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HEART FAILURE PREVENTION (W TANG, SECTION EDITOR)

Preemptive Cardioprotective Strategies in Patients Receiving Chemotherapy

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Abstract Chemotherapy agents have greatly improved outcomes and survival of patients with cancer but have also been associated with significant cardiotoxicity. The advent of cardiotoxicity is detrimental to patients both during cancer therapy, by limiting the extent of therapy and therefore chance of cure, and also during cancer survivorship, by causing devastating cardiac morbidity and mortality. In this article, we not only review the types of agents most often associated with cardiotoxicity, proposed mechanisms of cardiac injury, but more importantly, how to attenuate or prevent it all together. We review the available data and evidence for different strategies to prevent cardiac damage during chemotherpathy and propose our own protocols for risk stratification, monitoring, and prevention of cardiotoxicity.

Keywords Chemotherapy · Cardiotoxicity · Protective · Anthracyclines · Trastuzumab

Introduction

The discovery of drugs such as anthracyclines, HER2-antagonists and tyrosine kinase inhibitors have transformed some cancers into curable or chronic diseases, albeit at the cost of significant short and long-term cardiac toxicities. With over 18 million survivors expected in the United States alone by 2020 [1], long-term cardiac side-effects of therapy that can impair quality and length of survival [2] have become increasingly more relevant to patients and physicians alike. Whereas late cardiotoxicity can cause crippling cardiac morbi-mortality that may require advanced therapies [3••, 4], acute cardiotoxicity can hinder continued cancer treatment thwarting its success and decreasing survival [5•].

Mounting recognition of this problem has led to the advent of onco-cardiology [6, 7], a collaborative effort between cardiologists and oncologists aimed at reducing cardiotoxicity and mortality of cancer patients and survivors. Whereas much focus has been directed at monitoring and predicting onset of cardiotoxicity, it is clear that measures to prevent it altogether are likely to have a greater impact on outcomes.

Therefore, we herein review the available data on risk evaluation, early detection and, more importantly, prevention of cardiotoxicity in patients undergoing treatment with anthracyclines, HER-2 antagonists and tyrosine kinase inhibitors. We also offer our own approach to managing these patients.

Overview of Types and Mechanisms of Preventable Cardiotoxicity

It has been estimated that up to 42 % of patients receiving anthracyclines and trastuzumab for breast cancer develop heart failure or cardiomyopathy within 3 years of treatment [8]. Conservatively, there are an estimated 20,000-100,000 breast cancer patients with chemotherapy-related cardiotoxicity in the United States [9], and around 100,000-250,000 with established chemotherapy-induced cardiomyopathy [4, 5•, 10, 11]. While most patients are managed medically, some patients progress to end-stage heart failure and may require advanced therapies, such as mechanical circulatory support and heart transplantation [3••, 4].

Sadeer Al-Kindi and Ahmad Younes contributed to this work equally.

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Anthracyclines, widely used for breast cancer and lymphomas, have traditionally been associated with cardiotoxicity [12] that can be acute, early chronic, or late chronic [13]. Acute cardiotoxicity develops in 3.2 % of patients within days of administration, appears to be inflammatory in nature, and is usually reversible rarely resulting in refractory heart failure (<1 %). The main drawback of acute anthracycline cardiotoxicity is that it often leads to treatment interruption and typically discontinuation of further anthracycline-based therapy, causing the patient to be treated with second line agents that may not be as effective. Acute cardiotoxicity, therefore, needs to be avoided because it decreases the potency and efficacy of treatment and consequently, the chances of cure. The early-onset and late-onset chronic progressive types develop within and after the first year after therapy, respectively, with estimated incidences of 2 % and 5 % of patients [14]. The latter forms of cardiotoxicity can lead to end-stage HF with biventricular dysfunction and require advanced heart failure therapies. This type of cardiotoxicity reduces the quality of life and longevity of cancer survivors and requires enhanced awareness so that patients exposed to anthracyclines get screened at regular intervals for development of subclinical LV dysfunction. Early discovery and treatment of LV dysfunction at Stage B HF, may prolong survival and negate need for advanced therapies [15, 16].

Few risk factors for anthracycline cardiotoxicity have been identified [9, 17], but incidence increases with higher cumulative doses. Diastolic dysfunction occurs at accumulative dose of 200 mg/m^2 and systolic dysfunction usually appears at accumulative dose of 400-500 mg/m^2 [9, 18]. The risk of developing heart failure increases with the total dose of doxorubicin. The probability of developing heart failure is 5 % at 400 mg/m^2, 26 % at 550 mg/m^2 and goes up to 48 % at 700 mg/m^2 [18]. Other factors that can increase the risk of cardiotoxicity are extremes of age, concomitant or previous chemotherapy, female sex, pre-existing heart disease, hypertension and mediastinal radiation [14, 19, 20].

Trastuzumab is a HER2-antagonist that is used for HER2+ breast cancer as mono- or adjuvant therapy. In phase III trials, 27 % of patients who received trastuzumab-anthracyclines developed HF, compared with 8 % in the anthracycline-only group [21]. Similarly, 13 % of patients receiving trastuzumab-paclitaxel developed HF, compared with 1 % receiving paclitaxel alone [21]. Other studies have reported cardiotoxicity in 3-7 % of patients when trastuzumab is used alone, and as much as 27 % when combined with anthracyclines [22]. Trastuzumab not only increases the incidence of HF, but also its severity. Compared with anthracycline-only group and paclitaxel-only group, patients who received anthracycline-trastuzumab combination therapy were more likely to develop advanced (NYHA class III/IV) heart failure (3 % vs. 16 %, and 1 % vs. 2 %, respectively) [21]. In the experience of the authors and others [23], it is becoming increasingly apparent that trastuzumab alone is only capable of inducing transient LV dysfunction and heart failure, which is usually reversible once it is interrupted and HF treatment is started. The only patients that appear to progress to end-stage HF are those with previous exposure to anthracyclines and/or pre-existing structural heart disease.

Risk factors for trastuzumab-cardiotoxicity have been identified and are useful in selecting a population that may benefit the most from preemptive cardioprotection. Advanced age (>80 years) appears to be a significant risk factor for developing cardiotoxicity (HR, 1.53; 95 % CI, 1.16 - 2.10) [24]. Paradoxically, an abnormal baseline LVEF has not been associated with increased risk for cardiotoxicity [25], however, patients with low EF are usually excluded from therapy with trastuzumab. Also, while concurrent or previous anthracycline use certainly increases the likelihood of LV dysfunction from trastuzumab [21, 22], concomitant radiation therapy to the chest does not [26]. In general, patients with history of pre-existing structural cardiovascular disease and cardiovascular risk factors (diabetes, dyslipidemia, hypertension) are also more likely to develop cardiotoxicity with trastuzumab [27, 28].

Tyrosine kinase inhibitors (TKIs) are yet another group that has been associated with cardiotoxicity. This family of drugs is mainly used for treatment of leukemia and renal cell carcinoma [29–31]. They are multitargeted medications with affinity for VEGF receptor (VEGFR) 1–3, PDGFR, c-Kit, CSF-1R among others [32]. The major toxicities related to these drugs are hypertension, myocardial ischemia and left ventricular dysfunction. Hypertension results from VEGF pathway inhibition, leading to vasoconstriction and microvascular dysfunction, a pathway common to all TKIs targeting VEGF-receptors [33]. Hypertension occurs in more than half of the patients on several TKIs up to 66 % in patients with Lifinanib [34]. Acute coronary syndrome has been associated with sorafenib and occurred in 2.9 % (vs. 0.4 % in the placebo group) [35], a phenomenon that might be associated with angiogenesis inhibition and LV remodeling in response to hypertension. LV systolic dysfunction (grade 3/4) occurs in up to 5-28 % of patients treated with sunitinib [29]. These toxicities are usually managed medically and can be reversible, but little is known about their long-term prognosis [29, 36].

The antimetabolite 5-fluorouracil and its pro-drug capecitabine, are widely used for treatment of gastrointestinal tumors with a wide spectrum of cardiotoxicity reported at 1.2-18 % [37, 38]. The most common cardiac side effect is that of coronary vasospasm, through activation of protein-kinase C [39], which can be exacerbated by the presence coronary artery disease [40]. Anecdotal evidence suggests that vasodilators (e.g., nitroglycerin) and calcium channel blockers may protect against vasospasm [41, 42], however failure with this strategy has also been reported [43].

Diagnosis and Surveillance

Imaging

Conventional Echocardiography and Multiple Gated Acquisition (MUGA) scan

Cardiotoxicity is defined clinically as a greater than 10 % decrement in LVEF from baseline measurement. This definition has been endorsed by ASCO and guidelines recommend serial LVEF measurements in patients receiving high doses of doxorubicin [44]. Owing to its wide availability and wealth of information it provides, echocardiography is the modality of choice for monitoring and detection of cardiotoxicity. The major disadvantage of echocardiography is that it is largely operator-dependent and therefore has higher intra and inter-observer variability when compared to multiple gated acquisition (MUGA) scans [45, 46]. Although choice of modality is institution-dependent, it is important that the same method be used consistently for reliable LVEF comparisons. It is also essential that LVEF be always measured as recommended by the American Society of Echocardiography [47] and not be visually estimated, and although commonly used, ranges should be avoided and a definite number be given in the report. The reason for this is that small changes in LVEF can be predictors of significant future cardiotoxicity. For example, in patients with non-Hodgkin lymphoma receiving doxorubicin at doses of 200 mg/m^2, a decrease of 4 % in LVEF or more predicted later cardiotoxicity (decrease LVEF<10 %, and LVEF<50 %) [48]. However, not surprisingly, cardiotoxicity as expressed by LVEF reductions, has poor correlation with NYHA class.

While LVEF by 2D echocardiography is still the most commonly used method for monitoring and diagnosing cardiotoxicity, 3D LVEF measurements are more accurate and reproducible [49]. In a study of patients with breast cancer receiving cardiotoxic therapies, serial LVEF measurement by 3D echocardiography had less interobserver and intraobserver variability than biplane 2D LVEF measurements over 1 year follow-up (0.017 vs. 0.033, and 0.027 vs. 0.04) [50]. Indeed, among breast cancer patients treated with HER2 antagonists after doxorubicin, MUGA scan and LVEF by 3D echocardiography showed better correlation with cardiac MRI measurements than LVEF by 2D echocardiogram at 12 months (r=0.95 vs. r=0.90 vs. r=0.69) [51].

Lastly, although conventional echocardiography is reliable in diagnosing cardiotoxicity, EF reduction is a relatively late event in the cardiotoxic cascade, and once it occurs, the probability of recovery is just above 50 % [5•]. This realization has prompted development of newer techniques to detect cardiotoxicity more prematurely.

Strain Echocardiography

Strain and strain-rate (deformation imaging) have recently gained attention as potential early markers of cardiotoxicity [52]. Strain echocardiography uses two main methods: speckle tracking and tissue Doppler to assess myocardial dynamics. Strain is presented as percent change, with positive numbers referring to thickening, and negative numbers referring to shortening. Strain rate is the change of strain over time [53] and can measured in different axes, namely: longitudinal, circumferential, and radial (see Fig. 1) [54•]. In mouse models of doxorubicin-induced cardiotoxicity, changes in endocardial systolic velocity and strain rate correlated with hemodynamic changes, preceded changes in LVEF, were associated with late cardiotoxicity, and predicted doxorubicin-induced mortality [55]. Recent reports have validated these findings in humans [56, 57].

In a study of 43 patients with breast cancer followed by echocardiography, longitudinal strain decreased by 11 % at 3 months. This decrease was detected in the midwall (p=0.008) and the lateral (p=0.01) and anterior (p=0.01) segments. The change in longitudinal strain (OR 500, p=0.01) and radial strain (OR 250, p=0.02) at 3 months were significantly different in the cardiotoxicity group. Negative predictive value for 10 % decrease in longitudinal strain was 93 % [56]. Other studies have showed similar results with strain imaging. In a study of 81 patients with breast cancer receiving trastuzumab (+/- doxorubicin, +/- radiation), 11 % reduction in GLS had 95 % specificity for cardiotoxicity [58]. In another study of 74 patients with cancer receiving anthracycline-based therapy, 13 % relative reduction in global longitudinal shortening had 79 % sensitivity for cardiotoxicity [59].

In a systematic review on the use of strain for monitoring chemotherapy-induced cardiotoxicity, peak systolic longitudinal strain using Doppler-based strain imaging most consistently detected early cardiotoxicity during chemotherapy [54•]. In fact, a decrement in GLS by 10-15 % was the most useful parameter to predict LVEF reduction and heart failure [54•]. Reductions in circumferential and radial strains are also common, but less consistently reproducible [54•]. However, the management of cardiotoxicity based on strain data is yet to be validated.

Serum Biomarkers

Both animal [60] and human studies [60–62] have shown that troponin can be an early marker of chemotherapy-induced cardiotoxicity. Patients receiving chemotherapy who have high post-treatment troponin levels are more likely to develop LVEF reduction or HF [63]. The level of troponin elevation may even predict reversibility of LVEF abnormalities during treatment [64]. The duration of troponin elevation also seem to be a marker of late development of heart failure or other

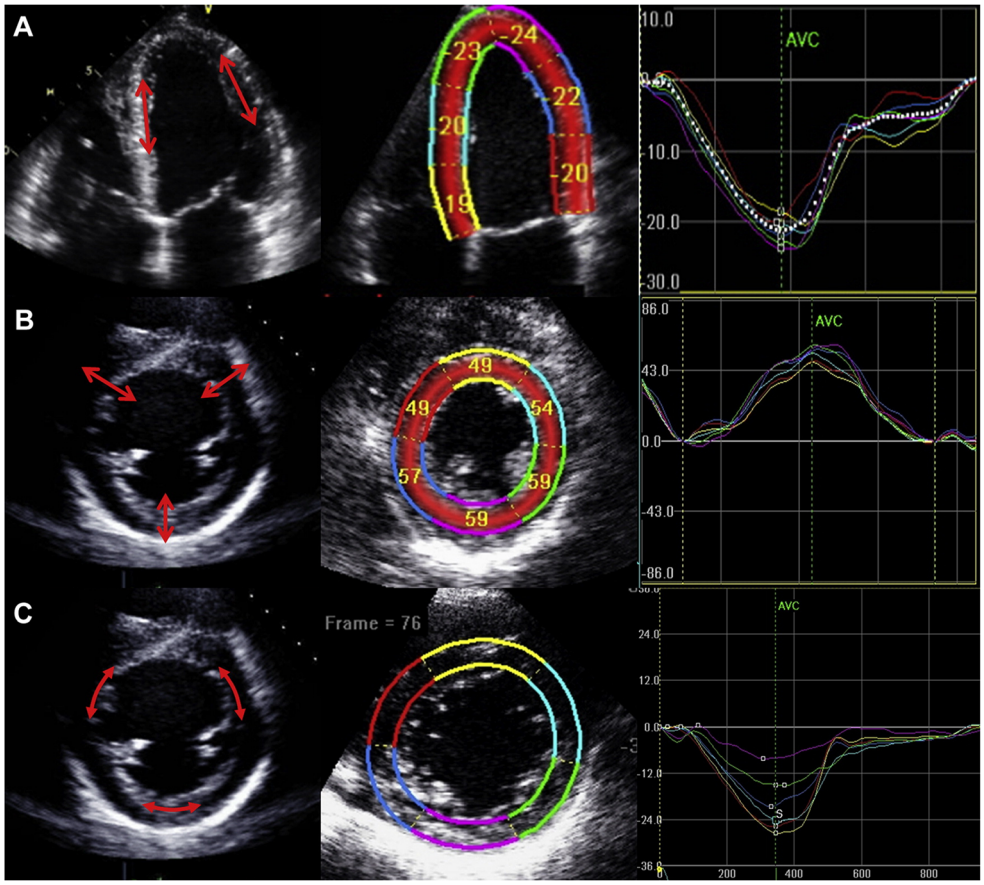


Fig. 1 Strain imaging in a patient starting chemotherapy (**a**) longitudinal, (**b**) radial, and (**c**) circumferential. Adapted from Thavendiranathan et al. [54•]

cardiac events. In 703 cancer patients, early elevation in troponin I was associated with 37 % cardiac events, and persistent elevation was associated with 84 % compared with 1 % cardiac events [62].

Despite these findings, troponin elevation has been an inconsistent marker of cardiotoxicity. Some studies failed to detect troponin elevations even in the presence of echocardiographic findings [65–67]. While sensitivity is unreliable, normal troponin levels during chemotherapy administration can identify patients with the lowest risk for cardiotoxicity (negative predictive value of 99 %) at least one year after chemotherapy while troponin elevation at 3 months can predict cardiotoxicity prior to changes in LVEF [56]. Further, the patterns of troponin elevations may correlate with the severity of cardiotoxicity [60]. Because of logistical issues with timing of blood draws and absence of assay standardization, troponin use is not routinely recommended for monitoring cardiotoxicity.

In a multicenter study of 78 patients with breast cancer receiving doxorubicin and trastuzumab, Ky et al. measured and followed eight biomarkers in association with cardiotoxicity. Risk of cardiotoxicity was higher with changes in troponin I (HR: 1.38 per SD, p=0.02), and myeloperoxidase (MPO) (HR: 1.34 per SD, p=0.048). In patients with largest changes in TnI (ΔTnI >121.8 μg/l; ΔMPO >422.6 pmol/l), risk of cardiotoxicity was 46.5 % [68].

Likewise, while some studies have shown increase in BNP levels after chemotherapy, evidence from animal studies have suggested that anthracyclines may decrease the production of BNP and thus levels may be paradoxically low [69].

Subsequent studies evaluating the role of BNP measurement in monitoring patients receiving chemotherapy are promising. Lenihan et al. followed 111 patients receiving anthracycline-based regimens with cardiac biomarkers (troponins and BNP) at baseline and before and after up to six cycles of treatment. BNP was elevated only in the group that developed cardiotoxicity ((heart failure, LVD, sudden death, or arrhythmia) [70].

Skovgaard et al. followed 333 patients receiving cardiotoxic agents for a mean of 1360 days. Sing a BNP of more than 100 pg/ml predicted CHF (HR 5.5; CI 1.8–17.2; p=0.003). Furthermore, BNP (>100 pg/ml) but not LVEF predicted overall death (HR 1.9; CI 1.3-2.9; p=0.002) [71].

While BNP can and should be used in patients at higher risk of developing HF for diagnostic purposes, its usefulness in monitoring cardiotoxicity is not yet established.

Endomyocardial Biopsy

Although not useful in trastuzumab or TKI-induced cardiotoxicity, endomyocardial biopsy (EMB) remains the gold standard for diagnosis and grading of anthracycline-induced myocardial damage. Despite being invasive and requiring transvenous approach, EMB carries less than a 6 % risk of complications [72], which include bleeding, transient arrhythmia, valvular injury, pulmonary embolism, and cardiac chamber perforation [73, 74]. Because there is variable myocardial regional involvement, 4-6 biopsies are usually taken from the right and occasionally left ventricle to maximize diagnostic yield [75]. Electron microscopy shows characteristic depletion of myofibrillar bundles, distortion and disruption of the Z-lines, mitochondrial disruption, and myocyte vacuolization [76]. Grading of cardiotoxicity has close correlation with development of left ventricular dysfunction and heart failure [9]. However, given its invasiveness and ready availability of imaging, EMB is usually reserved for cases where there is need to exclude alternative explanations for cardiotoxicity [77].

Medical Prevention of Cardiotoxicity

Advances in detection however, have not translated into significant attenuation of cardiotoxicity, and thus current focus has shifted toward prevention. While animal studies have shown promise in the prevention of chemotherapy, large-scale human studies are still lacking. In a meta-analysis of 14 cardiotoxicity prevention studies with 2015 patients treated with anthracyclines and/or trastuzumab, 83 cardiac events occurred in the treatment group compared with 304 in the control group (RR=0.31, p<0.00001). Reduction in cardiac events was attributed to statins (69 % reduction), beta-blockers (69 % reduction), angiotensin antagonists (89 % reduction), and dexrazoxane (65 % reduction) [78••], Table 1.

Statins

Statins have reduced mortality in patients with high risk cardiovascular profiles through lipid lowering and pleotropic effects [79]. However, their use as cardioprotective agents in chemotherapy-induced cardiomyopathy is still equivocal. With inflammation and oxidative stress playing a role in the development of cardiotoxicity, statins' anti-inflammatory and anti-oxidative properties have the potential to attenuate detrimental effects of chemotherapy on cardiomyocytes.

In cultured cardiomyocytes, pitavastatin attenuated doxorubicin-induced oxidative stress, DNA damage, and p53 accumulation and thus apoptosis [80]. In fact, fluvastatin-pretreated mice receiving doxorubicin, had higher cardiac outputs and lower LV pressures compared to non-statin treated mice. They also showed reduced cardiac expression of nitrotyrosine, enhanced expression of the mitochondrial located antioxidative SOD 2, attenuated mitochondrial apoptotic pathways, and diminished cardiac inflammatory response, thus reducing cardiac toxicity [81]. Iliskovic et al. reported complete prevention of adriamycin cardiotoxicity with probucol, a lipid reducing and antioxidant agent in rats, with improved glutathione peroxidase activity and reduced lipid peroxidation [82].

Similarly, Cheng et al. reported that pravastatin-pretreated mice receiving carbaplatin had decreased apoptosis, caspase 3, 9, and cyctochrome C activity, reactive oxygen species, with improved cardiac function and survival. This was achieved via Akt activation and restoration of normal mitochondrial HAX-1 in heart tissue, suggesting that pravastatin has cytoprotective effects in carboplatin-induced cardiotoxicity [83].

Small human studies have also been promising. In a retrospective observational study of patients with breast cancer who received anthracyclines, uninterrupted statin therapy reduced incident heart failure by 70 % compared with patients who did not receive statin [HR] of 0.3 (95 % confidence interval [CI]: 0.1 to 0.9; p=0.03) [84].

In the only randomized clinical trial so far, Acar et al. randomized 40 patients receiving anthracycline-based chemotherapy to atorvastatin (40 mg/day) versus placebo and found that significant decreases in LVEF were only noted in the control group but not in the statin-group [85].

From these preliminary data, it appears that statins may have a cardioprotective role in the prevention of chemotherapy-induced cardiotoxicity through reduction of the oxidative stress. Because of the paucity of other available cardioprotective therapies, the authors recommend use of statins in patients at moderate to high risk of cardiotoxicity.

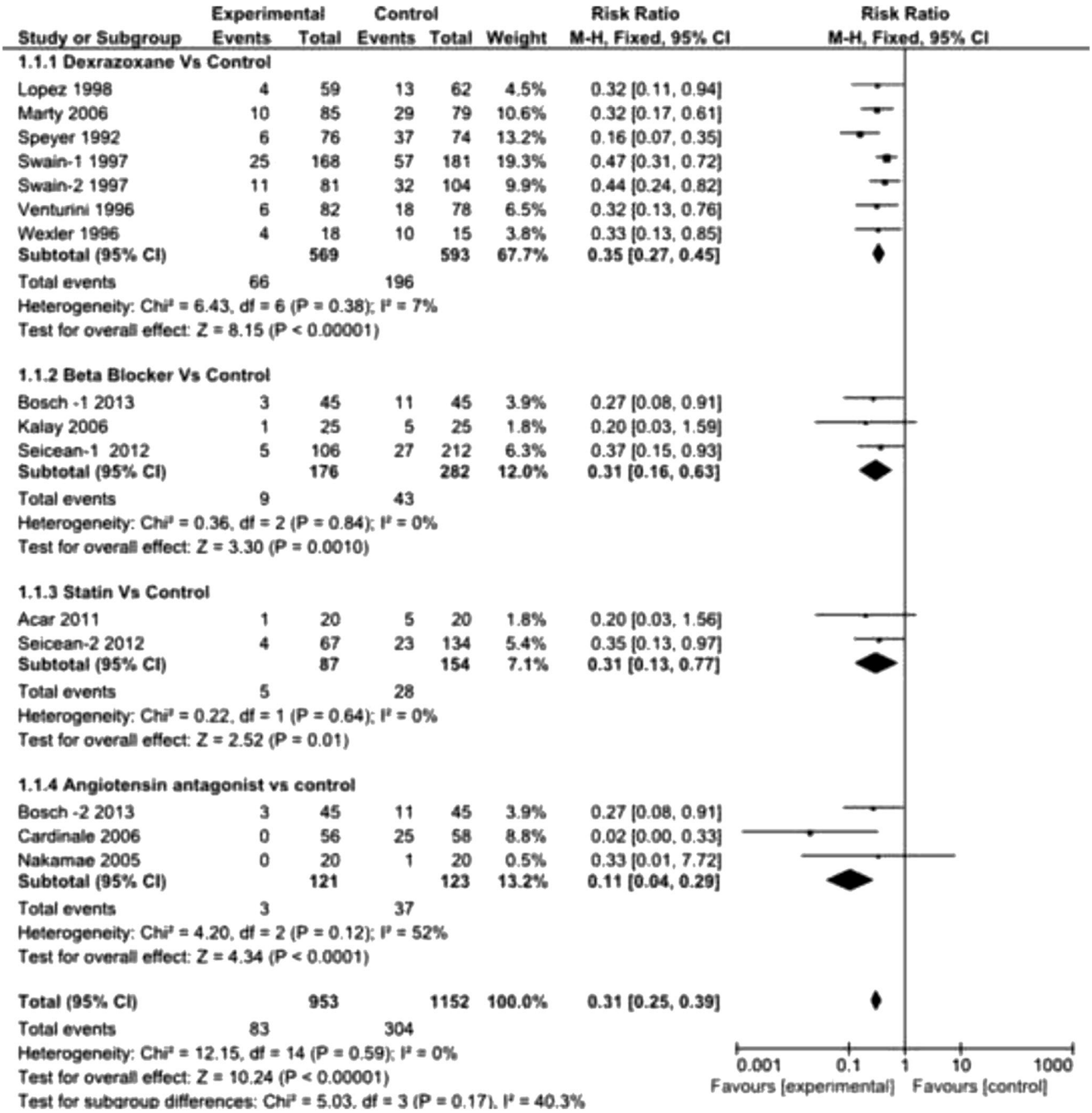
Beta-blockers

Cellular and animal studies suggest that beta-blockers may have protective activity against doxorubicin cardiotoxicity [86–88]. The suggested mechanism of cardioprotection is believed to be primarily through neurohormonal blockade [89], antioxidant effects [86], and inhibition of apoptosis [86].

To date, only a few studies have supported these effects in humans. Seicean et al. published a retrospective, database-derived study, reporting outcomes of 106 breast cancer patients who were on various beta-blockers while receiving anthracyclines or trastuzumab. Compared with propensity-matched controls, those on beta-blockers had a significant reduction in the risk for new HF events (HR 0.2, 95 % CI 0.1-0.5, p=0.003) [90].

Kalay et al. randomized 50 patients treated with anthracycline therapy to carvedilol (12.5 mg daily) or placebo. After completion of therapy, LVEF was higher in patients receiving carvedilol (69.9 % vs. 52.3 %), and both systolic

Table 1 Cardiac events in a meta-analysis of cardioprotective agents (reproduced with permission from Kalam et al. 2013 [78••])



and diastolic diameters were significantly increased compared with basal measures in the control group [91].

The only randomized, blinded placebo controlled trial to date, OVERCOME (Enalapril and Carvedilol for Preventing Chemotherapy-Induced Left Ventricular Systolic Dysfunction in Patients With Malignant Hemopathies) has provided further validation for the cardioprotective role of beta-blockers and ACE-I. Ninety patients with acute leukemias or malignant hemopathies without left ventricular systolic dysfunction were randomized to receive carvedilol and enalapril or placebo. At 6 month follow-up, LVEF did not change in the intervention group, but decreased in controls (-3.1 %, p=0.035) by echocardiography. More importantly, patients who received carvedilol/enalapril had lower incidence of death or heart failure (6.7 % vs. 22 %, p=0.036) [92••].

There is evidence, that not all beta-blockers confer the same degree of cardioprotection. For example, in mice treated with anthracyclines, carvedilol but not atenolol was effective in

reducing apoptosis [93]. Similarly, Georgakopoulos et al. reported a retrospective analysis of 42 patients treated for lymphoma with metoprolol versus placebo and were unable to demonstrate significant reduction in cardiotoxicity among the groups [94].

Based on these data, we currently consider carvedilol as the beta-blocker of choice for prevention of cardiotoxicity.

ACE-Inhibitors and Angiotensin Receptor Blockers

In addition to their pivotal role in HF [95, 96], angiotensin-converting enzyme inhibitors (ACE-I) appear to have cardioprotective properties against cardiotoxicity [97–99]. Through mechanisms other than attenuating remodeling and neurohormonal activation after an initial myocardial insult [100], ACE inhibition may prevent cardiotoxicity related to chemotherapy. Hiona el al. showed that enalapril protects against doxorubicin-induced LV dysfunction by preserving mitochondrial respiratory efficiency and reducing free radical generation [101].

In the largest study thus far, Cardinale et al. randomized 114 chemotherapy-treated patients with high troponins to received ACE-inhibitors or placebo, showing a 10 % reduction in LVEF and increase in end-diastolic and end-systolic volumes among the control but not the ACE-I group, with incidence of 43 % vs. 0 % ($p<0.001$). These data suggest that ACE-I may prevent late cardiomyopathy in patients with biomarker evidence of myocardial damage from chemotherapy [102]. However, in a smaller study of 43 patients with lymphoma receiving enalapril or placebo, failed to show significant reduction in cardiac events [94].

Angiotensin receptor blockers (ARBs) may have similar cardioprotective properties as ACE-I. Among 40 lymphoma patients receiving CHOP, valsartan 80 mg/day versus placebo, those on valsartan had lower increases in BNP and more favorable diastolic parameters [103].

The use combination of beta-blocker (metoprolol) and angiotensin-receptor blockers (candesartan) in prevention of cardiotoxicity from anthracyclines and HER2-antagonists is underway in the PRevention of cArdiac Dysfunction during Adjuvant breast cancer therapy (PRADA) study [104].

Despite the absence of randomized clinical trials, current data supports the use of ACE-I and ARBs for prevention of chemotherapy-induced cardiotoxicity. We recommend their use in patients at risk for cardiotoxicity.

Dexrazoxane

As oxidative stress is the main driving event toward cardiomyocyte apoptosis, antioxidants may be beneficial in the prophylaxis against chemotherapy-induced cardiomyopathy.

Dexrazoxane is an EDTA-chelating agent that may decrease cardiotoxicity by binding iron that is implicated in the formation of ROS, and preventing mitochondrial dysfunction and thus apoptosis [105]. The use of dexrazoxane in cardioprotection, however, has been controversial.

In a meta-analysis of six RCTs, dexrazoxane given with anthracycline-based therapy reduced risk of clinical cardiotoxicity ([OR]:0.21; 95 % CI: 0.13- 0.33; $p< 0.0001$), subclinical cardiotoxicity ([RR]:0.33; 95 % CI: 0.20-0.55; $p<0.0001$), and any cardiotoxic event (clinical and sub-clinical) ([RR]:0.34; 95 % CI: 0.27- 0.45; $p< 0.0001$) [106].

However, there is a concern that dexrazoxane may interfere with cancer response rate and be associated with an increase in secondary malignancies [107, 108]. The use of dexrazoxane was associated with increase in acute myeloid leukemia/myelodysplastic syndrome rate (2.55 % vs. 0.85 %) and secondary malignancy rate (3.43 % vs. 0.85 %) in children with Hodgkin's lymphoma and lymphoblastic leukemia [109]. In a trial of patients with breast cancer, dexrazoxane was associated with decreased response rate to anthracycline therapy, however other trials did not confirm this finding [110, 111].

Given the conflicting data and the uncertainty of its effects, ASCO guidelines do not recommend the routine use of dexrazoxane in patients with initial dose anthracyclines [44]. However, patients with metastatic disease, history of more than 400 mg/kg/m^2 of doxorubicin, and those whom continuous use of doxorubicin is recommended despite lower LVEF, may be good candidates for dexrazoxane therapy.

Other Therapies

Probucol is a lipid-lowering agent with antioxidant properties that can protect the myocardium from anthracycline by activation superoxidative dismutase and glutathione peroxidase in animals although its role in protection for anthracycline cardiotoxicity in human is not known [112].

In a meta-analysis [106] and Cochrane review [113] of cardioprotective agents in prevention of chemotherapy-induced cardiotoxicity, no conclusion was deducted on the effects of N-acetylcystine, amifostine, vitamin E, coenzyme Q10, phenethylamines, and L-carnitine.

Ascensão et al. showed that both short and long-term exercise can be protective from doxorubicin cardiotoxicity by up-regulation of antioxidant capacity and increased expression of heat shock protein (HSP) and other anti-apoptotic proteins through potentiating mitochondrial plasticity and adaptations to the toxic effect of doxorubicin [114].

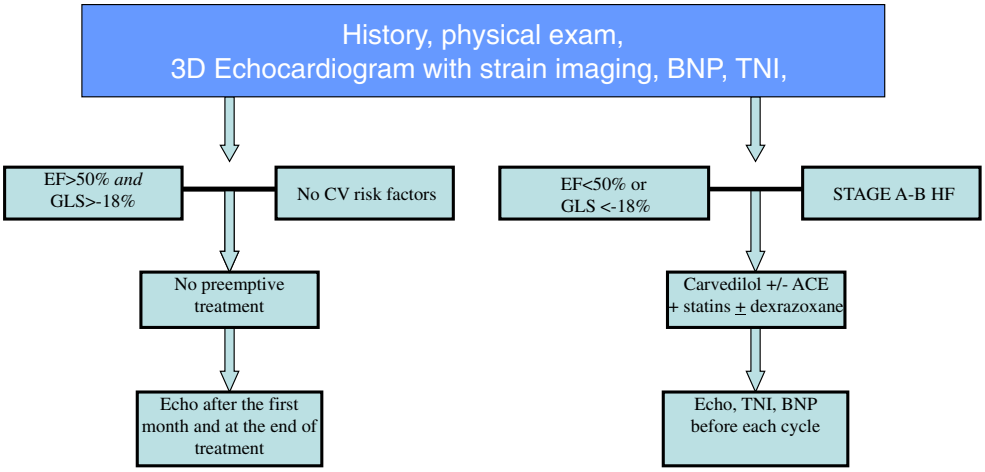


Fig. 2 Risk stratification for patients starting anthracycline-based regimens. Legend: 3D: 3-dimensional; EF: Ejection fraction; CV: cardiovascular; GLS: global longitudinal strain; ACE: angiotensin-converting enzyme inhibitor; HF: heart failure; TNI: troponins; BNP: B-type natriuretic peptide

Recommended Approach to Risk Stratification, Chemoprevention and Surveillance of Cardiotoxicity

Risk Stratification and Chemoprevention for Patients Prior to Anthracycline Therapy

In our Institution, all patients whose anti- neoplastic treatment plan includes cardiotoxic therapy, or have underlying heart disease are referred to the Onco-Cardiology Program. Within it, patients are evaluated with the objective of stratifying cardiovascular risk and optimizing pre-existing cardiovascular disease. In addition to a detailed history, physical examination, electrocardiography and baseline b-type natriuretic peptide and troponin I, risk stratification includes e 3D echocardiography (3D LVEF) with strain imaging (average peak systolic global longitudinal strain) prior to starting chemotherapy. Pre-emptive medical therapy is then recommended based on the perceived risk (Fig. 2).

Surveillance of Patients on Anthracyclines

During monitoring, if there is a drop in EF, but it remains≥ 50 % or there is a greater than 12 % decrement in GLS, patients are started on carvedilol with or without ACE inhibitors, statins and dexrazoxane (depending on discussions with the oncologists) and anthracyclines are continued. From then on, we repeat echocardiography with strain before each scheduled anthracycline cycle and obtain TNI at the end of each infusion. Conversely, if the EF decreases to less than 50 %, or there is development of clinical heart failure, anthracyclines

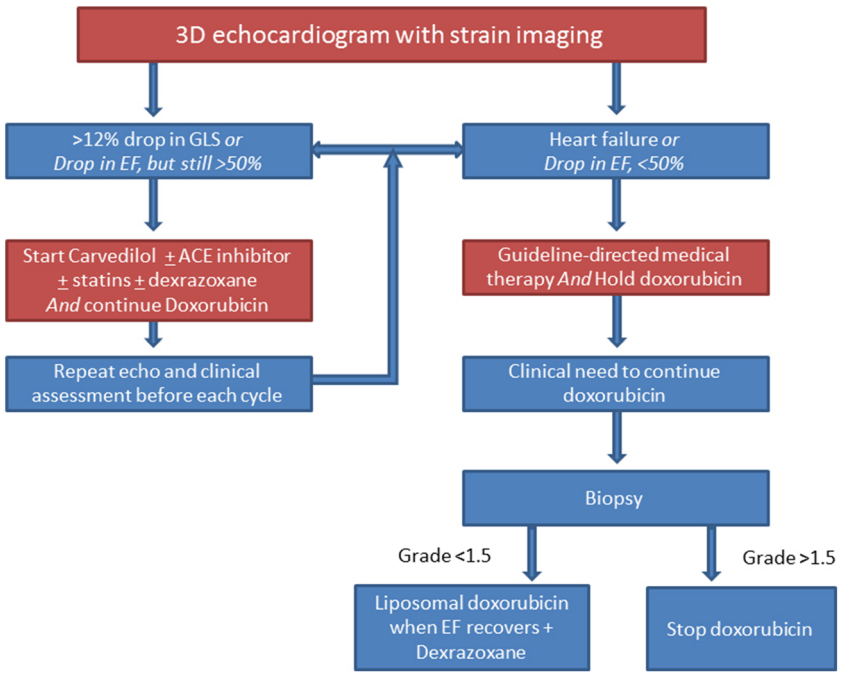


Fig. 3 Approach for monitoring and management of cardiotoxicity in patients receiving anthracycline-based therapy

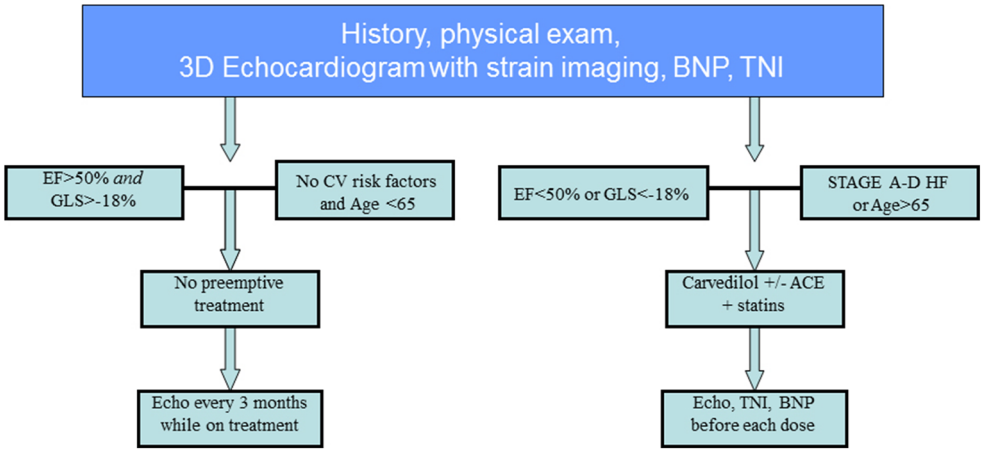


Fig. 4 Risk stratification for patients starting Trastuzumab or TKI-based regimens. Legend: 3D: 3-dimensional; EF: Ejection fraction; CV: cardiovascular; GLS: global longitudinal strain; ACE: angiotensin-converting enzyme inhibitor; HF: heart failure; TNI: troponins; BNP: B-type natriuretic peptide

are held, and appropriate guideline-directed medical HF therapy is initiated. If anthracyclines are required to continue, then an endomyocardial biopsy is done. If the biopsy shows a grade of <1.5, repeat echocardiograms are done monthly, and liposomal anthracyclines are started when EF is recovered, however with addition of dexrazoxane. If the biopsy shows a grade >1.5, anthracyclines are then permanently contraindicated, Fig. 3.

Risk Stratification and Chemoprevention for Patients on Trastuzumab and Other TKI's

Patients planned to start trastuzumab or TKIs are also seen in the oncocardiology program before intiating treatment. History and physical exam, biomarkers, and 3D echocardiogram with GLS measurement are obtained. If patients have preserved EF (>50 %) and GLS of more than -18 % or have no cardiovascular risk factors and they are below age of 65 years old, no preemptive treatment is required and we repeat echocardiogram every 3 months while on treatment. If patients have reduced EF (<50 %) or GLS<-18 % or they have HF or age 65 years or older, we usually start them on carvedilol and statin, with or without ACE inhibitors. We then proceed with trastuzumab treatment, and repeat echo with serum biomarkers before each dose, Fig. 4.

Surveillance of Patients on Trastuzumab and Other TKI's

A similar approach is taken for patients planned to receive trastuzumab (Fig. 4). Initial clinical assessment with echocardiogram is done prior to receiving trastuzumab, at one month and every 3 months while on the treatment. If repeat echocardiograms shows EF drop of 10 % or more, but still >50 %, or there is more than 12 % drop in GLS, carvedilol with or without ACE-inhibitors and statins are started, and monthly echocardiogram is required. If there is a drop in EF to less than 50 %, or there is clinical heart failure, we initiate guideline-directed medical therapy for heart failure, trastuzumab is held, and a monthly echocardiogram is indicated until EF recovers, at which time trastuzumab is resumed, Fig. 5.

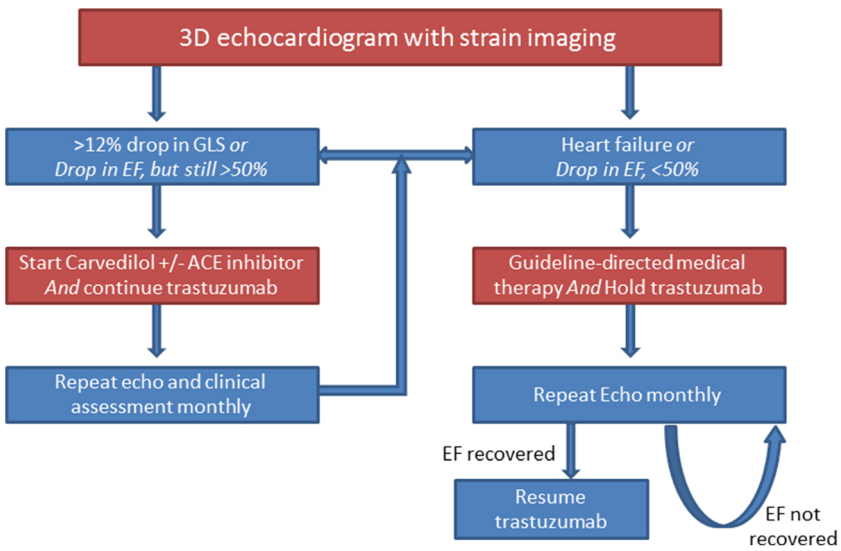


Fig. 5 Approach for monitoring and management of cardiotoxicity in patients receiving trastuzumab

Special Considerations in Other Chemotherapy Regimens

Patients who are started on TKIs are at high risk to develop hypertension. We usually pre-treat those patients with ACE-I, beta-blockers (e.g., Nebivolol), or calcium channel blockers (Nifedipine XL) to counteract the vasoconstriction in those patients as tolerated. Studies are required to validate this approach in prevention of hypertension in those patients.

Patients who receive 5-fluorouracil and capecitabine are at higher risk for coronary vasospasm. Although there is lack of evidence on this specific population, extrapolating data from idiopathic coronary vasospasm [115, 116], we recommend starting long-acting nifedipine and long acting nitrates on patients who develop angina while receiving 5-FU. In those who develop angina while on oral therapy, we admit them to the hospital and administer 5-FU in conjunction with intravenous nitrates and calcium channel blockers, such as nicardipine. Prophylactically, we recommend this regimen in patients without angina but with known coronary disease.

In all patients, we recommend statins for primary/secondary prevention of cardiovascular disease following the 2013 AHA/ACC guidelines on cholesterol treatment [117].

Conclusions

Compelling rationale and tentative evidence exist to support preventive medical interventions in cancer patients receiving potentially cardiotoxic chemotherapy. As better mechanistic understanding and stronger clinical data accrue, strategies to prevent cardiotoxicity will become more effective, hopefully rendering cardiotoxicity an ailment of the past.

Compliance with Ethics Guidelines

Conflict of Interest Guilherme H. Oliveira, Marwan Qattan, Sadeer Al-Kindi and Ahmad Younes have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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- • Of importance
- •• Of major importance

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