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Anthracycline-induced cardiotoxicity: mechanisms of action, incidence, risk factors, prevention, and treatment

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Abstract
Anthracycline is a mainstay in treatment of many cancers including lymphoma and breast cancer among many others. However, anthracycline treatment can be cardiotoxic. Although anthracycline-induced cardiotoxicity is dose dependent, it can also occur early at the onset of treatment and even up to several years following completion of treatment. This review article focuses on the understanding of mechanisms of anthracycline-induced cardiotoxicity, the treatments, and recommended follow-up and preventive approaches.

Keywords Anthracyclines · Heart failure · Cardio-oncology · Prevention

Background

Cancer survival rates are substantially improving. In 2016, survivors in the USA were estimated to be more than 15.5 million, and it is projected to reach more than 20 million by 2026. Breast cancer survivors alone exceeded 3.5 million patients [1]. Currently, 50% of newly diagnosed adults with cancer survive 10 years or more. Meanwhile, 75% of children with cancer survive 10 years or more [2]. These numbers are a reflection of improved screening, diagnostic imaging, and advancement of therapeutic modalities in oncology during the past several decades. However, this success comes with an increased incidence of cancer treatment–related toxicities.

Cardiovascular side effects are recognized as perhaps the leading cause of treatment-associated morbidity and mortality among cancer survivors [3]. This is especially related to anthracyclines as the primary cardiotoxic chemotherapeutic class of agents [2]. Approximately 1 million patients receive anthracycline derivatives annually in North America [4], and it is estimated that 9% of those patients will develop some form of anthracycline-induced cardiotoxicity [5]. Although there is a growing consensus on how to optimally monitor and treat anthracycline-induced cardiotoxicity, it continues to present challenges.

Anthracyclines

Since their discovery in the 1950s, anthracyclines have become one of the chemotherapeutic cornerstones in oncology due to their high efficacy. Moreover, anthracyclines' effectiveness in treating a wide range of cancers, primarily breast cancer and lymphomas, has led to a significant rise in their use. Other cancers that are treated by anthracyclines include soft tissue sarcomas, osteogenic sarcomas, Ewing sarcoma, small cell lung cancer, urinary bladder carcinoma, esophageal carcinoma, stomach carcinoma, hepatocellular carcinoma, and various leukemias [2, 6].

More recently, the development of newer antineoplastic agents has begun to limit the use of anthracyclines, especially in those patients with high cardiovascular risk. However, despite this change in practice, anthracyclines continue to be a major treatment in half of breast cancer and two-thirds of all childhood chemotherapy protocols. The high utilization of anthracycline in children is related to the increased 5-year survival rates for childhood cancer [4]. In addition, anthracycline-based regimens have been found to decrease breast cancer mortality by 20–30% [7]. Therefore, its use is unlikely to decline anytime soon.

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Mechanism of action

Anthracyclines have several modes of action: (1) intercalating with DNA base pairs and then stabilizing topoisomerase IIα complex after DNA cleavage, which increases DNA breaks and (2) preventing DNA and RNA synthesis [8]. This makes anthracyclines a very effective antineoplastic agent.

Although anthracyclines have been heavily utilized during the past six decades, the mechanism of anthracycline cardiotoxicity is still not fully understood. While many experts believe it is multifactorial, the two main accepted hypotheses are as follows: (1) Oxidative stress, which in the presence of iron, generates reactive oxygen species that cause lipid peroxidation of the cell membrane leading to damage of the cardiomyocytes [9–11]. (2) Inhibition of topoisomerase IIβ, which is active in quiescent nonproliferating cardiomyocytes, can result in the activation of cell death pathways and inhibition of mitochondrial biogenesis [10]. However, the two main hypotheses are not mutually exclusive, and several other mechanisms have also been proposed (Figs. 1 and 2) [12, 13].

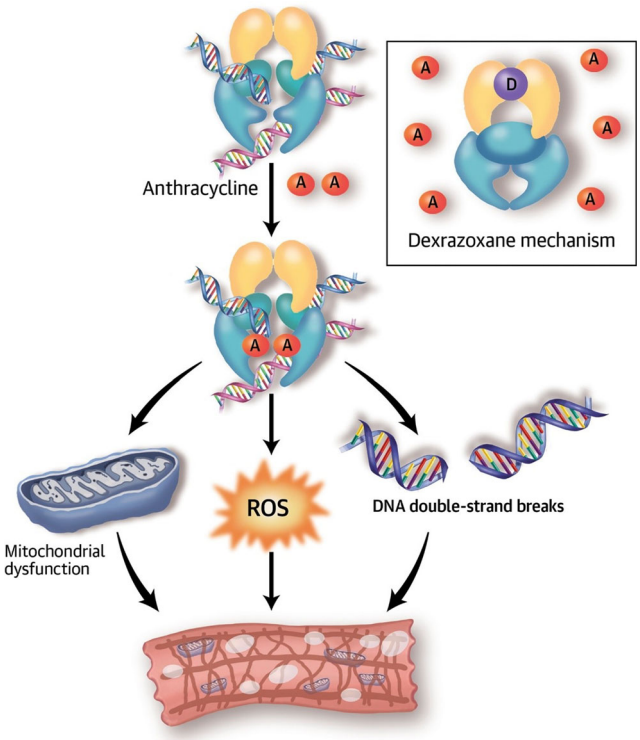

Fig. 1 Mechanism of anthracycline-induced cardiotoxicity. Doxorubicin disrupts the normal catalytic cycle of topoisomerase IIβ (top), causing deoxyribonucleic acid (DNA) double-stranded breaks. It further changes the transcriptome, leading to defective mitochondrial biogenesis and increase in reactive 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. Vejpongsa and Yeh [13]

Incidence

Anthracycline safety profile is highly variable among patients. While many patients tolerate anthracyclines without long-term complications, in some patients, treatment-related cardiotoxicity may occur soon after the first dose [14]. Due to the different definitions of cardiotoxicity and the wide range of pathology caused by anthracyclines, the reported incidence is highly variable among studies, especially in early reports. Accordingly, congestive heart failure (CHF) is reported in 2–4%, subclinical structural change occurs in around 10%, arrhythmia (mainly atrial fibrillation) in > 12%, and cardiac biomarker rise in 30–35% of patients [15]. Cardinale et al. conducted a prospective study involving 2625 patients with a mean follow-up of 5.2 years that demonstrated a 9% overall incidence of cardiotoxicity with anthracycline treatment [5]. The study defined cardiotoxicity as left ventricular ejection fraction (LVEF) < 50% with a decrease in > 10 absolute points. However, in a retrospective study of 640 patients on doxorubicin, 32 patients (5%) developed CHF. Of those, 38% had mild heart failure (New York Heart Association (NYHA) Class I or II), 34% developed moderate heart failure (NYHA Class III), and 28% experienced severe heart failure (NYHA Class IV) [16]. Meanwhile, in children, subtle signs of cardiotoxicity detected by biomarkers or echocardiography can occur in up to 59% of patients [17]. Given the higher incidence of toxicity in children, several experts now believe that young hearts may be at higher risk than adult hearts [4].

It is now well established that anthracycline cardiotoxicity is dose dependent. One large study demonstrated that left ventricular dysfunction (defined as reduction in ejection fraction of > 10% below normal) occurred in 10%, 16%, 32%, and 65% at cumulative doxorubicin doses of 250, 300, 400, and 550 mg/m^2, respectively [4]. Thus, even at the lowest dose, anthracyclines can result in significant left ventricular dysfunction.

Risk factors

As mentioned earlier, the pathophysiology underlying cardiotoxicity with anthracyclines is not well understood. However, several risk factors have now been identified including age > 65 years or < 18 years, female gender, cumulative dose of the anthracyclines, valvular heart disease, baseline left ventricular dysfunction, arterial hypertension, African-American ancestry, renal failure, concomitant exposure to radiation and/or trastuzumab, iron overload, and genetic factors (Table 1) [2]. Moreover, Dranitsaris et al. developed a model to estimate the absolute risk of cardiac toxicity in metastatic breast cancer using patient's age, weight, WHO performance status, number of treatment cycles, and the dose and type of anthracycline used. The model is used to provide risk prediction regarding the utilization of anthracyclines [18].

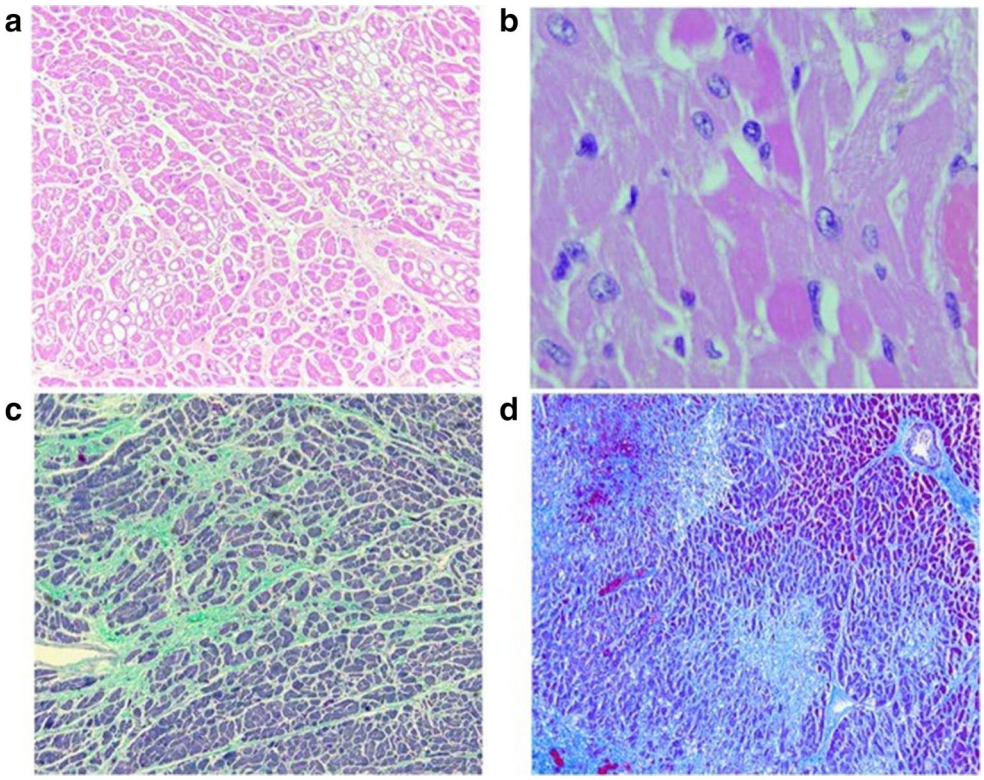

Fig. 2 Pathological lesions (ventricle wall) associated with treatment with anthracyclines. **a** Myocytolysis or vacuolization of cardiac myocytes (hematoxylin and eosin (H&E) staining, 125). **b** Patched myocardial necrosis into areas of preserved myocardium (H&E staining, 500). **c** Interstitial fibrosis (Masson trichrome staining, 62.5). **d** Patched myocardial fibrosis, with a multifocal distribution that disrupts the myocardial structure (Masson trichrome staining, 12.5). Cascales et al. [91]

Although many of the risk factors are non-modifiable, recognizing treatable cardiovascular risk factors is essential in management before, during, and after chemotherapy. This is of paramount importance to decrease the incidence of anthracycline-induced cardiotoxicity. Furthermore, patients with one or more risk factors need to be monitored carefully, and if risks persist after management, then alternative chemotherapeutics should be considered [19].

Table 1 Risk factors for developing anthracycline-induced cardiotoxicity

Cumulative anthracycline dose
African-American ancestry
Female sex
Age
> 65 years old
Pediatric population (< 18 years)
Pre-existing conditions
Cardiac diseases associating increased wall stress
Arterial hypertension
Valvular heart disease
Renal failure
Genetic factors
Concomitant chemotherapy
Alkylating or antimicrotubule agents
Immunotherapy and targeted therapy
Concomitant or previous radiation therapy involving the heart

Cardiotoxicity

Anthracycline cardiotoxic effects were unrecognized until 1967 when Karnofsky et al. first observed that anthracyclines were associated with CHF [20]. A decade later, anthracycline cardiotoxicity was classified into three types: acute, early-onset chronic, and late-onset chronic [21, 22].

1. *Acute toxicity* can develop immediately after anthracycline infusion and up to 2 weeks from the end of treatment. This only occurs in 1% of the patients. Typically, acute toxicity presents predominantly with supraventricular arrhythmia, transient left ventricular dysfunction, and electrocardiographic changes. Usually, all acute toxicity manifestations are reversible. Nevertheless, acute cardiac dysfunction has the potential to evolve into early or late cardiotoxicity. Unfortunately, there are no effective strategies to determine the course of the disease [19].

2. *Early-onset chronic toxicity* occurs within the first year of treatment, and it is the most common form of toxicity. It constitutes 98% of all patients. The most common presentation is an asymptotic decline in left ventricular function

that usually progresses to symptomatic heart failure with a further decline in left ventricular function [5].

3. *Late-onset chronic toxicity* manifests several years or even decades after receiving anthracyclines (median of 7 years after treatment) and is often irreversible [5, 23, 24]. Experts have regarded this process as a late manifestation of early-onset toxicity with superimposed cardiac injury. The rationale is that early anthracycline injury can cause subclinical damage which makes these hearts more vulnerable to future insult. Consequently, adults develop dilated cardiomyopathy while occasionally long-term survivors of childhood cancers can progress from dilated cardiomyopathy to restrictive cardiomyopathy (Grinch syndrome) [25].

Screening

Patients started on anthracyclines should be evaluated clinically for signs and symptoms of heart failure. It is recommended that a baseline electrocardiogram (EKG) be obtained before initiating therapy to serve as a basis for future comparison and specifically to monitor for QT prolongation because arrhythmias can occur in early stages of anthracycline therapy [19]. Although history, clinical exam, and EKG may help detect patients in active heart failure who would be at a higher risk of developing anthracycline-induced cardiotoxicity, it is critical to detect subclinical cardiac abnormalities more objectively. Nowadays, there are several biomarkers and imaging modalities that can be utilized for early detection of anthracycline-induced cardiotoxicity.

Imaging

In earlier trials, there was no standardized definition of chemotherapy-induced cardiotoxicity. This contributed to variability in the interpretation of results [26]. However, in 2014, the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) defined Cancer Therapeutics-Related Cardiac Dysfunction (CTRCD) as a decrease in the LVEF of 10 percentage points to a value below 53% by echocardiography [27, 28]. This decrease should be confirmed by repeat imaging performed 2–3 weeks apart [28]. Once CTRCD is confirmed, it could be further stratified into the following: (1) "Reversible" if it returns to within 5 percentage points of the baseline, (2) "Partially reversible" if improved by more than 10 percentage points from the nadir but remaining 5 percentage points below the baseline, (3) "Irreversible" if improved by less than 10 percentage points from the nadir but remaining more than 5 percentage points below the baseline, (4) "Indeterminate" if the patient is not available for re-evaluation. Therefore, evaluation with imaging modalities should be performed before, during, and after anthracycline therapy. Nevertheless, this classification is relatively new to the cardio-oncology community and has not yet become standard of practice. Since several options are available, the choice of imaging modalities depends on local expertise and availability (Fig. 3).

Echocardiography

Echocardiography is the most commonly used method for screening. It has the advantage of being widely available, avoids exposure to radiation, and can obtain hemodynamics and assess cardiac structures. However, its limitations include image quality, inter-observer variability, and failure to detect small changes in left ventricular (LV) contractility. To overcome these limitations, the guidelines recommend using 3-dimensional echocardiography (3DE), as it is more accurate in determining LVEF. If 3DE is not available, then modified biplane Simpson's technique is the method of choice. In addition, the calculation of LVEF should be combined with an assessment of the wall motion score index [29] as it has been demonstrated to be a more sensitive marker of anthracycline-induced CTRCD than the LVEF alone. Moreover, echocardiography contrast agents can provide better images, and it increases the accuracy and reproducibility of echocardiography in general, but there is very limited data regarding contrast use in cardio-oncology [30].

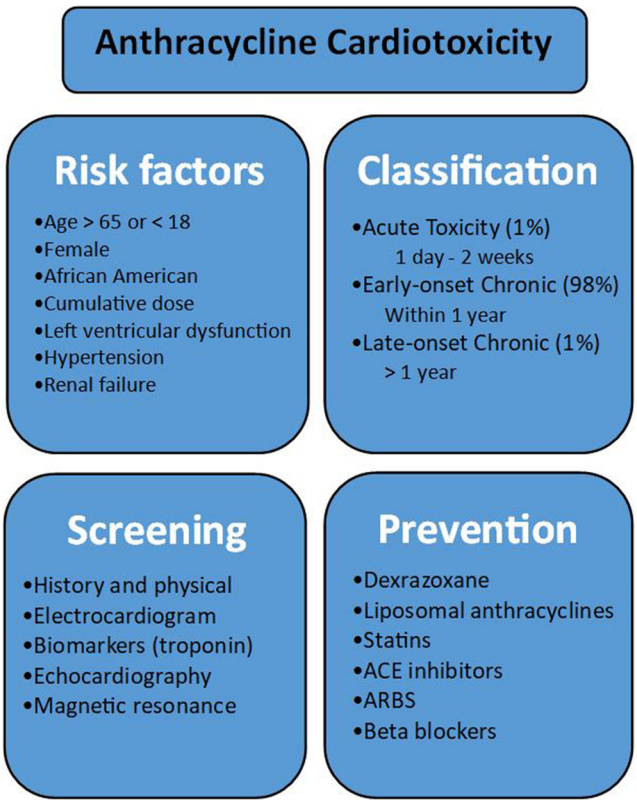

Fig. 3 Summary of risk factors, toxicity, screening, and prevention for anthracyclines

Diastolic dysfunction is common in patients with cancer but has failed to predict CTRCD. Currently, the ASE and EAE acknowledge the lack of usefulness of diastolic dysfunction in monitoring patients on therapy, but they still recommend that a comprehensive assessment of LV diastolic function be performed [31]. However, a study in breast cancer patients demonstrated that anthracycline therapy was associated with a modest but sustained worsening of diastolic function parameters that was associated with a small increased risk of systolic dysfunction [32]. Hence, currently, the role of diastology remains controversial in predicting CTRCD.

Recently, strain and strain rate have shown promising results in early detection of cardiotoxicity [33]. After evaluation of several studies, the ESC guidelines concluded that the optimal parameter in strain is the global longitudinal strain (GLS). A 15% drop in GLS compared with baseline measurement is considered an early marker of cardiotoxicity and is predictive for LV systolic dysfunction while a reduction < 8% excludes the diagnosis (Fig. 4). However, it is important to recognize that strain packages for different manufacturers can vary, and the exact number for defining the abnormal strain is still not standardized. Given this variation, it is recommended to conduct follow-up studies using the same vendor to achieve reproducibility [28], but overall, a normal GLS measurement should range between − 15.9 and − 22.1 [34].

MUGA scan

Since the late 1970s, nuclear cardiac imaging (MUGA) was used to identify decline in LVEF before the development of CHF in patients receiving anthracyclines [35]. It was widely used and had one main advantage, reproducibility. On the other hand, it had the disadvantage of radiation exposure and offered very limited structural and functional information of other cardiac structures. Initially, it was the best method for screening as it has consistently outperformed standard 2-dimensional echocardiogram with respect to the accuracy and reproducibility of LVEF measurement [36, 37]. However, in the past two decades, the rapid evolution of other imaging modalities has decreased the use of MUGA because of comparable results obtained with cardiac magnetic resonance (CMR) and 3D echocardiography [36, 38].

Cardiac magnetic resonance

CMR is a highly reproducible method in quantifying LVEF and is considered to be the gold standard for the evaluation of LV, RV volumes, and LVEF [39]. In addition, CMR offers an accurate characterization of myocardial tissue, making it suitable for the detection of

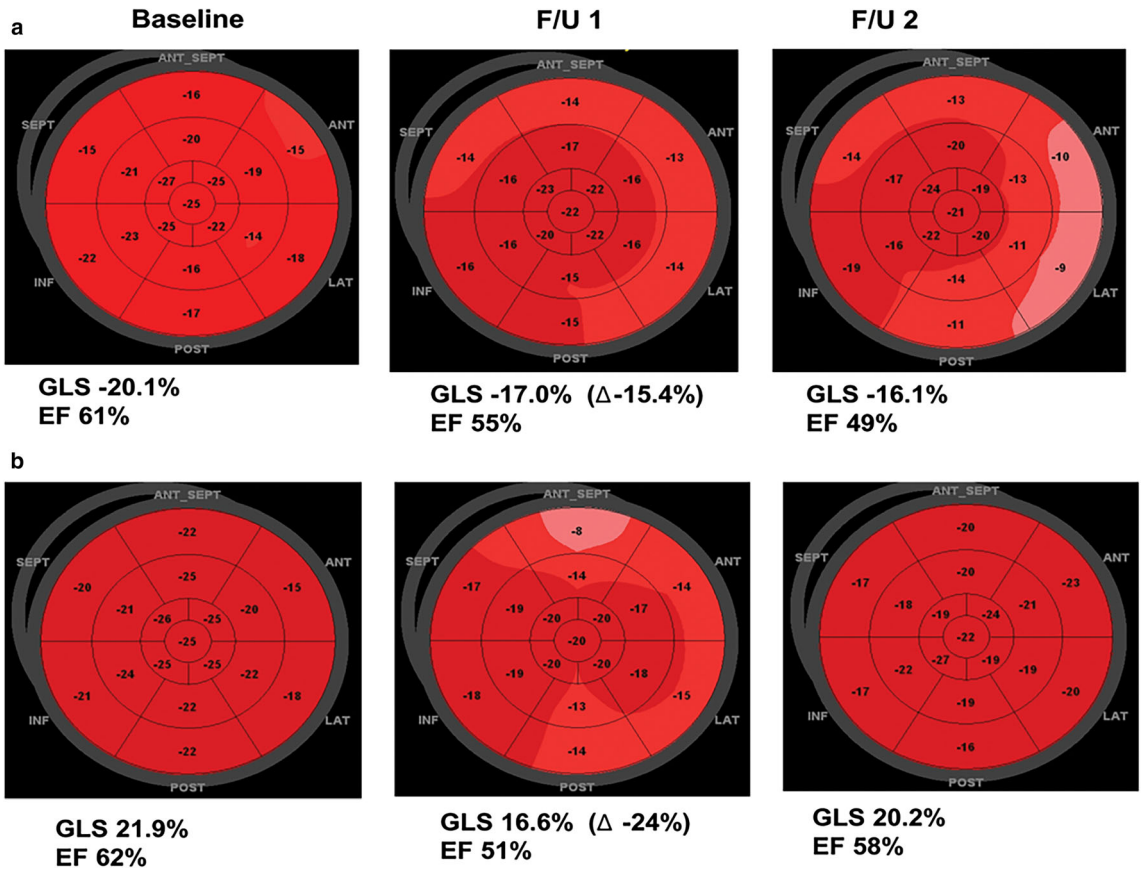

Fig. 4 Representative cases with and without beta-blocker therapy. **a** A patient without beta-blocker therapy. There was a continuous deterioration of cardiac function. **b** A patient with beta-blocker therapy. There was a recovery of cardiac function at F/U2. Negishi et al. [92]

myocardial edema and diffuse myocardial fibrosis which are present at various stages of anthracycline-induced cardiotoxicity [40–42]. In a recent study, pigs were administered intracoronary doxorubicin during which weekly CMR was performed. Intracardiomyocyte edema on T2 images was the earliest marker of anthracycline-induced cardiotoxicity, and it was detected even in the absence of LV motion defects. The occurrence of these changes at a reversible disease stage demonstrates the clinical value of CMR [43]. However, CMR has several limitations, including limited availability, cost, and patient's adaptation problems (claustrophobia, breath holding, and long acquisition times). Of note, in most studies, CMR and echocardiographical measurements were highly correlated. Recently, a cohort study of adult survivors of childhood cancer demonstrated similar mean LVEF values by CMR and 3DE, whereas 2DE values were higher by approximately 5%. The study also demonstrated that both 3DE and 2DE were suboptimal at identifying patients with LVEFs below a threshold of 50% as defined by CMR [44]. Hence, CMR should be considered if other techniques are nondiagnostic or to confirm the presence of LV dysfunction if LVEF is borderline low.

It is important to realize that different techniques use different normal reference values. Thus, using the same technique for baseline assessment and follow-up studies would yield better results unless this technique is considered inadequate [19].

Biomarkers

Although different imaging modalities have improved dramatically over the past decade, they still lack the sensitivity to detect early subclinical changes or predict subsequent declines in LV function with anthracycline treatment [45]. Given their high sensitivity, cardiac biomarkers, specifically high-sensitivity troponin, have the potential to be the diagnostic tool to address that void. Moreover, troponin has the advantage of being minimally invasive, widely available, accurate, and reproducible.

Troponin has been proven to be useful in detecting patients at risk for the subsequent development of CTRCD. It was established as a useful biomarker when Cardinale et al. stratified 703 patients receiving anthracycline to whether they exhibited increased troponin levels. In 20% of the patients, there was an increase in troponin levels within 72 h of anthracycline infusion. The troponin level remained elevated 1 month later in only 8% of the patients. Moreover, a persistent troponin elevation was associated with an increase in the severity of CTRCD and a higher incidence of cardiac events compared with transient elevations [46]. Overall, CTRCD incidence was higher in troponin-positive patients. In a small study, combining high-sensitivity troponin to GLS measured at the completion of anthracycline therapy had a sensitivity of 93% and negative predictive value of 91% in predicting future cardiotoxicity [33]. Several other studies have also demonstrated correlations between troponin elevations and subsequent LVEF decline as well [47–49]. In addition, a recent study demonstrated that even low-cardiovascular-risk patients receiving low doses of anthracyclines could have troponin elevation [50]. Although it is a very promising modality for early detection, there are still several barriers to the widespread application of troponin as a clinical biomarker in CTRCD. First, the determination of the optimal timing of troponin assessment remains debatable because it is unclear if a single measurement of high troponin has sufficient predictive value or several measurements would be required. Moreover, defining the cut-off point for positivity that maximizes the positive and negative predictive value remains controversial [28]. On the other hand, serum concentrations of natriuretic peptides are a well-known marker for heart failure, and several studies have investigated trends in BNP and NT-pro BNP levels in patients receiving anthracycline. However, the results have not been consistent [51–54].

Guidelines

In 2016, the American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines provided good insight on anthracycline cardiotoxicity [19, 55]. ASCO recommend recognizing and monitoring patients at increased risk for developing cardiac dysfunction. For asymptomatic patients, consider routine surveillance echocardiography during treatment. The frequency of surveillance should be determined by health care providers. Patients at higher risk for cardiotoxicity should get a baseline echocardiogram or CMR if echocardiogram is not available or technically feasible prior to initiation of treatment. An echocardiogram should be performed between 6 and 12 months after completion of a cancer-directed therapy. During the follow-up period, evaluation and management of cardiovascular risk factors and a healthy lifestyle, including the role of diet and exercise, should be discussed [55].

Regarding patients identified to have asymptomatic cardiac dysfunction during routine surveillance, referral to a cardiologist with cardio-oncology expertise for further assessment and management is recommended. In patients with clinical signs or symptoms of cardiac dysfunction, an echocardiogram (preferably with strain imaging) is recommended. If echocardiography is not feasible, then CMR or MUGA is recommended. Moreover, serum troponins and natriuretic peptides are recommended. The continuation or discontinuation of cancer therapy in individuals with evidence of cardiac dysfunction needs to be discussed between the oncologist and cardiologist [55].

The expert consensus of adult patients during and after cancer therapy by the ASE and the EACVI recommended a

baseline evaluation including measurements of LVEF, GLS, and troponin. If any are abnormal, then cardiology consultation is recommended with follow-up at 6 months later for doses < 240 mg/m^2 or its equivalent. Once this dose is exceeded, measurements of LVEF, GLS, and troponin are recommended before each additional 50 mg/m^2 (Fig. 5) [28].

Because CHF may occur even up to years following treatment, screening for cardiac toxicity in children is more comprehensive [56]. Thus, lifelong surveillance using echocardiography should be performed at a minimum of every 5 years. Also, given the increased cardiometabolic demand on the heart of a mother during pregnancy, closer monitoring of survivors during pregnancy is also warranted. Overall, at-risk cancer survivors should be regularly screened for traditional cardiovascular risk [56].

Prevention

Anthracycline administration

Since the various anthracyclines have a wide range of cardiotoxicity (0.9–48%), the choice of a specific agent may greatly impact the level of cardiotoxicity (Table 2) [19]. Furthermore, in addition to choosing the chemotherapeutic agent, several strategies may be employed to prevent anthracycline cardiotoxicity while maintaining antineoplastic efficacy. These include prolonged infusion delivery times and the use of liposomal-encapsulated anthracyclines.

In the 1970s, Pacciarini et al. demonstrated that continuous anthracycline infusion compared with bolus injection was

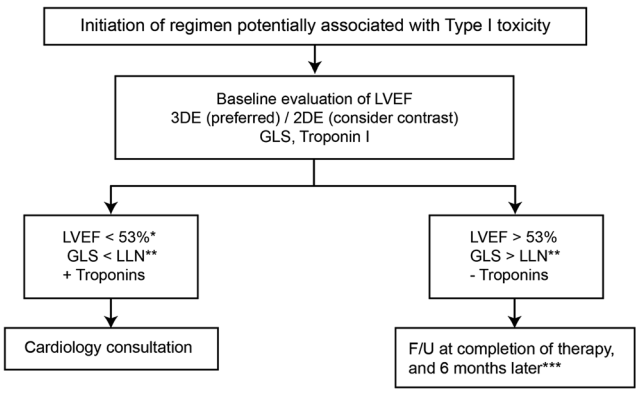

Fig. 5 Initiation of a regimen potentially associated with type I toxicity. A baseline evaluation including measurements of LVEF, GLS, and troponin is recommended. If any are abnormal, a cardiology consultation is recommended. Follow-up is recommended at the completion of therapy and 6 months later for doses < 240 mg/m^2 or its equivalent. Once this dose is exceeded, measurements of LVEF, GLS, and troponin are recommended before each additional 50 mg/m^2. Plana et al. [28]

associated with lower cardiac concentrations in mice [57]. Subsequently, Legha et al. demonstrated in adult humans that decreasing peak plasma levels of doxorubicin by continuous infusion reduces cardiotoxicity with solid tumors without compromising the antitumor activity [58]. However, in children with acute lymphoblastic leukemia, continuous doxorubicin infusion over 48 h did not offer a cardioprotective advantage over bolus infusion [59]. A recent meta-analysis investigated the relationship between duration of anthracycline infusion and cardiotoxicity. The study demonstrated a lower rate of CHF with an infusion duration of 6 h or longer as compared with a shorter infusion duration (risk ratio (RR) 0.27, 5 studies, 557 participants) [60]. The proposed reasoning behind these findings is that the pharmacokinetic determinates of cardiotoxicity are different from the antitumor activity. While the antitumor activity is mainly affected by total plasma exposure to anthracyclines, cardiotoxicity correlates with the peak plasma levels [61].

Another strategy to reduce cardiotoxicity is to use liposomal encapsulation, which modifies the biodistribution of the drug. It results in enhanced targeting of the cancer by increasing the concentration of the drug released to neoplastic tissue [62]. A meta-analysis investigated the incidence of cardiotoxicity in liposomal-encapsulated doxorubicin vs. conventional doxorubicin [63]. In patients treated with liposomal-encapsulated doxorubicin, there was a significantly lower rate of CHF (risk ratio (RR) = 0.20). Although liposomal anthracyclines are safer and do not compromise antitumor efficacy, in the USA, its use is limited to ovarian cancer, Kaposi's sarcoma, and multiple myeloma because of its high cost [2, 13].

Dexrazoxane

Dexrazoxane is an iron chelator that blocks iron-mediated oxidative radical production and inhibits the topoisomerase IIβ isoenzyme, hence decreasing anthracycline cardiotoxicity [10, 64, 65]. Since the 1980s, several trials have demonstrated that dexrazoxane can prevent or reduce LVEF dysfunction in addition to reducing the release of cardiac biomarkers [66–69]. The most notable trial randomized 534 patients with advanced breast cancer on doxorubicin to either dexrazoxane or placebo and monitored them with serial MUGA scans. In the dexrazoxane arm, there was a significant cardioprotective effect as measured by noninvasive testing and CHF. However, time to progression and survival were not significantly different between the treatment arms [67]. Based on early studies, the FDA approved dexrazoxane for the prevention of anthracycline-induced cardiotoxicity. However, it fell out of favor after concerns that dexrazoxane interfered with the antineoplastic properties and outcome benefits of anthracyclines [67]. Furthermore, one study noted an increased incidence of secondary malignancies with dexrazoxane use [70]. Given

Table 2 Incidence of anthracycline-induced cardiotoxicity with different agents

Drug	Incidence of left ventricular dysfunction
Doxorubicin	
400 mg/m^2	3–5%
550 mg/m^2	7–26%
700 mg/m^2	18–48%
Idarubicin (> 90 mg/m^2)	5–18%
Epirubicin (> 900 mg/m^2)	0.9–11.4%
Mitoxantrone (> 120 mg/m^2)	2.6%
Liposomal anthracyclines (> 900 mg/m^2)	2%

these concerns, the FDA restricted dexrazoxane use to patients with metastatic breast cancer who have received at least 300 mg/m^2 of doxorubicin with an ongoing indication to receive doxorubicin-based chemotherapy.

To further evaluate the role of dexrazoxane, van Dalen et al. conducted a meta-analysis that included 10 studies and 1619 patients. It demonstrated a statistically significant benefit in favor of dexrazoxane for the occurrence of heart failure (RR 0.29, 95% CI 0.20 to 0.41). In addition, there was no difference in response rate, survival, or in the occurrence of secondary malignancies between the dexrazoxane and control groups [71]. Most recently, a meta-analysis was done involving seven randomized trials and 2 retrospective trials with a total of 2177 patients who received anthracyclines. Dexrazoxane reduced the risk of CHF and cardiac events irrespective of previous exposure to anthracyclines. In addition, the rate of oncological response, overall survival, and progression-free survival were not affected [72]. Despite the evidence supporting dexrazoxane efficacy in the reduction of anthracycline-induced cardiotoxicity, conflicts regarding its safety and effect on cancer-related outcomes remain controversial. Hence, further studies are needed to establish the safety of its routine use.

Statins

Statins are known for their pleiotropic effects including decreased vascular inflammation and oxidative stress [73, 74]. Since one of the main theories of anthracycline-induced cardiotoxicity is damage through oxygen free radicals, several investigators evaluated statins for the prevention of cardiotoxicity. Riad et al. [75] demonstrated that pretreatment with fluvastatin attenuated anthracycline-induced cardiomyopathy in mice. Acar et al. [76] randomized 40 patients with hematological malignancies to either atorvastatin or no treatment. Follow-up echocardiography at 6 months demonstrated that those receiving atorvastatin did not experience worsening echocardiographic parameters compared with those receiving placebo who did experience worsening parameters. Seicean et al. [77] noted that statin prescription was linked with a lower incidence of heart failure in anthracycline-treated patients with breast cancer in a retrospective analysis (Table 3). Although previous trials demonstrated some evidence in favor of statins, those studies were not powered enough to recommend statin use to prevent anthracycline-induced cardiotoxicity. Recent studies have demonstrated that many solid tumors have extensive cholesterol crystal formations within the tumor matrix [78]. Although their role has yet to be defined in the tumorigenesis, statins have been shown to dissolve cholesterol crystals [79], and this area is currently under investigation. Therefore, further prospective randomized studies are needed to establish if there is a clear role of statins in preventing anthracycline-induced cardiotoxicity.

Renin-angiotensin-aldosterone system blockade

Renin-angiotensin system (RAS) activation is recognized to be a major contributor to the progression of heart failure. Moreover, RAS activation has been shown to enhance anthracycline-induced cardiomyopathy in preclinical studies [80, 81]. Several authors investigated using RAS blocking agents to prevent anthracycline-induced cardiotoxicity. In a study conducted by Cardinale et al., 473 patients of which 114 showed a troponin rise soon after anthracycline therapy were randomized to receive enalapril or no treatment. Enalapril was started 1 month after chemotherapy. The incidence of an absolute decrease > 10% units in LVEF was significantly greater in control subjects than in the angiotensin-converting enzyme inhibitor group (43% vs. 0%, $p < 0.001$). In addition, a significant reduction in LVEF and an increase in end-diastolic and end-systolic volumes were observed in the control group [82]. These results were very promising; however, later, Georgakopoulos et al. randomized 147 lymphoma patients on doxorubicin to prophylactic therapy with enalapril, metoprolol, or no treatment. Enalapril did not reduce the risk of cardiotoxicity in patients treated with doxorubicin. The incidence of CHF and subclinical cardiotoxicity was lower in the enalapril group in comparison with that in the control group, but it did not achieve statistical significance [83]. In the OVERCOME trial, 90 patients diagnosed with malignant hemopathies treated with anthracyclines were randomized to either treatment with enalapril combined with carvedilol at least 24 h prior to receiving chemotherapy vs. no treatment.

Table 3 Clinical trials looking into statins for prevention of anthracycline-induced cardiotoxicity

Study/year	Patients	Medications used	Primary end point	Follow-up	Results	Notes
Acar et al. [76] 2011 Turkey	40 (hematologic malignancies)	Atorvastatin vs. no treatment	Change in LVEF from baseline	6 months	LVEF change pre/post No treatment 62.9%/55.0% Atorvastatin 61.3%/62.6%	
Seicean et al. [77] 2012 USA	67 (breast cancer)	Statins prescribed for other indication Propensity-matched controls ($n = 134$)	None	None	Heart failure hospitalizations were less for those receiving a statin.	Retrospective Observational

The incidence of troponin increase was not statistically different in the intervention group compared with the controls; however, at 6 months, LVEF did not change in the intervention group but significantly decreased in the controls, resulting in a − 3.1% absolute difference by echocardiography [84]. In the PRevention of cArdiac Dysfunction during Adjuvant breast cancer therapy (PRADA) trial [85], 130 breast cancer patients on anthracyclines were randomized to candesartan, metoprolol, or placebo. The overall decline in LVEF was 2.6 (95% CI 1.5, 3.8) percentage points in the placebo group and 0.8 (95% CI − 0.4, 1.9) in the candesartan group. Although candesartan was given before anthracycline therapy, there was no reduction in troponins in comparison with the control group. In the ICOS-ONE trial, 273 patients were randomly assigned to enalapril started before chemotherapy, and enalapril was started only in patients with an increase in troponin during or after anthracycline therapy. The incidence of troponin elevation was 23% in the prevention group and 26% in the troponin-triggered group. Only three patients (1.1%), two in the prevention and one in the troponin-triggered group, developed cardiotoxicity, which is significantly lower than anthracycline-induced cardiotoxicity in most of the previous

Table 4 Clinical trials looking into ACE-I/ARBS for prevention of anthracycline-induced cardiotoxicity

Study/year	Patients	Medications used	Primary end point	Follow-up	Results	Notes
Cardinale et al. [82] 2006 Italy	473 (breast cancer, lymphoma, and sarcoma) 114 with elevated troponin	Enalapril vs. no treatment	Cardiotoxicity (absolute fall > 10 percentage points to below normal limit of 50%)	12 months	Cardiotoxicity incidence Control 43% Enalapril 0%	Only 114 patients with elevated troponin following chemotherapy were randomized.
Georgakopoulos et al. [83] 2010 Greece	147 (lymphoma)	Enalapril vs. metoprolol vs. no treatment	LVEF change at 12 months	31-month mean follow--up	Mean LVEF% point reduction Control 1% Enalapril 1.3%	No difference in cardiotoxicity. Heart failure cases were numerically lower in patients receiving cardioprotection.
Bosch et al. [84] 2013 Spain	90 (acute leukemia or receiving bone marrow transplant)	Enalapril and carvedilol vs. no treatment	Change in LVEF from baseline	6 months	Mean LVEF % point reduction Control 3.3% Treatment 0.2%	OVERCOME study: Death and heart failure reduced in treatment group 6.7% vs. 24.4%
Gulati et al. [85] 2016 Norway	130 breast cancer patients	Placebo vs. candesartan vs. metoprolol vs. candesartan + metoprolol	Change in LVEF	3–5 months	Mean LVEF % point reduction Placebo 2.6% Candesartan 0.8%	MRI was used.
Cardinale et al. [50] 2018 Italy	273 patients (different cancers, 76% had breast cancer)	Enalapril started before chemotherapy vs. enalapril started only in patients with an increase in troponin	Incidence of troponin elevation	12 months	Incidence of troponin rise: Prevention 23% Troponin-triggered 26%	Only 1.1% of patients developed cardiotoxicity, defined as 10% point reduction of LV ejection fraction, with values lower than 50%.

LVEF left ventricular ejection fraction

Table 5 Clinical trials looking into beta-blockers for the prevention of anthracycline-induced cardiotoxicity

Study/year	Patients	Medications used	Primary end point	Follow-up	Results	Notes
Kalay et al. [88] 2006	50 (breast, lymphoma, others)	Carvedilol vs. placebo	Change in LVEF from baseline	6 months	LVEF change pre/post Placebo 68.9%/52.3% Carvedilol 70.5%/69.7%	High cumulative anthracycline doses
Georgakopoulos et al. [83] 2010 Greece	147 (lymphoma)	Enalapril vs. metoprolol vs. no treatment	LVEF change at 12 months	31-month mean follow-up	LVEF% baseline/12 months Control 67.6/66.6 Metoprolol 65.7/63.3 Enalapril 65.2/63.9	No difference in cardiotoxicity. Heart failure cases were numerically lower in patients receiving cardioprotection.
Bosch et al. [84] 2013	90 (acute leukemia or receiving bone marrow transplant)	Enalapril + carvedilol vs. no treatment	Change in LVEF from baseline	6 months	Mean LVEF % point reduction Control 3.3% Treatment 0.2%	OVERCOME study: Death and heart failure reduced in the treatment group 6.7% vs. 24.4%
Kaya et al. [89] 2013	45 (breast cancer)	Nebivolol vs. placebo	Change in LVEF from baseline	6 months	LVEF change pre/post Placebo 66.6%/57.5% Nebivolol 65.6%/63.8%	NT-pro BNP was increased in the placebo group but unchanged in the nebivolol group.
Elitok et al. [93] 2014 Turkey	80 (breast cancer)	Carvedilol vs. no treatment	Change in LVEF from baseline strain	6-month follow-up period	LVEF change pre/post Placebo 65%/63.3% Carvedilol 66%/64.1%	A significant decrease in LV basal septal and basal lateral peak systolic strain in the control group compared with the carvedilol group.
Gulati et al. [85] 2016 Norway	130 (breast cancer)	Placebo-controlled trial Candesartan vs. metoprolol vs. candesartan + metoprolol	Change in LVEF	3–5 months	No significant effect on change in LVEF with metoprolol vs. placebo	MRI was used.
Tashakori et al. [94] 2016 Iran	70 (breast cancer)	Carvedilol vs. placebo	Strain/strain rate	1 week	Carvedilol group presented no significant reduction in strain and strain rate parameters while there was a significant reduction in the control group	
Nabati et al. [95] 2017 Iran	91 (breast cancer)	Carvedilol vs. placebo	Change in LVEF from baseline	6 months	LVEF change pre/post Placebo 61.1%/51.6% Carvedilol 58.7%/57.4%	LV end-systolic volume and LA diameter were significantly increased in the control group. Troponin level was significantly higher in the control group at 30 days.
Avila et al. [90] 2018 Brazil	192 (breast cancer)	Carvedilol vs. placebo	≥ 10% reduction in LVEF	6 months	≥ 10% reduction in LVEF Carvedilol 14.5% of patients Placebo group 13.5% of patients	No differences in changes of LVEF or BNP were noted between groups. A lower incidence of diastolic dysfunction was noted in the carvedilol group. Troponin I elevation was significant and attenuated by carvedilol use.

LVEF left ventricular ejection fraction, *LV* left ventricle, *LA* left atrium

trials (Table 4) [50]. The use of spironolactone has been evaluated in a group of 90 patients and demonstrated some benefit by helping to preserve systolic and diastolic function. It is believed that aldosterone antagonists are protective by an anti-oxidant effect [86].

From the previous studies, we can conclude that RAS inhibition had a cardio-protective effect in the majority of the studies; however, it failed to decrease the troponin release, suggesting that RAS is not involved in direct cardiotoxicity of anthracyclines of anthracyclines but plays a role in the myocardial remodeling that occurs after cardiac injury. Also, this leaves an open question of whether RAS blockade should be used as primary prevention for patients on anthracyclines or initiated after the rise in troponin levels.

Beta-blockers

Beta-blockers have a well-established role in reducing morbidity and mortality in heart failure patients. In addition, extensive preclinical literature has shown that beta-blockers have antioxidant and antiapoptotic properties in the setting of anthracycline-induced cardiomyocyte injury. Carvedilol in particular has been shown to mitigate anthracycline-induced mitochondrial dysfunction [87]. Hence, several trials were conducted to evaluate their role in the prevention of anthracycline-induced cardiomyopathy.

In 2006, Kalay et al. randomized 50 patients to carvedilol or placebo in whom anthracycline therapy was planned. Echocardiography was performed at baseline and after 6 months. The mean EF was found to be significantly lower in the control group after 6 months (68.9 vs. 52.3, $p < 0.001$). Also, systolic and diastolic LV chamber dimensions were significantly increased in the placebo group compared with that in the carvedilol group [88]. In 2010, Georgakopoulos et al. randomized 147 lymphoma patients planned for anthracycline therapy to prophylactic therapy with metoprolol, enalapril, or placebo [82]. After 1 year, metoprolol was not found to reduce the risk of cardiotoxicity in patients treated with doxorubicin. However, a statistically non-significant lower incidence of CHF and subclinical cardiotoxicity was noted in the metoprolol group. In 2013, Kaya et al. enrolled 45 patients with planned chemotherapy for breast cancer. Patients were randomly assigned to receive nebivolol or placebo. At 6 months, the left ventricular end-systolic and end-diastolic diameters increased in the placebo group but remained unchanged in the nebivolol group. The placebo group also had lower LVEF than the nebivolol group ($57.5 \pm 5.6\%$ vs. $63.8 \pm 3.9\%$, $p = 0.01$). In addition, the BNP level did not change in the nebivolol group while it increased in the placebo group [89]. In 2016, the PRADA trial randomized 130 breast cancer patients to candesartan, metoprolol, or placebo, and LVEF was assessed by cardiac CMR after 3–5 months of therapy [84]. Metoprolol was found to have no effect on the overall decline in the LVEF. In 2018, Tashakori et al. enrolled 70 patients with breast cancer on doxorubicin to carvedilol vs. placebo [89]. Both groups were evaluated 1 week before and 1 week after chemotherapy by measuring the LVEF and strain/strain rate. In the carvedilol group, no significant reduction in strain and strain rate parameters was noted while there was a significant reduction in these parameters in the control group. In 2017, Nabati et al. randomized 91 breast cancer patients to either carvedilol or placebo. At 30 days, the troponin level was significantly higher in the control group than in the carvedilol group ($p = 0.036$). After 6 months, LVEF did not change in the carvedilol group but was significantly reduced in the control group ($p < 0.001$). Moreover, the left ventricular end-systolic volume and LA diameter were significantly increased compared with the baseline measures in the control group.

Unfortunately, there is inconsistency in the role of beta-blockers in the prevention of anthracycline-induced cardiomyopathy. This may be explained by small underpowered studies that were single blinded and in single centers. However, in 2018, the Carvedilol Effect in Preventing Chemotherapy-Induced Cardiotoxicity (CECCY) trial was the largest randomized, placebo-controlled trial of beta-blockade for the primary prevention of anthracycline cardiotoxicity performed. A total of 192 patients with breast cancer and normal LVEF were randomized to receive carvedilol or placebo. There was $\geq 10\%$ reduction in LVEF at 6 months in 14 (14.5%) in the carvedilol group and 13 (13.5%) in the placebo group ($p = 1.0$). No differences in changes of LVEF or BNP were noted between groups. However, a significant difference in troponin levels existed between groups over time, with lower levels in the carvedilol group ($p = 0.003$). Additionally, a lower incidence of diastolic dysfunction was noted in the carvedilol group ($p = 0.039$) (Table 5) [90]. The CECCY and several other trials demonstrated lower levels of troponins in patients receiving beta-blockers after anthracycline therapy, substantiating that beta-blockers may have a role in selected patients to prevent CTRCD. Nonetheless, their role in the prevention of LVEF decline is still not substantiated. Given that the incidence of CTRCD is relatively low with the current doses of anthracyclines, further multicenter large trials with longer follow-up durations are needed to elucidate the role of beta-blockers in CTRCD prevention.

Conclusion

Anthracycline chemotherapy is a cornerstone in the treatment of breast cancer and hematological malignancies. So far, the exact mechanism of anthracycline cardiotoxicity is not well defined. Since cancer survivors are increasing in numbers, anthracycline-induced cardiotoxicity remains a major concern. Patients who receive anthracycline treatment need to be followed up to monitor left ventricular function over time.

That is especially important for children cancer survivors. Preventive treatment has not been well established. Dexrazoxane proved its efficacy in the reduction of anthracycline-induced cardiotoxicity, yet its safety and effect on cancer-related outcomes remain controversial. The very few trials conducted with statins had promising results. RAS inhibition trials demonstrated favorable results in the prevention of left ventricular function decline. However, it did not blunt the troponin rise, which suggests that RAS is not involved in the direct cardiotoxic effect of anthracyclines but has a role in the myocardial remodeling that occurs after anthracycline administration. On the other hand, beta-blockers were able to blunt the troponin rise in several trials, but they had inconsistent results in the prevention of LVEF decline. Accordingly, multicenter large clinical trials on the previously discussed drug classes are necessary to further understand and prevent anthracycline-induced cardiotoxicity.

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