JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2014 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.

VOL. 64, NO. 9, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.06.1167

REVIEW TOPIC OF THE WEEK

Prevention of Anthracycline-Induced Cardiotoxicity

Challenges and Opportunities

Pimprapa Vejpongsa, MD,* Edward T.H. Yeh, MD*†

ABSTRACT

Anthracycline compounds are major culprits in chemotherapy-induced cardiotoxicity, which is the chief limiting factor in delivering optimal chemotherapy to cancer patients. Although extensive efforts have been devoted to identifying strategies to prevent anthracycline-induced cardiotoxicity, there is little consensus regarding the best approach. Recent advances in basic mechanisms of anthracycline-induced cardiotoxicity provided a unified theory to explain the old reactive-oxygen species hypothesis and identified topoisomerase 2β as the primary molecular target for cardioprotection. This review outlines current strategies for primary and secondary prevention of anthracycline-induced cardiotoxicity resulting from newly recognized molecular mechanisms and identifies knowledge gaps requiring further investigation. (J Am Coll Cardiol 2014;64:938-45) © 2014 by the American College of Cardiology Foundation.

The U.S. National Cancer Institute estimates that at least 13.7 million cancer survivors were alive in the United States in 2012 and that this number will approach 18 million by 2022 (1). A total of 67% of adults diagnosed with cancer today will be alive in 5 years, and 75% of children diagnosed with cancer today will be alive in 10 years. Cancer chemotherapy or radiotherapy can cause short- and long-term cardiovascular complications. In a U.S. National Health and Nutrition Examination survey of 1,807 cancer survivors followed for 7 years, 33% died of heart diseases and 51% of cancer (2).

The primary cause of chemotherapy-induced cardiotoxicity is anthracycline compounds, which are used extensively to treat lymphoma, sarcoma, breast cancer, and pediatric leukemia (**Table 1**). Despite efforts to identify risk factors, develop less-toxic derivatives, and detect subclinical toxicity earlier, there is no consensus on the best approach to prevent anthracycline-induced cardiotoxicity. Recent advances in the molecular basis of anthracycline-induced cardiotoxicity might lead to better cardioprotective strategies.

RISK FACTORS FOR ANTHRACYCLINE-INDUCED CARDIOTOXICITY

Cardiac complications were first reported a few years after the introduction of daunorubicin (3). In 1979, a dose-toxicity curve was generated by plotting the incidence of heart failure (defined by clinical signs and symptoms such as shortness of breath, neck vein distension, S3 gallop, cardiomegaly, hepatomegaly, or pericardial effusion) against the total anthracycline dose used in many studies (4). Heart failure incidences were 3%, 7%, and 18% in patients who had received a cumulative dose of 400, 550, or 700 mg/m^2 of doxorubicin, respectively. Therefore, oncologists usually limited the cumulative anthracycline dose to ≤550 mg/m^2 (5). The introduction of cardiac imaging technology that allows detection of heart failure or even asymptomatic left ventricular (LV)

From *The University of Texas MD Anderson Cancer Center, Houston, Texas; and the †Texas Heart Institute, Houston, Texas. This work was supported in part by the Cancer Prevention Research Institute of Texas and the Moon Shot Program of the University of Texas MD Anderson Cancer Center (to Dr. Yeh). Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received April 20, 2014; revised manuscript received May 30, 2014, accepted June 10, 2014.

dysfunction led to the realization that incidence of anthracycline-induced cardiotoxicity was higher than previously estimated. In 2003, heart failure incidences of 5%, 16%, and 26% were estimated for cumulative doxorubicin doses of 400, 500, and 550 mg/m^2, respectively (6), resulting in a modification to limit the cumulative anthracycline dose to 400 to 450 mg/m^2.

Cardiac biopsy has been used to evaluate cardiac damage in patients who received anthracycline treatment, with morphological changes graded by the Billingham system (7). This system assesses the severity of cardiotoxicity using the degree of myofibrillar loss or vacuolization. Some patients exhibited morphologic changes with a cumulative dose of as low as 200 mg/m^2 (8). However, cardiac biopsy is not routinely performed in current practice because of its invasiveness.

Detecting troponin leakage in the peripheral blood during or after anthracycline treatment positively correlated with cardiac event rate and is a good, less invasive alternative to biopsy for identifying cardiac injury from anthracycline treatment. Troponin is detectable in some patients as early as the end of the first anthracycline administration cycle (9); thus, there is no safe cut-off point for anthracycline-induced cardiotoxicity.

Anthracycline-induced cardiomyopathy has been classified as early or late onset using a cutoff of 1 year after anthracycline treatment (10). Cumulative incidences of cardiac events peaked at 1 year after anthracycline treatment (11,12). The actual incidence of late cardiotoxicity is difficult to ascertain because of a lack of good studies. The multicenter Childhood Cancer Survivor Study reported that additional cancer treatment or other cardiovascular risk factors might play an important role in causing late-onset cardiomyopathy (13). This study also reported that cardiovascular risk factors, such as hypertension, diabetes, dyslipidemia, and obesity, are significantly higher in cancer survivors than in the healthy population (13).

MECHANISMS OF ANTHRACYCLINE-INDUCED CARDIOTOXICITY

Previously, the most widely accepted hypothesis for anthracycline-induced cardiomyopathy was the generation of excess reactive oxygen species (ROS) by electron exchange between the anthracycline quinone moiety and oxygen molecules and other cellular electron donors (14). Anthracyclines also form complexes with iron that undergo redox cycling and generate oxygen radicals (15). Although in vivo and in vitro studies confirmed increased ROS production in cardiomyocytes after anthracycline therapy, neither antioxidants nor iron chelation prevented cardiomyopathy (16,17).

Topoisomerase (Top) 2β was recently revealed as the key mediator of anthracycline-induced cardiotoxicity (18). Top2 unwinds deoxyribonucleic acid (DNA) strands during DNA replication, transcription, or recombination (19). In humans, there are 2 types of Top2 enzymes: Top2α and Top2β (20). Top2α, found predominantly in proliferating cells, is required for DNA replication and is considered the molecular basis of anthracycline's tumoricidal activity (21). In contrast, Top2β is present in all quiescent cells, including cardiomyocytes (22). Top2 inhibition by anthracycline causes double-stranded breaks in DNA, which can lead to cardiomyocyte death (18).

Activation of p53 and the apoptotic pathway are implicated in doxorubicin-induced cardiotoxicity (23). Top2β is required for p53 activation in response to anthracycline-induced DNA damage in cardiomyocytes (18), whereas anthracycline-induced ROS production is due to a reduction in antioxidant enzyme gene transcription, which is also Top2β-dependent (18). Doxorubicin also reduces expression of uncoupling proteins 2 and 3, which regulate mitochondrial ROS production (24). Furthermore, Top2β and anthracycline profoundly reduce peroxisome proliferator-activated receptor-γ coactivator 1-α and peroxisome proliferator-activated receptor-γ coactivator 1-β, which are critical for mitochondrial biogenesis (18). These findings suggest that Top2β initiates anthracycline-induced cardiotoxicity (**Central Illustration**). Most importantly, Top2β deletion from the heart protects mice from anthracycline-induced cardiomyopathy, which strongly implicates Top2β as the primary mediator of anthracycline-induced

ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ALL = acute lymphoblastic leukemia

ARB = angiotensin receptor blocker

DNA = deoxyribonucleic acid

FDA = U.S. Food and Drug Administration

LV = left ventricular

LVEF = left ventricular ejection fraction

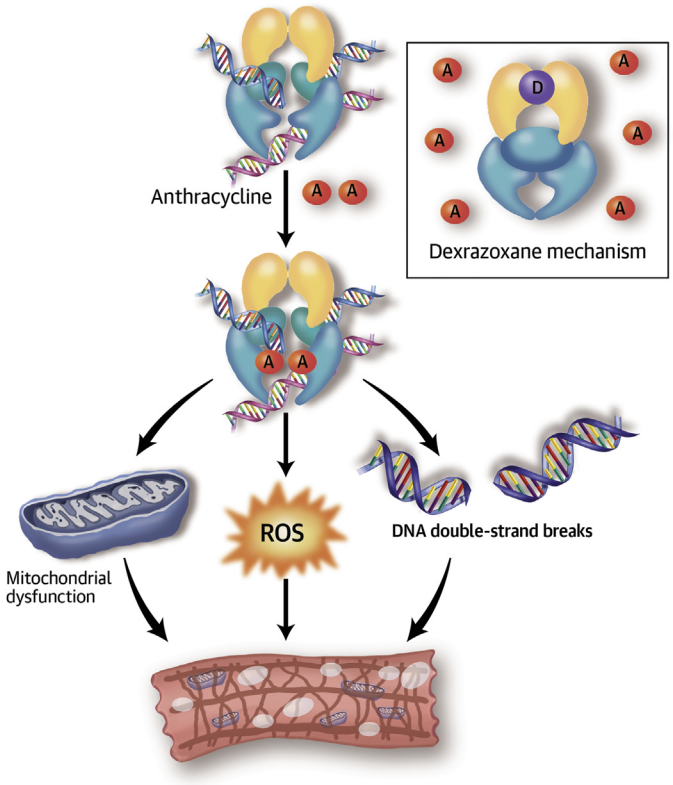
ROS = reactive oxygen species

Tn = troponin

Top = topoisomerase

TABLE 1 Anthracycline Regimens in the Most Widely Used Protocols for 4 Types of Cancer

Type of Cancer	Anthracycline Regimens	Other Considerations
Breast cancer	Doxorubicin 50–60 mg/m^2 × 4–6 cycles Epirubicin 75–100 mg/m^2 × 4–8 cycles	Increased cardiotoxicity with trastuzumab (11) Bolus over 15 min
Sarcoma	Doxorubicin 75–90 mg/m^2 × 6–8 cycles	Continuous infusion over 48–72 h or bolus over 15 min + dexrazoxane
Lymphoma	Doxorubicin 40–50 mg/m^2 × 6–8 cycles	Continuous infusion over 48–72 h or bolus over 15 min
Pediatric leukemia	Doxorubicin 30 mg/m^2 × 10 cycles	Bolus over 30 min ± dexrazoxane



CENTRAL ILLUSTRATION **Mechanism of Anthracycline-Induced Cardiotoxicity**

Doxorubicin disrupts the normal catalytic cycle of topoisomerase **(Top)** 2β, causing deoxyribonucleic acid (DNA) double-stranded breaks. It further changes the transcriptome, leading to defective mitochondrial biogenesis and increase in reactive oxygen species (ROS). As a result, cardiomyocytes showed myofibrillar disarray and vacuolization. In the **inset**, dexrazoxane was shown to bind to Top2β to prevent anthracycline binding.

cardiotoxicity (25). Other mechanisms may amplify this effect. For example, hemochromatosis accumulates iron, which amplifies the ROS response during anthracycline treatment (26).

GENETIC TESTING. Because cardiomyocyte-specific Top2β deletion prevents anthracycline-induced cardiotoxicity in mice (18), low cardiac Top2β expression would be similarly expected to prevent cardiotoxicity in patients. Peripheral blood leukocyte Top2β was investigated as a surrogate biomarker for individual susceptibility to anthracycline-induced cardiotoxicity (27). Top2β levels were compared between 21 anthracycline-sensitive patients (decreased left ventricular ejection fraction [LVEF] ≥10% from baseline and LVEF <50%, despite receiving a cumulative doxorubicin dose ≤250 mg/m^2) and 15 anthracycline-resistant patients (received a cumulative doxorubicin dose ≥450 mg/m^2 with LVEF ≥50%). Top2β was significantly higher in the anthracycline-sensitive group than in the resistant group (0.4 ± 0.28 ng/μg vs. 0.23 ± 0.1 ng/μg, p = 0.026). Top2β levels in the anthracycline-resistant group were all below a 0.5 ng/μg cutpoint. Although confirmation requires larger prospective studies, these results suggest that Top2β levels might be useful to stratify patients for cardiotoxicity risk from anthracyclines.

Although Top2β is the primary mediator for anthracycline-induced cardiomyopathy, other genes might also have an influence. Iron accumulation can amplify the ROS response to anthracycline exposure (26). Therefore, patients with higher tissue iron concentrations, as in hereditary iron metabolism disorders, have an elevated risk of cardiac damage. Hemochromatosis gene C282Y carriers had a greater myocardial injury risk than noncarriers (28). In a study of single nucleotide polymorphisms of selected genes involved in anthracycline transport or ROS production, human nicotinamide adenine dinucleotide phosphate oxidase variant rs1883112 was associated with risk of chronic anthracycline-induced cardiotoxicity (29). Prospective studies are needed to validate these genetic markers for clinical application.

PRIMARY PREVENTION STRATEGIES

Two approaches for primary prevention of anthracycline-induced cardiotoxicity are: 1) reduce cardiotoxic potency by administering via continuous infusion, liposome encapsulation, or using a less cardiotoxic derivative (e.g., epirubicin or idarubicin); and 2) use a cardioprotective agent (e.g., dexrazoxane) in conjunction with treatment. Other investigated agents include beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) (**Table 2**).

CONTINUOUS INFUSION. Various anthracycline schedules were evaluated in early clinical trials, including 1 bolus dose every 3 weeks, 3 divided doses every week, or 3 divided doses given 3 consecutive days every 3 weeks. Endomyocardial biopsies revealed that divided doses cause significantly less damage than bolus doses (30). Moreover, patients who received divided doses tolerated a higher cumulative doxorubicin dose. Tumor response rates and overall survival rates among the groups did not significantly differ, and the weekly schedule offered a longer duration of response than the bolus dose (30).

Whereas peak plasma level determines the severity of cardiotoxicity, antitumor efficacy corresponds to the area under the plasma distribution curve (31). Pharmacodynamics and pharmacokinetics studies in animal models demonstrated that although

TABLE 2 Primary Prevention for Anthracycline-Induced Cardiotoxicity

Prevention Strategy	Cost*	Comments
Continuous doxorubicin infusion (48–72 h)	$67/50 mg†	Effective in cardioprotection in sarcoma and lymphoma, but not in the pediatric population
Liposomal doxorubicin	$2,851/50 mg	FDA-approved for ovarian cancer, AIDS-related Kaposi sarcoma, and multiple myeloma, after failure of at least 1 prior therapy
Dexrazoxane	$362/500 mg	FDA-approved only for women with metastatic breast cancer who received at least 300 mg/m^2 doxorubicin and need additional doxorubicin to maintain tumor control
ACEI/ARB/β-blockers	$4/month	Unknown whether they were cardioprotective or simply changed hemodynamics

*2014 Walmart pharmacy prices. †May be higher, depending on hospital stay or infusion pump care costs.

ACEI = angiotensin-converting enzyme inhibitor; AIDS = acquired immune deficiency syndrome; ARB = angiotensin receptor blocker; FDA = U.S. Food and Drug Administration.

anthracycline concentrations in tumor tissue were the same with continuous or bolus administration, anthracycline concentration in the heart was higher with the bolus dose, leading to higher clinical cardiotoxicity (31). Increasing infusion duration clearly reduced cardiotoxicity without compromising oncological efficacy (32), but an infusion lasting longer than 96 h is associated with higher incidence of stomatitis and a prolonged need for an infusion pump and indwelling catheter. Continuous doxorubicin infusion over 48 to 72 h is widely used in sarcoma or lymphoma patients.

In children with acute lymphoblastic leukemia (ALL), continuous doxorubicin infusion is no more cardioprotective than a bolus dose (33). Participants who received either treatment had similar echocardiographic measurements in all parameters at 8-year follow-up, which were significantly worse in both groups than at baseline (33), perhaps due to different responses in children's developing hearts.

LIPOSOMAL DOXORUBICIN. Another strategy to reduce cardiotoxicity from conventional anthracyclines is to use liposomal encapsulation, which modifies pharmacokinetics and tissue distribution without compromising antitumor efficacy (34). Active doxorubicin is trapped within the internal aqueous compartment by the ion gradient difference. Whereas liposomal doxorubicin is thought to be restricted to inside the vessel wall of organs with tight capillary junctions (such as the heart), it has been shown to more readily penetrate through tumor vasculature, which is more fragile and permeable than healthy tissue (34). Thus, doxorubicin's anticancer properties are preserved with less cardiotoxicity.

Two types of liposomal doxorubicin are used clinically: pegylated (Doxil, Janssen, Titusville, New Jersey) or nonpegylated, of which the pegylated version is more widely used in the United States. Pegylation involves covalent attachment of surface-bound methoxypolyethylene glycol to the liposomal phospholipid bilayer. This masks liposomes from the mononuclear phagocyte system, lowering their antigenicity and increasing their half-lives (35). Because of its cost (**Table 2**), liposomal doxorubicin is not widely used, and it is only approved by the U.S. Food and Drug Administration (FDA) in ovarian cancer, acquired immune deficiency syndrome-related Kaposi sarcoma, and multiple myeloma after failure of at least 1 prior therapy (36).

DEXRAZOXANE. Dexrazoxane is the only FDA-approved cardioprotective agent for anthracycline-induced cardiotoxicity (37). It is an effective cardioprotective agent against anthracyclines in a variety of cancer types in children and adults (38,39). Dexrazoxane's ability to chelate iron was previously thought to be the primary mechanism of cardioprotection (40). However, other iron chelators, such as deferasirox or ICRF-161, do not provide cardioprotection (17,41). Lyu et al. (42) demonstrated that dexrazoxane changes Top2's configuration to a closed-clamp form through tight binding to Top2's ATP-binding sites, thus preventing anthracyclines from binding to the Top2 complex (**Central Illustration**).

Two multicenter breast cancer studies (clinical studies 088001 and 088006) demonstrated dexrazoxane's cardioprotective efficacy (43,44). More than 500 patients with advanced breast cancer undergoing anthracycline therapy were randomized to receive either placebo or dexrazoxane. A cardiac event was defined as an LVEF decline ≥10% from baseline and below the institution's normal limit, an LVEF decline ≥20% to at least 5% below the institution's normal limit, or development of heart failure. Hazard ratios of placebo to dexrazoxane for cardiac events were 2.63 (95% confidence interval: 1.61 to 4.27, $p < 0.001$) in the 088001 trial and 2.00 (95% confidence interval: 1.01 to 3.96, $p = 0.038$) in the 088006 trial, clearly establishing dexrazoxane's efficacy in preventing cardiac damage from anthracycline

(43,44). However, concurrently administered dexrazoxane might interfere with anthracycline's antitumor efficacy (44). In the 088001 trial, the dexrazoxane arm had a lower response rate; however, times to progression and survival rates were not significantly different (44). Of note, this study was not replicated by other clinical trials (44), and animal studies suggest that dexrazoxane synergizes with anthracycline (45,46). The FDA approved dexrazoxane only for women with metastatic breast cancer who need additional doxorubicin to maintain tumor control after they received at least 300 mg/m^2 of doxorubicin (37).

Multiple trials have demonstrated dexrazoxane's efficacy for primary prevention of anthracycline-induced cardiotoxicity in children. More than 200 children with ALL were randomized to receive doxorubicin 30 mg/m^2 (cumulative dose 300 mg/m^2) with or without dexrazoxane (38). Blinded troponin (Tn) T measurements were obtained at multiple time points before, during, and after doxorubicin infusion. At the end of the course, TnT levels were elevated in only 20% of children who received doxorubicin plus dexrazoxane and in 47% of those in the doxorubicin group (38). At 5-year follow-up, LV fractional shortening and end-systolic dimension were similar to those of normal children in the dexrazoxane group but were worse than normal children in the doxorubicin-only group (38).

Consistent with another retrospective study identifying female sex as an independent risk factor for anthracycline-induced cardiotoxicity (47), reduced LV fractional shortening was greater in girls than in boys in the doxorubicin-only group across a 5-year period (38). Moreover, dexrazoxane provides greater cardioprotection for girls than for boys (38). Five years after treatment, girls who received doxorubicin with dexrazoxane had better fractional shortening and a better end-diastolic thickness-to-dimension ratio than those who received doxorubicin alone (38). Animal studies suggest that hormonal status or body fat percentage might cause the higher incidence of cardiotoxicity found in girls (48). Although the reason for its potency in girls is unknown, dexrazoxane clearly provides long-term cardioprotection without compromising anthracycline's antitumor efficacy. With a median 8.7-year follow-up interval, event-free survival rates were similar in patients who received concurrent dexrazoxane and in those who received doxorubicin alone (76% vs. 77%, p = 0.99) (38).

Another controversy is the potential risk of increased secondary malignancy, which was reported in 1 study that added dexrazoxane to the standard pediatric Hodgkin lymphoma regimen (49). At 4-year follow-up, 8 patients in the dexrazoxane arm developed secondary malignancy: 6 with acute myeloid leukemia/myelodysplastic syndrome, 1 with thyroid carcinoma (within the radiation field), and 1 with osteosarcoma. If only acute myeloid leukemia/myelodysplastic syndrome patients are considered, the 2 arms did not differ significantly (p = 0.152) (49). Two other studies of childhood ALL reported no differences in secondary malignancy incidence between dexrazoxane and placebo groups at 5- or 10-year follow-up (50,51). Taken together, dexrazoxane is unlikely to increase secondary malignancy risk.

BETA-BLOCKERS, ACE INHIBITORS, OR ARBS. Beta-blockers, ACE inhibitors, and ARBs were evaluated in randomized controlled trials for primary prevention of anthracycline-induced cardiotoxicity (**Table 3**). LVEF dropped significantly after chemotherapy in placebo or control groups, but not in intervention

TABLE 3 Summary of β-Blocker and/or ACE Inhibitor Studies for Primary Prevention of Anthracycline-Induced Cardiotoxicity

First Author (Ref. #)	Medication	Patients*	Follow-Up, Months	Results
Kalay et al. (54)	Carvedilol 12.5 mg daily vs. placebo	50 (25/25)	6	Placebo: LVEF 68.9% → 52.3%† Carvedilol: LVEF 70.5% → 69.7%
Georgakopoulos et al. (55)	Metoprolol‡ vs. enalapril‡ vs. placebo§	125 (42/43/40)	31	Cardiotoxicity incidence not statistically different among 3 groups No difference in echocardiographic parameters among 3 groups at 12 months
Kaya et al. (53)	Nebivolol 5 mg daily vs. placebo‖	45 (27/18)	6	Placebo: LVEF 66.6% → 57.5%† Nebivolol: LVEF 65.6% → 63.8%
Bosch et al. (52)	Enalapril‡ + carvedilol‡ vs. no treatment‖	90 (45/45)	6	Control: LVEF 64.6% → 57.9%† Enalapril + carvedilol: LVEF 63.3% → 62.9% TnI levels not significantly different between 2 groups (p = 0.59)

*Numbers in parentheses represent the numbers of patients in intervention and control/placebo groups, respectively. †Statistically significant between baseline and 6 months (p < 0.05). ‡Medications titrated as tolerated. §Medications started on the first day of chemotherapy and continued throughout the study. ‖Medications started within 1 week before the first chemotherapy cycle and continued for 6 months.

ACE = angiotensin-converting enzyme; LVEF = left ventricular ejection fraction; TnI = troponin I.

groups. Despite these declines, LVEFs remained >50% (52–54). The major limitation of these studies is the short-term (5 to 6 months) follow-up. Whether beneficial hemodynamic effects or primary protection were responsible for these results is unclear. Over a median 31-month follow-up period (the longest of 4 studies), no differences in echocardiographic parameters or heart failure incidence were observed during doxorubicin treatment in lymphoma patients randomized to receive metoprolol, enalapril, or nothing (55). Another trial monitored TnI, the best cardiac injury marker, during anthracycline therapy. TnI leakage did not differ significantly between the control and intervention groups (4 patients vs. 7 patients, p = 0.59) (52). In summary, whether beta-blockers, ACE inhibitors, or ARBs are useful in primary prevention is uncertain.

SECONDARY PREVENTION STRATEGIES

DETECTION. Cardiac injury from anthracycline therapy is detected as LVEF changes that are measured by echocardiography, multigated acquisition scans, or magnetic resonance imaging (56–58). Echocardiographic strain imaging has recently emerged as a promising method for detection of cardiotoxicity prior to LV dysfunction (57). Cardiotoxicity is defined as an LVEF decline of ≥5% to <55% with heart failure symptoms or an asymptomatic decrease of LVEF ≥10% to <55% (59). Factors influencing LVEF in patients receiving anthracycline-containing regimens include fluid overload, sepsis, ischemic heart disease, or other chemotherapy drugs.

Biomarkers are often used to identify patients with early clinical signs of cardiotoxicity. Although the peak value and duration of troponin elevation are closely correlated with the degree of LV dysfunction, the optimal time for blood sampling is unknown (9). Troponin combined with LV systolic strain provided better sensitivity and specificity (57) than other biomarkers tested in prospective studies, such as brain natriuretic peptide and N-terminal pro-brain natriuretic peptide (60,61).

BETA-BLOCKERS OR ACE INHIBITORS. Several studies examined beta-blockers or ACE inhibitors for secondary prevention in high-risk patients after anthracycline treatment; however, each study defined high-risk features differently. One enalapril trial enrolled patients with troponin leaks within 72 h after high-dose chemotherapy (62). In this trial, the enalapril group displayed significantly higher LVEF than the control group at 1-year follow-up, and significant LVEF drops occurred in 43% of control patients (>10% to LVEF <50%) and in none of the enalapril patients (62). An observational study evaluated the efficacy of enalapril + carvedilol in preventing deterioration of LV function in patients with LVEF ≤45%, although it lacked a control group. They found that LVEF recovery was more likely with early initiation of an ACE inhibitor and beta-blocker after completion of anthracycline treatment (63). A small, retrospective study in childhood cancer survivors questioned whether ACE inhibitors improve long-term outcomes of anthracycline-induced cardiomyopathy (64). In this study, progressive improvements in echocardiographic parameters after enalapril initiation did not persist after 6 years of treatment; all patients either required heart transplant or experienced cardiac-related death (64), perhaps due to late initiation of treatment.

SUMMARY

The ideal primary prevention protocol would involve genetic susceptibility testing for markers such as Top2β or hemochromatosis gene C282Y. However, these genetic tests have not yet been validated in prospective clinical trials and cannot be recommended for general use at present. Both American College of Cardiology Foundation/American Heart Association and European Society of Cardiology guidelines support the use of dexrazoxane to reduce the occurrence and severity of anthracycline-induced cardiotoxicity (65,66). However, questions regarding antitumor effects or secondary malignancy limit dexrazoxane's wider use. New clinical trials to expand the clinical indications for dexrazoxane are crucial. Current recommendations for primary prevention are to treat high-risk patients with

TABLE 4 Primary and Secondary Prevention Strategies

Clinical Setting	Primary Prevention	Level of Evidence*	Class of Recommendation*
High-risk profile from genetic testing	Dexrazoxane Liposomal doxorubicin Continuous infusion	C	IIb
Breast cancer (metastatic >300 mg/m²)†	Dexrazoxane	A	I
Sarcoma‡	Dexrazoxane Continuous infusion	A	IIa
High-risk pediatric ALL§	Dexrazoxane	A	IIa
All patients receiving anthracycline	β-blockers, ACEI, ARB	C	IIb
	Secondary Prevention		
Abnormal strain/LV function ± elevated cardiac biomarkers	β-blockers, ACEI, ARB	B	IIa

*According to American College of Cardiology Foundation/American Heart Association guideline criteria (65). †Metastatic breast cancer patients requiring doxorubicin >300 mg/m². ‡To receive doxorubicin >450 mg/m². §Patients age <12 months or 10 to 18 years; white blood cell count ≥50,000 cells/μl; or have T-cell phenotype, presence of anterior mediastinal mass, or any lymphoblasts in a cerebrospinal fluid sample.

ALL = acute lymphoblastic leukemia; LV = left ventricular; other abbreviations as in Table 2.

dexrazoxane, liposomal doxorubicin, or continuous infusion (**Table 4**).

Clinicians should be alerted to early signs of anthracycline-induced cardiotoxicity by a combination of biomarker and imaging studies. Guidelines developed through expert consensus recommend the frequency and modality of testing for secondary prevention (59). Standard heart failure treatment should generally be initiated with the earliest detection of cardiotoxicity (66) (**Table 4**).

Although there are ample primary or secondary prevention opportunities, definitive clinical studies demonstrating efficacy are lacking. These gaps should be filled with carefully planned, multi-institutional studies. We look forward to the days when patients can be treated with anthracycline without worrying about cardiotoxicity.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Edward T.H. Yeh, Department of Cardiology, The University of Texas MD Anderson Cancer Center, 1400 Pressler Street, Houston, Texas, 77030. E-mail: etyeh@mdanderson.org.

REFERENCES

1. Siegel R, DeSantis C, Virgo K, et al. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin 2012;62:220–41.

2. Ning Y, Shen Q, Herrick K, et al. Cause of death in cancer survivors (abstr). Cancer Res 2012; 72:LB-339.

3. Tan C, Tasaka H, Yu KP, et al. Daunomycin, an antitumor antibiotic, in the treatment of neoplastic disease. Clinical evaluation with special reference to childhood leukemia. Cancer 1967;20: 333–53.

4. Von Hoff DD, Layard MW, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med 1979;91:710–7.

5. Lefrak EA, Pitha J, Rosenheim S, et al. A clinicopathologic analysis of adriamycin cardiotoxicity. Cancer 1973;32:302–14.

6. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer 2003;97:2869–79.

7. Billingham M, Bristow M. Evaluation of anthracycline cardiotoxicity: predictive ability and functional correlation of endomyocardial biopsy. Cancer Treat Symp 1984:71–6.

8. Ewer MS, Ali MK, Mackay B, et al. A comparison of cardiac biopsy grades and ejection fraction estimations in patients receiving adriamycin. J Clin Oncol 1984;2:112–7.

9. Cardinale D, Sandri MT, Colombo A, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. Circulation 2004;109: 2749–54.

10. Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. J Am Coll Cardiol 2009;53:2231–47.

11. 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;26:1231–8.

12. Tan-Chiu E, Yothers G, Romond E, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol 2005;23:7811–9.

13. Armstrong GT, Oeffinger KC, Chen Y, et al. Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. J Clin Oncol 2013;31:3673–80.

14. Doroshow JH. Effect of anthracycline antibiotics on oxygen radical formation in rat heart. Cancer Res 1983;43:460–72.

15. Link G, Tirosh R, Pinson A, et al. Role of iron in the potentiation of anthracycline cardiotoxicity: identification of heart cell mitochondria as a major site of iron-anthracycline interaction. J Lab Clin Med 1996;127:272–8.

16. Dresdale AR, Barr LH, Bonow RO, et al. Prospective randomized study of the role of N-acetyl cysteine in reversing doxorubicin-induced cardiomyopathy. Am J Clin Oncol 1982;5:657–63.

17. Hasinoff BB, Patel D, Wu X. The oral iron chelator ICL670A (deferasirox) does not protect myocytes against doxorubicin. Free Radic Biol Med 2003;35:1469–79.

18. Zhang S, Liu X, Bawa-Khalfe T, et al. Identification of the molecular basis of doxorubicin-induced cardiotoxicity. Nat Med 2012;18:1639–42.

19. Liu LF, Wang JC. Supercoiling of the DNA template during transcription. Proc Natl Acad Sci U S A 1987;84:7024–7.

20. Drake FH, Zimmerman JP, McCabe FL, et al. Purification of topoisomerase II from amsacrine-resistant P388 leukemia cells. Evidence for two forms of the enzyme. J Biol Chem 1987;262: 16739–47.

21. Tewey KM, Rowe TC, Yang L, et al. Adriamycin-induced DNA damage mediated by mammalian DNA topoisomerase II. Science 1984;226:466–8.

22. Capranico G, Tinelli S, Austin CA, et al. Different patterns of gene expression of topoisomerase II isoforms in differentiated tissues during murine development. Biochim Biophys Acta 1992;1132:43–8.

23. Zhu W, Soonpaa MH, Chen H, et al. Acute doxorubicin cardiotoxicity is associated with p53-induced inhibition of the mammalian target of rapamycin pathway. Circulation 2009;119:99–106.

24. Bugger H, Guzman C, Zechner C, et al. Uncoupling protein downregulation in doxorubicin-induced heart failure improves mitochondrial coupling but increases reactive oxygen species generation. Cancer Chemother Pharmacol 2011;67: 1381–8.

25. Vejpongsa P, Yeh ET. Topoisomerase 2beta: a promising molecular target for primary prevention of anthracycline-induced cardiotoxicity. Clin Pharmacol Ther 2014;95:45–52.

26. Miranda CJ, Makui H, Soares RJ, et al. Hfe deficiency increases susceptibility to cardiotoxicity and exacerbates changes in iron metabolism induced by doxorubicin. Blood 2003;102: 2574–80.

27. Vejpongsa P, Massey MR, Acholonu SA, et al. Topoisomerase 2β expression in peripheral blood predicts susceptibility to anthracycline-induced cardiomyopathy (abstr). Circulation 2013;128: A11619.

28. Lipshultz SE, Lipsitz SR, Kutok JL, et al. Impact of hemochromatosis gene mutations on cardiac status in doxorubicin-treated survivors of childhood high-risk leukemia. Cancer 2013;119: 3555–62.

29. 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;112:3754–62.

30. Valdivieso M, Burgess MA, Ewer MS, et al. Increased therapeutic index of weekly doxorubicin in the therapy of non-small cell lung cancer: a prospective, randomized study. J Clin Oncol 1984; 2:207–14.

31. Pacciarini MA, Barbieri B, Colombo T, et al. Distribution and antitumor activity of adriamycin given in a high-dose and a repeated low-dose schedule to mice. Cancer Treat Rep 1978;62:791–800.

32. Legha SS, Benjamin RS, Mackay B, et al. Reduction of doxorubicin cardiotoxicity by prolonged continuous intravenous infusion. Ann Intern Med 1982;96:133–9.

33. Lipshultz SE, Miller TL, Lipsitz SR, et al. Continuous versus bolus infusion of doxorubicin in

children with ALL: long-term cardiac outcomes. Pediatrics 2012;130:1003–11.

34. Gabizon AA. Stealth liposomes and tumor targeting: one step further in the quest for the magic bullet. Clin Cancer Res 2001;7:223–5.

35. Waterhouse DN, Tardi PG, Mayer LD, et al. A comparison of liposomal formulations of doxorubicin with drug administered in free form: changing toxicity profiles. Drug Saf 2001;24:903–20.

36. U.S. Food and Drug Administration. Drug safety and availability. FDA statement on DOXIL® (doxorubicin HCl liposome injection) for intravenous infusion. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050718s043lbl.pdf. Accessed June 26, 2014.

37. U.S. Food and Drug Administration. Drug Safety and Availability. FDA statement on dexrazoxane. Jul 20, 2011. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm263729.htm. Accessed June 23, 2014.

38. Lipshultz SE, Scully RE, Lipsitz SR, et al. Assessment of dexrazoxane as a cardioprotectant in doxorubicin-treated children with high-risk acute lymphoblastic leukaemia: long-term follow-up of a prospective, randomised, multicentre trial. Lancet Oncol 2010;11:950–61.

39. Speyer JL, Green MD, Zeleniuch-Jacquotte A, et al. ICRF-187 permits longer treatment with doxorubicin in women with breast cancer. J Clin Oncol 1992;10:117–27.

40. Schroeder PE, Hasinoff BB. The doxorubicin-cardioprotective drug dexrazoxane undergoes metabolism in the rat to its metal ion-chelating form ADR-925. Cancer Chemother Pharmacol 2002;50:509–13.

41. Martin E, Thougaard AV, Grauslund M, et al. Evaluation of the topoisomerase II-inactive bisdioxopiperazine ICRF-161 as a protectant against doxorubicin-induced cardiomyopathy. Toxicology 2009;255:72–9.

42. Lyu YL, Kerrigan JE, Lin CP, et al. Topoisomerase IIbeta mediated DNA double-strand breaks: implications in doxorubicin cardiotoxicity and prevention by dexrazoxane. Cancer Res 2007;67:8839–46.

43. Swain SM, Whaley FS, Gerber MC, et al. Delayed administration of dexrazoxane provides cardioprotection for patients with advanced breast cancer treated with doxorubicin-containing therapy. J Clin Oncol 1997;15:1333–40.

44. Swain SM, Whaley FS, Gerber MC, et al. Cardioprotection with dexrazoxane for doxorubicin-containing therapy in advanced breast cancer. J Clin Oncol 1997;15:1318–32.

45. Wadler S, Green MD, Muggia FM. Synergistic activity of doxorubicin and the bisdioxopiperazine (+)-1,2-bis(3,5-dioxopiperazinyl-1-yl)propane (ICRF 187) against the murine sarcoma S180 cell line. Cancer Res 1986;46:1176–81.

46. Pearlman M, Jendiroba D, Pagliaro L, et al. Dexrazoxane in combination with anthracyclines lead to a synergistic cytotoxic response in acute myelogenous leukemia cell lines. Leuk Res 2003;27:617–26.

47. Lipshultz SE, Lipsitz SR, Mone SM, et al. Female sex and drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. N Engl J Med 1995;332:1738–43.

48. Zhang J, Knapton A, Lipshultz SE, et al. Sex-related differences in mast cell activity and doxorubicin toxicity: a study in spontaneously hypertensive rats. Toxicol Pathol 2014;42:361–75.

49. Tebbi CK, London WB, Friedman D, et al. Dexrazoxane-associated risk for acute myeloid leukemia/myelodysplastic syndrome and other secondary malignancies in pediatric Hodgkin's disease. J Clin Oncol 2007;25:493–500.

50. Vrooman LM, Neuberg DS, Stevenson KE, et al. The low incidence of secondary acute myelogenous leukaemia in children and adolescents treated with dexrazoxane for acute lymphoblastic leukaemia: a report from the Dana-Farber Cancer Institute ALL Consortium. Eur J Cancer 2011;47:1373–9.

51. Salzer WL, Devidas M, Carroll WL, et al. Long-term results of the pediatric oncology group studies for childhood acute lymphoblastic leukemia 1984–2001: a report from the children's oncology group. Leukemia 2010;24:355–70.

52. Bosch X, Rovira M, Sitges M, et al. Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: the OVERCOME trial. J Am Coll Cardiol 2013;61:2355–62.

53. Kaya MG, Ozkan M, Gunebakmaz O, et al. Protective effects of nebivolol against anthracycline-induced cardiomyopathy: a randomized control study. Int J Cardiol 2013;167:2306–10.

54. Kalay N, Basar E, Ozdogru I, et al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. J Am Coll Cardiol 2006;48:2258–62.

55. Georgakopoulos P, Roussou P, Matsakas E, et al. Cardioprotective effect of metoprolol and enalapril in doxorubicin-treated lymphoma patients: a prospective, parallel-group, randomized, controlled study with 36-month follow-up. Am J Hematol 2010;85:894–6.

56. de Geus-Oei LF, Mavinkurve-Groothuis AM, Bellersen L, et al. Scintigraphic techniques for early detection of cancer treatment-induced cardiotoxicity. J Nucl Med 2011;52:560–71.

57. Sawaya H, Sebag IA, Plana JC, et al. Early detection and prediction of cardiotoxicity in chemotherapy-treated patients. Am J Cardiol 2011;107:1375–80.

58. Wassmuth R, Lentzsch S, Erdbruegger U, et al. Subclinical cardiotoxic effects of anthracyclines as assessed by magnetic resonance imaging: a pilot study. Am Heart J 2001;141:1007–13.

59. Curigliano G, Cardinale D, Suter T, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. Ann Oncol 2012;23 Suppl 7:vii155–66.

60. Okumura H, Iuchi K, Yoshida T, et al. Brain natriuretic peptide is a predictor of anthracycline-induced cardiotoxicity. Acta Haematol 2000;104:158–63.

61. Sandri MT, Salvatici M, Cardinale D, et al. N-terminal pro-B-type natriuretic peptide after high-dose chemotherapy: a marker predictive of cardiac dysfunction? Clin Chem 2005;51:1405–10.

62. Cardinale D, Colombo A, Sandri MT, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. Circulation 2006;114:2474–81.

63. Cardinale D, Colombo A, Lamantia G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. J Am Coll Cardiol 2010;55:213–20.

64. Lipshultz SE, Lipsitz SR, Sallan SE, et al. Long-term enalapril therapy for left ventricular dysfunction in doxorubicin-treated survivors of childhood cancer. J Clin Oncol 2002;20:4517–22.

65. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147–239.

66. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787–847.

KEY WORDS cancer, cardiomyopathy, cardioprotection, chemotherapy, doxorubicin, heart failure