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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.

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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