumor responses in patients [48], so this may not be an ideal treatment for preventing AIC.

Various forms of heart failure, including AIC, are associated with elevated levels of endothelin-1 [49]. In animal studies, pretreatment with an endothelin-1 receptor antagonist (bosentan) prior to doxorubicin is cardioprotective, preserves LV function, decreases inflammatory markers (TNF- α) and the expression of apoptotic signaling proteins (Bax), and increases GATA4 expression [50]. The exact mechanism by which endothelin-1 antagonism is cardioprotective during anthracycline exposure remains unclear. Endothelin-1 is a potent endothelium-derived peptide that regulates cardiovascular function much like

angiotensin II and catecholamines. Endothelin-1 has multiple effects, including vasoconstriction, increased cardiac contractility, and induction of myocyte hypertrophy. Further work is needed to determine the role of endothelin-1 and its translational potential as an AIC protective therapy.

Cardiac progenitor cells (CPC's) may one day play a role in the treatment of AIC. Preclinical studies in rats that develop AIC have improved survival and LV functions when treated with intramyocardial injections of immunocompatible CPC's (51). De Angelis et al. demonstrated that rats which developed AIC three weeks of doxorubicin treatment, which were subsequently treated with CPC's had a 66% decrease in animal mortality at six weeks compared to normal control rats treated with only vehicle (51). Additionally there was an improvement in ventricular function (51). The data suggest that CPC's may be considered as a potential translational therapy in the future by helping promote cardiac repair after anthracycline cardiotoxicity.

Conclusions

Cardiotoxicity, a well-known adverse effect of anthracyclines, may become manifest as late as 20 years after chemotherapy. Research demonstrates numerous forms of myocardial injury that contribute to this clinical problem. In spite of much effort, there is no consensus regarding the standard of care for cardiac monitoring, prophylactic cardiac treatment, or selective therapies to reverse AIC. Large multicenter, prospective studies examining biologic parameters, genetic alterations, and functional imaging techniques will be needed to better predict, prevent, and treat AIC. Continuing to grow collaborative interdisciplinary teams involving both cardiology and oncology is likely to enhance the care of cancer patients by providing improved cardiac monitoring, early detection of AIC, and eventually new therapies to treat this serious problem.

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References and Recommended Reading

Recently published papers of interest have been highlighted as

- Of importance
  - Of major importance
1. Shankar SM, Marina N, Hudson MM, et al. Monitoring for cardiovascular disease in survivors of childhood cancer: report from the Cardiovascular Disease Task Force of the Children's Oncology Group. *Pediatrics*. 2008; 121:e387–e396. [PubMed: 18187811]
  2. Steinherz LJ, Steinherz PG, Tan CT, et al. Cardiac toxicity 4 to 20 years after completing anthracycline therapy. *JAMA*. 1991; 266:1672–1677. [PubMed: 1886191]
  - 3•. Cardinale D, Colombo A, Lamantia G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. *J Am Coll Cardiol*. 2010; 55:213–220. In a prospective clinical trial, 201 patients with AIC were treated with enalapril and carvedilol promptly after diagnosis of LV ejection fraction of 45% or less. Complete recovery of the ejection fraction occurred in 85 patients (42%). The percentage of responders decreased when the

time from chemotherapy to diagnosis of reduced ejection fraction was greater than 4 months. [PubMed: 20117401]

4. Lipshultz SE, Alvarez JA, Scully RE. Anthracycline associated cardiotoxicity in survivors of childhood cancer. *Heart*. 2008; 94:525–533. A review of results from the Childhood Cancer Survivor Study (CCSS) discussing increased cumulative incidence of chronic health conditions 30 years after treatment. The review highlights proposed pathophysiology that occurs during late-onset cardiotoxicity after childhood exposure and recommendations for monitoring and treatment. [PubMed: 18347383]
5. Shan K, Lincoff AM, Young JB. Anthracycline-induced cardiotoxicity. *Ann Intern Med*. 1996; 125:47–58. [PubMed: 8644988]
6. Perez EA, Suman VJ, Davidson NE, et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. *J Clin Oncol*. 2008; 26:1231–1238. [PubMed: 18250349]
7. Peng X, Chen B, Lim CC, Sawyer DB. The cardiotoxicology of anthracycline chemotherapeutics: translating molecular mechanism into preventative medicine. *Mol Interv*. 2005; 5:163–171. [PubMed: 15994456]
8. Unverferth DV, Magorien RD, Unverferth BP, et al. Human myocardial morphologic and functional changes in the first 24 hours after doxorubicin administration. *Cancer Treat Rep*. 1981; 65:1093–1097. [PubMed: 7296554]
9. Childs AC, Phaneuf SL, Dirks AJ, et al. Doxorubicin treatment in vivo causes cytochrome C release and cardiomyocyte apoptosis, as well as increased mitochondrial efficiency, superoxide dismutase activity, and Bcl-2:Bax ratio. *Cancer Res*. 2002; 62:4592–4598. [PubMed: 12183413]
10. Lipshultz SE, Rifai N, Sallan SE, et al. Predictive value of cardiac troponin T in pediatric patients at risk for myocardial injury. *Circulation*. 1997; 96:2641–2648. [PubMed: 9355905]
11. Horenstein MS, Vander Heide RS, L'Ecuyer TJ. Molecular basis of anthracycline-induced cardiotoxicity and its prevention. *Mol Genet Metab*. 2000; 71:436–444. [PubMed: 11001837]
12. Tokarska-Schlattner M, Zaugg M, Zuppinger C, et al. New insights into doxorubicin-induced cardiotoxicity: the critical role of cellular energetics. *J Mol Cell Cardiol*. 2006; 41:389–405. [PubMed: 16879835]
13. Sawyer DB, Fukazawa R, Arstall MA, Kelly RA. Daunorubicin-induced apoptosis in rat cardiac myocytes is inhibited by dexrazoxane. *Circ Res*. 1999; 84:257–265. [PubMed: 10024299]
14. Yen HC, Oberley TD, Vichitbandha S, et al. The protective role of manganese superoxide dismutase against Adriamycin-induced acute cardiac toxicity in transgenic mice. *J Clin Invest*. 1996; 98:1253–1260. [PubMed: 8787689]
15. Tewey KM, Chen GL, Nelson EM, Liu LF. Intercalative antitumor drugs interfere with the breakage-reunion reaction of mammalian DNA topoisomerase II. *J Biol Chem*. 1984; 259:9182–9187. [PubMed: 6086625]
16. Liu J, Mao W, Ding B, Liang CS. ERKs/p53 signal transduction pathway is involved in doxorubicin-induced apoptosis in H9c2 cells and cardiomyocytes. *Am J Physiol Heart Circ Physiol*. 2008; 295:H1956–H1965. [PubMed: 18775851]
17. Fukazawa R, Miller TA, Kuramochi Y, et al. Neuregulin-1 protects ventricular myocytes from anthracycline-induced apoptosis via erbB4-dependent activation of PI3-kinase/Akt. *J Mol Cell Cardiol*. 2003; 35:1473–1479. [PubMed: 14654373]
18. Zhao YY, Sawyer DR, Baliga RR, et al. Neuregulins promote survival and growth of cardiac myocytes. Persistence of ErbB2 and ErbB4 expression in neonatal and adult ventricular myocytes. *J Biol Chem*. 1998; 273:10261–10269. [PubMed: 9553078]
19. Rohrbach S, Yan X, Weinberg EO, et al. Neuregulin in cardiac hypertrophy in rats with aortic stenosis. Differential expression of erbB2 and erbB4 receptors. *Circulation* 1999. 100:407–412.
20. Bains OS, Takahashi RH, Pfeifer TA, et al. Two allelic variants of aldo-keto reductase 1A1 exhibit reduced in vitro metabolism of daunorubicin. *Drug Metab Dispos* 2008. 36:904–910.
21. Wojnowski L, Kulle B, Schirmer M, et al. NAD(P)H oxidase and multidrug resistance protein genetic polymorphisms are associated with doxorubicin-induced cardiotoxicity. *Circulation* 2005. 112:3754–3762.

22. Deng S, Wojnowski L. Genotyping the risk of anthracycline-induced cardiotoxicity. *Cardiovasc Toxicol.* 2007; 7:129–134. [PubMed: 17652817]
23. Charron F, Nemer M. GATA transcription factors and cardiac development. *Semin Cell Dev Biol.* 1999; 10:85–91. [PubMed: 10355032]
24. O'Prey J, Ramsay S, Chambers I, Harrison PR. Transcriptional up-regulation of the mouse cytosolic glutathione peroxidase gene in erythroid cells is due to a tissue-specific 3' enhancer containing functionally important CACC/GT motifs and binding sites for GATA and Ets transcription factors. *Mol Cell Biol.* 1993; 13:6290–6303. [PubMed: 8413228]
25. Jeyaseelan R, Poizat C, Baker RK, et al. A novel cardiac-restricted target for doxorubicin. CARP, a nuclear modulator of gene expression in cardiac progenitor cells and cardiomyocytes. *J Biol Chem.* 1997; 272:22800–22808. [PubMed: 9278441]
26. Saadane N, Alpert L, Chalifour LE. TAFII250, Egr-1, and D-type cyclin expression in mice and neonatal rat cardiomyocytes treated with doxorubicin. *Am J Physiol.* 1999; 276:H803–814. [PubMed: 10070062]
27. Chen S, Garami M, Gardner DG. Doxorubicin selectively inhibits brain versus atrial natriuretic peptide gene expression in cultured neonatal rat myocytes. *Hypertension.* 1999; 34:1223–1231. [PubMed: 10601122]
28. Granzier H, Wu Y, Siegfried L, LeWinter M. Titin: physiological function and role in cardiomyopathy and failure. *Heart Fail Rev.* 2005; 10:211–223. [PubMed: 16416044]
29. Lim CC, Zuppinger C, Guo X, et al. Anthracyclines induce calpain-dependent titin proteolysis and necrosis in cardiomyocytes. *J Biol Chem.* 2004; 279:8290–8299. [PubMed: 14676206]
30. De Angelis A, Piegari E, Cappetta D, et al. Anthracycline cardiomyopathy is mediated by depletion of the cardiac stem cell pool and is rescued by restoration of progenitor cell function. *Circulation.* 2010; 121:276–292. [PubMed: 20038740]
31. Huang C, Zhang X, Ramil JM, et al. Juvenile exposure to anthracyclines impairs cardiac progenitor cell function and vascularization resulting in greater susceptibility to stress-induced myocardial injury in adult mice. *Circulation.* 2010; 121:675–683. [PubMed: 20100968]
32. Lipshultz SE, Giantris AL, Lipsitz SR, et al. Doxorubicin administration by continuous infusion is not cardioprotective: the Dana-Farber 91-01 Acute Lymphoblastic Leukemia protocol. *J Clin Oncol.* 2002; 20:1677–1682. [PubMed: 11896119]
33. Ewer MS, Martin FJ, Henderson C, et al. Cardiac safety of liposomal anthracyclines. *Semin Oncol.* 2004; 31(6 Suppl 13):161–181. [PubMed: 15717742]
34. van Dalen EC, Michiels EM, Caron HN, Kremer LC. Different anthracycline derivatives for reducing cardiotoxicity in cancer patients. *Cochrane Database Syst Rev.* 2010; 5 CD005006.
35. van Dalen EC, Caron HN, Dickinson HO, Kremer LC. Cardioprotective interventions for cancer patients receiving anthracyclines. *Cochrane Database Syst Rev.* 2005; 1 CD003917.
36. Kapusta L, Groot-Loonen J, Thijssen JM, et al. Regional cardiac wall motion abnormalities during and shortly after anthracyclines therapy. *Med Pediatr Oncol.* 2003; 41:426–435. [PubMed: 14515381]
37. Tassan-Mangina S, Codorean D, Metivier M, et al. Tissue Doppler imaging and conventional echocardiography after anthracycline treatment in adults: early and late alterations of left ventricular function during a prospective study. *Eur J Echocardiogr.* 2006; 7:141–146. [PubMed: 15941672]
38. Walker J, Bhullar N, Fallah-Rad N, et al. Role of three-dimensional echocardiography in breast cancer: comparison with two-dimensional echocardiography, multiple-gated acquisition scans, and cardiac magnetic resonance imaging. *J Clin Oncol.* 2010; 28:3429–3436. [PubMed: 20530277]
39. Dagaard G, Lassen U, Bie P, et al. Natriuretic peptides in the monitoring of anthracycline induced reduction in left ventricular ejection fraction. *Eur J Heart Fail.* 2005; 7:87–93. [PubMed: 15642537]
40. Cil T, Kaplan AM, Altintas A, et al. Use of N-terminal pro-brain natriuretic peptide to assess left ventricular function after adjuvant doxorubicin therapy in early breast cancer patients: a prospective series. *Clin Drug Investig.* 2009; 29:131–137. In a prospective study, 33 patients with newly diagnosed breast cancer undergoing a total dose of doxorubicin of 240 mg/m² were monitored for changes in ejection fraction and N-terminal pro-brain natriuretic peptide (NT-

proBNP). A significant association was found between high NT-proBNP and reduced ejection fraction.

41. Felker GM, Thompson RE, Hare JM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med*. 2000; 342:1077–1084. [PubMed: 10760308]
42. Silber JH, Cnaan A, Clark BJ, et al. Enalapril to prevent cardiac function decline in long-term survivors of pediatric cancer exposed to anthracyclines. *J Clin Oncol*. 2004; 22:820–828. [PubMed: 14990637]
43. Bristow MR. Mechanism of action of beta-blocking agents in heart failure. *Am J Cardiol*. 1997; 80:26L–40L.
44. Kalay N, Basar E, Ozdogru I, et al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. *J Am Coll Cardiol*. 2006; 48:2258–2262. [PubMed: 17161256]
45. Tokudome T, Mizushige K, Noma T, et al. Prevention of doxorubicin (Adriamycin)-induced cardiomyopathy by simultaneous administration of angiotensin-converting enzyme inhibitor assessed by acoustic densitometry. *J Cardiovasc Pharmacol*. 2000; 36:361–368. [PubMed: 10975594]
46. Riad A, Bien S, Westermann D, et al. Pretreatment with statin attenuates the cardiotoxicity of doxorubicin in mice. *Cancer Res*. 2009; 69:695–699. [PubMed: 19147586]
47. Kim KH, Oudit GY, Backx PH. Erythropoietin protects against doxorubicin-induced cardiomyopathy via a phosphatidylinositol 3-kinase-dependent pathway. *J Pharmacol Exp Ther*. 2008; 324:160–169. [PubMed: 17928571]
48. Bohlius J, Langensiepen S, Schwarzer G, et al. Recombinant human erythropoietin and overall survival in cancer patients: results of a comprehensive meta-analysis. *J Natl Cancer Inst*. 2005; 97:489–498. [PubMed: 15812074]
49. Sayed-Ahmed MM, Khattab MM, Gad MZ, Osman AM. Increased plasma endothelin-1 and cardiac nitric oxide during doxorubicin-induced cardiomyopathy. *Pharmacol Toxicol*. 2001; 89:140–144. [PubMed: 11589785]
50. Bien S, Riad A, Ritter CA, et al. The endothelin receptor blocker bosentan inhibits doxorubicin-induced cardiomyopathy. *Cancer Res*. 2007; 67:10428–10435. [PubMed: 17974986]
51. De Angelis A, Piegari E, Cappetta D, et al. Anthracycline Cardiomyopathy Is Mediated by Depletion of the Cardiac Stem Cell Pool and Is Rescued by Restoration of Progenitor Cell Function. *Circulation*. 2009; 121:276–292. [PubMed: 20038740]

Table 1

Established methods to prevent and modulate anthracycline cardiotoxicity

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• Limit cumulative dose (<500 mg/m²) of anthracyclines.   • Avoid concurrent use of anthracyclines with trastuzumab (monoclonal HER2 antibody).   • If cumulative dose is greater than 500 mg/m² and/or patient has increased risk factors for cardiotoxicity (age >65 y, hypertension, prior coronary heart disease, diabetes mellitus, radiation exposure), dexrazoxane may reduce the risk.   • In patients with hypertension, consider adding angiotensin-converting enzyme (ACE) inhibitors prior to anthracycline exposure.   • Current evidence suggests that cardiac recovery is improved with early detection of anthracycline-induced cardiotoxicity and initiation of ACE-inhibitor and beta-blocker therapy.   • The best current methods to detect cardiotoxicity are serial monitoring of ventricular function and cardiac biomarkers (B-type natriuretic peptide, cardiac troponin).

Table 2

Experimental strategies to prevent anthracycline cardiotoxicity

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- **Statins** potentially alter the anti-inflammatory and anti-oxidative effects of anthracyclines.
  - **Erythropoietin** may promote cell survival signaling of myocytes.
  - An **endothelin-1 receptor antagonist**, bosentan, an may decrease inflammatory markers and inhibit apoptotic cell signaling.
  - **Stem cell therapy** may replete lost progenitor cells and promote cardiovascular repair.
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