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Concepts in cardio-oncology: definitions, mechanisms, diagnosis and treatment strategies of cancer therapy-induced cardiotoxicity

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There has been considerable improvement in cancer survival rates, primarily through improved preventive strategies and novel anticancer drugs. Cancer is now becoming a chronic illness and as such both short and long-term cardiotoxic effects of cancer therapy are becoming more apparent. This has led to the emergence of a new multidisciplinary specialty known as cardio-oncology, with the purpose of identifying patients who are at a higher risk for developing cardiotoxicity so that appropriate surveillance, treatment and follow-up strategies may be instituted early. The mechanisms of cardiotoxicity caused by commonly used anticancer agents are reviewed, along with the latest advances in diagnostic and preventative strategies, with the overall objective of allowing cancer patients to continue both lifesaving and palliative treatments for their malignancy.

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The advent of improved cancer screening and modern individualized systemic cancer therapy has led to significant improvements in cancer survival over the past two decades [1]. As a result, the numbers of cancer survivors continue to grow in the USA. As of 2014, there were 14.5 million cancer survivors living in the USA; this number is projected to increase to 19 million by 1 January 2024 [2,3]. Although cancer therapies enable longer survival, many agents have both short-term and long-term cardiotoxic manifestations. Because of the high prevalence of cardiovascular disease among adult men and women, these men and women are at an even higher risk of developing both short- and long-term cardiovascular complications [4]. Therefore, there is an essential need to identify strategies to identify and intervene upon those at risk for cardiotoxicity during cancer therapy, and determine optimal surveillance intervals for the development of short and long-term cardiotoxic sequelae. This recognition has led to collaboration between cardiologists and oncologists, resulting in a relatively nascent multidisciplinary field known as cardio-oncology. Two of the main goals of cardio-oncology are to better understand the pathophysiology of cancer therapy associated cardiotoxicity, and to provide early recognition and treatment of cardiac complications in patients with, or who survive cancer. The ultimate goal of cardio-oncology is to maximize the benefits attained from modern cancer therapy by minimizing its immediate and future deleterious effects on the cardiovascular system [5].

This review will focus on the following subjects which are of significant interest within cardio-oncology: 1) the deleterious effects of select anticancer agents on left ventricular function and their proposed mechanisms of injury; 2) the clinical utility of imaging modalities and biomarkers for surveillance of cardiotoxicity; 3) the role of cardioprotective agents in preventing cardiotoxicity;

KEYWORDS

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- cardio-oncology
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- cardiotoxicity
- chemotherapy
- congestive heart failure
- echocardiography
- tyrosine kinase inhibitors

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and 4) current recommendations for screening for cardiotoxicity. While cardiac effects of radiation therapy have been extensively described, specific radiation related effects are beyond the scope of this paper, although the effects of concurrent radiation and cancer therapy will be discussed. We performed a literature search of PubMed between 1 January 1960 and 1 April 2015, using the search terms cardio-oncology, cardiomyopathy, cardiotoxicity, heart failure, cardioprotective, biomarkers and left ventricular dysfunction.

What constitutes cardiotoxicity & are there standard definitions?

Despite the known deleterious effects of certain anticancer agents (anthracyclines, monoclonal antibody targeting HER2/neu receptor and small molecule tyrosine kinase inhibitors) on cardiac function, at present there is no universally accepted definition or clinical end points. Left ventricular ejection fraction (LVEF) is the parameter commonly used to define cardiac toxicity and different organizations and societies have their own diagnostic criteria based on clinical symptoms, biomarkers and cardiac imaging [6]. The previous recommendations for chamber quantification from the American Society of Echocardiography (ASE) and European Association of Echocardiography (EAE) established LVEF $\geq 55\%$ as a normal reference range. However, new data indicate that the normal LVEF using the biplane method of disks is $63 \pm 5\%$, with LVEF in the range of 53–73% being classified as normal. Hence, the 2014 Expert Consensus Statement for Multimodality Imaging Evaluation of Adult Patients during and after cancer therapy from the ASE and the European Association of Cardiovascular Imaging (EACVI) defined cancer therapeutics-related cardiac dysfunction (CTCRD) as a decrease in the LVEF of $>10\%$ to a value $<53\%$ [7].

It is noteworthy to mention that the above is simply a guide and not an absolute cutoff as individual patient factors, disease processes and imaging protocols have wide variations, which must be taken into account when arriving at a diagnosis of cardiotoxicity. Furthermore, functional impairment is often present by the time there is a visible decline in left ventricular (LV) systolic function. In addition, a preserved LVEF does not exclude early subclinical myocardial dysfunction; thus, much attention has been focused on other potential parameters

that may be present prior to a decline in LVEF, including measures of myocardial deformation, serum biomarkers and measures of myocardial fibrosis [8–10].

Cardiotoxicity can be classified into two distinct forms based on presence of structural abnormalities and extent of reversibility. Type 1 cardiotoxicity is characterized by myocardial injury and is more likely to be irreversible whereas cardiac dysfunction associated with type 2 cardiotoxicity has a higher likelihood of recovery after discontinuation of the offending agent (Table 1) [7,11–12]. These classifications are by no means concrete, as timely institution of pharmacotherapy has been shown to lead to some resolution of the cardiomyopathy observed in type 1 cardiotoxicity [13,14]. In addition, one may encounter both forms of cardiotoxicity in the same patient due to combinations of anti-cancer agents used in present day clinical practice [12]. One of the overriding theories behind the mechanism of cardiotoxicity is the ‘multiple-hit’ hypothesis, which suggests that genetic and patient factors such as pre-existing cardiovascular risk factors (i.e., diabetes mellitus, hypertension, dyslipidemia) are themselves strong predictors for development of cardiovascular disease (CVD) after chemotherapy. This is further compounded by cancer treatment itself causing both direct and indirect detrimental effects on cardiovascular reserve by altering dietary and lifestyle factors, lessening adherence to potentially cardioprotective medications, making the overall cardiotoxicity risk higher in this cohort of patients [15].

Effects of select classes of cancer therapy agents on left ventricular function

• Anthracyclines

Anthracyclines, an agent derived from *Streptomyces*, are among the most widely used class of cancer drugs, being used in the treatment of breast cancer, small-cell lung cancer, myeloma, sarcoma, lymphoma and leukemia [16]. Anthracyclines are highly effective chemotherapeutic agents but their dose-dependent propensity for type 1 cardiotoxicity can limit their utility.

Despite advances in research methodology and intense scrutiny, the exact mechanism of anthracyclines remains unclear. There are several proposed theories but the most widely accepted mechanism appears to be the iron and free radical-hypothesis [17,18]. This hypothesis suggests

Table 1. Type 1 and 2 cancer therapy related cardiac dysfunction.

Class	Type 1: anthracyclines	Type 2: monoclonal antibody (i.e., trastuzumab)
Reversible with cessation of therapy	No	Yes
Dose dependent	Yes	No
Pathological findings	Necrosis, vacuoles and disruption of sarcomeres	No ultrastructural disruption

that anthracyclines upon entering cells undergo redox cycling which results in the formation of free radicals through the mitochondrial electron transport chain. These radicals release iron from ferritin and thereby increase the concentration of intracellular free iron [19]. The free iron then reacts with superoxide [$O_2^{\cdot-}$] and hydrogen peroxide (H_2O_2) to form hydroxyl radical (OH $\cdot$), which exerts potent oxidative stress and results in impaired mitochondrial function and cytotoxicity [20]. Anthracyclines impair oxidative phosphorylation and ATP synthesis, predisposing cells more susceptible to reactive oxygen species [21]. Nitric oxide synthase further aids in the generation of anthracycline-mediated reactive nitrogen species that further worsen nitrosative stress [21].

More recently there has been data suggesting a role for topoisomerase 2 β as a key mediator of anthracycline-induced cardiotoxicity [22]. Topoisomerase 2 isoenzymes play a pivotal role in DNA transcription, replication and recombination by regulating the over and under winding of the DNA double helix. Topoisomerase 2 α is present in rapidly proliferating cells such as cancer cells and topoisomerase 2 β is present in cardiac myocytes. Both of these enzymes are disrupted by anthracyclines. The effect of the latter is DNA breakage and apoptosis in cardiac myocytes [22]. Zhang *et al.* showed that cardiomyocytes from wild type mice exposed to doxorubicin had activation of genes in the tumor suppressor protein p53 and β -adrenergic signaling pathways as well as abnormalities in mitochondrial function, oxidative phosphorylation and apoptotic pathways compared with cardiomyocytes from topoisomerase 2 β knockout mice [11]. Other proposed mechanisms of anthracycline induced cardiotoxicity include Rac1 mediated activation of NADPH oxidase resulting in reactive oxygen species generation, decrease in c-Kit cardiac progenitor cells rendering myocytes more susceptible to injury, and impaired prosurvival signaling pathways via NRG-1 and ErbB receptor inhibition [23–25].

Congestive heart failure (CHF) is the most common manifestation of anthracycline induced cardiotoxicity [26]. Studies involving patients

receiving anthracycline therapy have demonstrated that the incidence of doxorubicin induced CHF is dose-dependent: up to 3–5% have been seen at 400 mg/m², 7–26% at 550 mg/m² and 18–48% at 700 mg/m² [26]. Since the risk of cardiotoxicity increases with cumulative dose, the recommended maximum lifetime cumulative dose for doxorubicin is no more than 400–550 mg/m². Early studies of doxorubicin also demonstrated weekly dosing to be associated with less incidence of CHF compared with receiving the agent every 3 weeks [27]. Doxorubicin is used as the standard agent for isotoxic equivalent for risk stratification with conversion factors suggested for other agents (Table 2).

Anthracycline induced cardiotoxicity can be further defined by the acuteness of its effects. The acute form is rare, occurring in less than 1% of patients and develops at the time or within 1 week of administration of the drug and is characterized by a transient decline in myocardial contractility, which is usually reversible within weeks after discontinuation of the drug. The more frequently described chronic form can be further divided into early-onset (within the first year after treatment) versus late-onset (at least 1 year after completion of therapy), both of which are dose dependent and irreversible. The early-onset chronic form occurs in 1.6–2.1% of patients with peak incidence of 3 months post-treatment and the late-onset chronic form occurs in 1.6–5% of patient and may occur as late as 10–30 years after the first dose of treatment [28].

Anthracycline induced cardiotoxicity is exacerbated by concurrent administration of radiation therapy. A recent study of Hodgkin's lymphoma survivors showed that the risk of a

Table 2. Isotoxic conversion to doxorubicin dose equivalent.

Agent	Conversion factor (multiply with dose)
Daunorubicin	1
Epirubicin	0.67
Idarubicin	6
Mitoxantrone	4

first heart failure event was significantly greater in those who received concurrent mediastinal radiotherapy; hazard ratio (HR): 1.6; 95% CI: 0.3–7.5 versus HR: 5.4; 95% CI: 2.5–11.9 [29]. In another study of lymphoma survivors, the risk of left ventricular systolic dysfunction was significantly increased in those who received both anthracycline and radiation therapy compared with anthracycline therapy alone; odds ratio (OR): 6.0; 95% CI: 1.8–20 versus OR: 19.8; 95% CI: 5.9–66 [30].

• Trastuzumab

Trastuzumab is a humanized monoclonal antibody that targets the extracellular domain of the HER2/neu (also known as ErbB-2) receptor and is used in the treatment of HER2-positive breast cancer, gastric and esophageal cancer [31–33]. There is an overexpression of this HER2/neu receptor in about 20–30% of breast cancers and inhibition of this receptor by trastuzumab has led to significant improvement in breast cancer outcomes – studies have demonstrated up to a 40–50% reduction in recurrence of breast cancer and a 30% reduction in risk of death from breast cancer [31,32]. The HER2/neu receptor is found on cell membranes and is activated upon binding of mitogens (such as epidermal growth factor) to its extracellular domain. Once activated, several downstream pathways including PI3K/Akt and MAPK pathway promote cell proliferation and angiogenesis [34]. In addition, phosphorylation of Akt allows cells to undergo uncontrolled mitosis without being checked by cdk2. The binding of trastuzumab to HER2/neu receptor leads to inhibition of ErbB2 receptor dimerization and downstream activation of the PI3K/Akt and MAPK pathways, which cause cellular cytotoxicity, inhibition of angiogenesis, impaired DNA repair and cell cycle arrest [35].

Despite the target specific nature of trastuzumab, it is associated with a high incidence of cardiotoxicity (type 2). Data from clinical trials indicate up to a 9.8% incidence of LV dysfunction and 2.7% incidence of severe symptomatic cardiomyopathy [36,37]. The risk of cardiotoxicity with trastuzumab increases substantially when administered in combination with anthracyclines. Some studies report cardiotoxicity risks as high as 27% when trastuzumab is co-administered with anthracyclines [36]. Unlike anthracyclines, cardiotoxicity is not known to be dose dependent [38]. The exact mechanism behind trastuzumab induced cardiotoxicity remains to

be clearly elucidated. One speculation is that inhibition of HER2/neu receptor prevents activation of the NRG-1/ErbB ligand-dependent signaling pathway [39]. NRG-1 is an important signaling protein that activates the ErbB family of receptors expressed in cardiac myocytes and binding of NRG-1 to the ErbB4 receptor leads to ErbB4/ErbB2 heterodimerization that further activate downstream pathways which play an important role in cardiac myocytes ability to adapt to stress [40].

• VEGF signaling pathway tyrosine kinase inhibitors

Small tyrosine kinase inhibitors that target the intracellular domain of VEGF receptor exert their anticancer properties via halting angiogenesis [41]. At present, these drugs are among the fastest growing anticancer agents approved by or under review by the US FDA for treatment of numerous solid tumor malignancies. In addition to inhibiting VEGF receptors, these agents have effects on other tyrosine kinase mediated receptors such as PDGF, c-kit, BRAF and many others. Sorafenib and sunitinib are two of the most commonly used such agents and were FDA approved in 2005 and 2006, for multiple solid organ tumors. Sorafenib is used in the treatment of renal cell carcinoma (RCC), hepatocellular and thyroid cancer while sunitinib is used primarily in RCC, gastrointestinal stromal tumors and pancreatic neuroendocrine tumors. Initial reports suggest the incidence of heart failure to be estimated around 4–8% while the incidence of asymptomatic LV dysfunction (LVEF decline $\geq 10\%$) to be high as 28% with these agents [42,43]. However, the data on LV dysfunction secondary to these agents are based on retrospective analyses, as clinical trials involving these agents did not routinely screen for cardiomyopathy. Therefore, the true incidence of cardiomyopathy may be underestimated. Furthermore, the full extent of cardiotoxicity is yet to be determined given the novel nature of these agents.

Both sunitinib and sorafenib competitively bind and inhibit the ATP binding pocket, which is conserved across more than 500 kinases in humans [44]. Studies have demonstrated that myocardial angiogenesis inhibition by VEGF results in myocardial capillary rarefaction leading to myocardial hypoxia and activation of hypoxia-inducible genes [44]. One such hypoxia inducible gene is the HIF-1 α . HIF-1 α impairs the ability of cardiac myocytes to adapt to

pathological stress and leads to myocardial dysfunction. Interestingly, stabilization of HIF-1 α in mice has shown to reverse the cardiomyopathy suggesting that cardiotoxicity from these agents is reversible upon discontinuation of the agent [45]. More recently, animal studies have also shown that inhibition of PDGF leads to impaired activation of prosurvival pathways and increased apoptosis under conditions of increased pressure overload [46]. In addition, inhibition of PDGF by sunitinib results in coronary microvascular dysfunction due to impaired survival of pericytes, cells which are thought to play a crucial role in supporting the coronary microvasculature [46]. Interestingly, recent studies have shown that late pregnancy promotes a strong antiangiogenic environment due to secretion by the placenta of soluble Flt1 (sFlt1), which inhibit soluble members of the VEGF family, leading to myocyte dysfunction and eventually heart failure. Hence, it is postulated that the VEGF inhibitor like properties of the sFlt1 may contribute to peripartum cardiomyopathy [47]. Finally, the inhibition of multiple other kinases and downstream regulatory pathways, which are yet to be clearly elucidated, likely contribute to the cardiotoxicity of these agents.

• Hypertension

Hypertension is a common and dose dependent complication of angiogenesis inhibiting agents such as the small molecule VEGF receptor tyrosine kinase inhibitors. The incidence of all-grade hypertension due to VEGF pathway inhibitors range from 22.5 to 57.7% per a meta-analysis by Wu *et al.* [48]. The major mechanisms responsible for hypertension is yet to be clearly elucidated but a few of the proposed theories include decrease in nitric oxide in arteriolar walls [49], increased capillary permeability [50] and increased production of the potent vasoconstrictor endothelin-1 [51]. Poorly controlled pre-existing hypertension further increases the risk of developing hypertensive complications.

Screening for cardiotoxicity

At present, there are no guidelines for a single screening strategy for chemotherapy induced cardiotoxicity due to a lack of sufficient evidence base to provide recommendations on screening and surveillance intervals. Oncological and cardiac societies have provided expert consensus statements to provide guidance on the usage of varying imaging modalities, but prospective

trials are needed to validate proposed strategies. Research into more modern imaging technologies and biomarkers are ongoing in an effort to establish protocols that may aid in early recognition of patients at risk for immediate and long-term cardiotoxicity.

At present, the European Society of Medical Oncology provides comprehensive recommendations for patient monitoring for both cardiac and noncardiac sequelae based on risk factors and cumulative dose [52]. For long-term effects in survivors of childhood and young adult cancers, the Children's Oncology Group recommends yearly LVEF screening for patients who were treated at the age of 5 years or greater with a total cumulative anthracycline dose of ≥ 300 mg/m², either with or without mediastinal radiation therapy [53]. The International Late Effects of Childhood Cancer Guideline Harmonization Group, in a recent review of international consensus statements and in an attempt to provide consistency among varying surveillance recommendations, determined that patients treated for cancer as children and adolescents who were treated with a lifetime cumulative dose of ≥ 250 mg/m² and ≥ 35 Gy of chest radiation were at the highest risk of developing CHF, with no 'safe' cutoff of anthracycline dosing. They advised, at a minimum, that cardiomyopathy surveillance with echocardiography be performed no later than 2 years after completion of cardiotoxic therapy, 5 years after the diagnosis of malignancy and every 5 years after; more frequent surveillance was reasonable for high-risk individuals [54]. For active treatment surveillance in adults, the ASE and the EACVI recently released a 2014 expert consensus document for multimodality imaging evaluation during and immediately after cancer therapy, which will be summarized below [7].

• Patient selection & risk factor modification

Appropriate selection of cancer therapies and strategies is perhaps the most important factor in reducing the risk of cardiotoxicity. Every patient should undergo a detailed history and physical examination with particular attention to prior cancer treatments, cardiovascular risk factors and the cardiovascular exam. Attempts must be made to optimize pre-existing CVD risk factors prior to subjecting the patient to potentially cardiotoxic cancer drugs. Finally, the benefits of therapy must clearly outweigh the risk of cardiotoxicity.

Clinical utility of imaging modalities & biomarkers

• Echocardiography

Echocardiography is a low cost, validated, reproducible and nonradiating imaging modality for the measurement of LVEF. In addition, it allows for a comprehensive evaluation of cardiac chambers, valves, proximal great vessels and the pericardium. LVEF serves as a good surrogate of systolic function and remains the measurement of choice for diagnosing chemotherapy induced heart failure because of its availability and low cost. However, there are varying thresholds for what constitutes a clinically significant decline in LVEF. In addition factors such as loading conditions, poor imaging quality, inter-reader variability and geometric assumptions introduce further error to accurate assessment of LVEF by 2DE, which is an obstacle towards timely recognition of cardiotoxicity. Furthermore, different methods of measurement (Teicholz, Simpson's biplane or area-length) lead to variable calculations of LVEF, which further limit the ability to compare data across different centers. The accuracy of LVEF by conventional 2D echo (2DE) fails to detect small changes in LV contractility indicative of myocardial dysfunction, which precedes the decline in LVEF.

According to joint recommendations from the ASE and the EAE, the method of choice for LV volume quantification and LVEF calculation is the modified biplane Simpson's technique (method of disks) by 2DE (Figure 1). In addition, contrast is also advised for more accurate endocardial enhancement if two or more wall segments cannot be visualized [7]. A recent study using the ASE recommendations for biplane calculation of LVEF concluded that 2DE is capable of recognizing differences in sequential measurements of LVEF close to 10% in cancer patients undergoing chemotherapy who were free of HF symptoms [55]. This is the same degree of change in LVEF used to determine the presence of chemotherapy related cardiac dysfunction as well as the potential to discontinue/modify therapy, illustrating the critical need to be as precise as possible in LVEF assessment.

3DE offers better accuracy, reproducibility and lower variability in sequential measurements for monitoring LV function but its availability, high reliance on image quality and need for trained personal limit its application in the clinical setting. Studies looking at use of contrast, diastolic parameters and stress echocardiography failed to show that these indices add significant prognostic

information to that obtained from measurement of LVEF alone by 3DE [55]. Finally, no echocardiographic studies to date that have shown that changes in diastolic parameters or early subclinical drop in LVEF can accurately predict subsequent clinical cardiotoxicity. Recently, there has been a growing interest in alternative echo parameters such as myocardial strain that detect early myocardial dysfunction when the LVEF is still normal and predict subsequent LV dysfunction and progression to overt cardiomyopathy. This has important clinical implications due to a high rate of failure – up to 58% – for complete recovery of LVEF if there is a significant delay from time of diagnosis of LV dysfunction to initiation of pharmacologic therapy [56–58].

Studies looking at chemotherapy induced myocardial dysfunction have demonstrated changes in myocardial deformation prior to changes in LVEF [59]. Myocardial deformation can be easily quantified by measuring LV strain [60]. Strain is a mechanical property inherent to any material. It is a dimensionless index and reflects the total deformation or stretch of the ventricular myocardium during a cardiac cycle as a percentage of its initial length [60,61]. The strain rate is the rate of this deformation. Both these indices can be measured in the longitudinal, radial and circumferential direction and possess the ability to differentiate active versus passive movement within a myocardial segment [61]. Initially, myocardial strain and strain rate was measured with tissue Doppler imaging (TDI). However, TDI is limited by angle dependency, aliasing and significant noise. In comparison, speckle tracking echocardiography (STE) based strain can be obtained at lower frame rates using standard 2D images and has superior reproducibility to TDI [61].

A recent systematic review looking at the use of myocardial strain imaging by echo for early detection of cardiotoxicity in patients during and after cancer chemotherapy showed that changes in myocardial deformation occurred earlier than changes in LVEF and at anthracycline doses lower than previously thought to be cardio-toxic [59]. With TDI, peak systolic longitudinal strain rate was the most consistent parameter that detected myocardial changes during therapy while peak systolic global longitudinal strain (GLS) was the best parameter using STE [59]. A 10–15% early reduction in GLS by STE during chemotherapy was the most useful parameter for prediction of cardiotoxicity (Figure 2) [59]. Further research is needed to validate these findings in larger

Figure 1. Example of modified biplane Simpson's technique for left ventricular volume quantification and left ventricular ejection fraction assessment. The left ventricular endocardium is traced in both the (A) four-chamber apical view and the (B) two-chamber apical view for more precise assessment of left ventricular ejection fraction.

studies as well as examine the clinical utility of novel parameters such as 3DE strain and RV dysfunction.

• Cardiac MRI

Cardiac MRI (CMR) has superseded planar multigated radionuclide angiography (MUGA) to become the noninvasive reference standard for volumetric measurement of cardiac chamber size and ventricular function due to its excellent spatial resolution, lack of ionizing radiation exposure and assessment of cardiac chamber volumes, valvular function and other extracardiac vascular structures. CMR provides excellent image quality regardless of body habitus. As a nonionizing imaging technique, the strength of CMR lies in its ability to manipulate and measure tissue characteristics based upon relaxation properties of the myocardial tissue, which are quantified and measured as T1, T2 or T2* [62]. Myocardial tissue characteristics (inflammation, edema, fibrosis, fibrofatty infiltration) based upon the macromolecular properties and microstructural composition of the myocardium can be described by using select pulse sequences (Figure 3). Moving beyond ventricular function, chamber volume and tissue characteristics, CMR can also quantify myocardial perfusion (useful for diagnosis of coronary disease and microvascular changes), myocardial tissue deformation, valvular disease and vascular distensibility. At select institutions, coronary artery imaging, large vessel plaque imaging and dynamic vascular imaging

can also be performed in the context of a CMR examination.

As an example, Wassmuth *et al.* assessed myocardial inflammation using T1-weighted fast-spin sequences in a cohort of patients receiving anthracycline [63]. They found that a ratio of signal intensity differences between myocardial and skeletal tissue between pre- and post-contrast acquisition ≥ 5 arbitrary units on day 3 was associated with a reduction in LVEF at 28 days. Additional studies based on T2-weighted imaging with T2 mapping also indicate a possible association with myocardial edema [64]. Data also exist to correlate abnormal myocardial deformation [65] and diffuse myocardial fibrosis (measured by extracellular volume using T1 mapping) with functional capacity [66].

Overall, CMR should be viewed as a secondary modality in the evaluation of cardiotoxicity, particularly when cardiopulmonary symptoms are present in the absence of systolic dysfunction by echocardiography, or if there is equivocal and/or suboptimal visualization of the LVEF. However, availability of expertise, higher cost, and exam duration limit its wide clinical utility. CMR may be less ideal for those with profound claustrophobia. For patients with arrhythmias, image quality may be impaired, but solutions are available to accommodate certain rhythms. In addition, implantable cardiac devices (i.e., pacemakers) have been an impediment to undergoing CMR. Because of the comprehensive nature of CMR, communication between the imagers and ordering

Figure 2. Measurement of myocardial strain using speckle tracking echocardiography in detecting subclinical cardiotoxicity. Shown is serial echocardiographic myocardial strain imaging in a 62-year-old female with breast cancer undergoing chemotherapy with anthracyclines, demonstrating an apical four-chamber global longitudinal strain decreasing from (A) -13.0% to (B) -10.0% over a 5-month period – a relative >10% reduction in global longitudinal strain. This is indicative of subclinical cardiotoxicity despite having no obvious change in left ventricular systolic function.

providers is often recommended to optimize the quality and shorten the exam duration as much as feasible. Active technical development and clinical research efforts are underway to streamline clinical imaging techniques and explore CMR markers of early cardiotoxicity. The 2014 ASE/ESCAI expert consensus statement now also advises follow-up imaging with CMR for abnormal LVEFs that are less than 53% for more precise assessment.

• Nuclear imaging

MUGA was a widely used modality to accurately assess LVEF prior to the wide availability of echocardiography. Studies have shown that it is better than conventional 2D with respect to accuracy and reproducibility making it very desirable for serial testing [67]. The main disadvantages of MUGA are radiation exposure and inability to provide additional information on RV function, atria, valvular disease, or pericardial abnormalities. Furthermore, recent advances in echocardiographic imaging (3DE and deformation indices) have resulted in a decline in the utility of MUGA for routine screening of cardiotoxicity. However, it may continue to serve as an appropriate imaging modality in patients with poor acoustic windows and devices (pacemakers and defibrillators) in whom, echocardiography and CMR data may be suboptimal. Other advanced functional imaging techniques are being evaluated for applications

in evaluating subclinical cardiotoxicity, such as ^{123}I -metaiodobenzylguanidine scintigraphy, which images the efferent sympathetic nervous innervation distribution of the heart, sympathetic neuronal PET, and ^{111}In -antimyosin which visualizes myocardial cell injury and necrosis can potentially yield further insights into cardiotoxicity. However, prospective trials to evaluate efficacy and prognosis in these technologies are lacking [68].

Biomarkers

Screening of patients for cardiotoxicity has traditionally relied on measurement of LVEF to detect systolic dysfunction. However, this approach lacks sensitivity to detect subclinical myocardial dysfunction that is observed in the early stages of chemotherapy induced cardiotoxicity. Newer metrics are needed to help identify at risk patients during the early preclinical stage of cardiotoxicity. Certain biomarkers have been studied for this purpose and offer additional prognostic value when combined with imaging to identify patients at increased risk for adverse outcomes. Even prior to cancer treatment, elevated cardiovascular hormone levels (i.e., NT-proBNP, proadrenomedullin high sensitivity troponin-T, pro-endothelin-1) in cancer patients are associated with an increase in all-cause mortality [69]. Such cardiac biomarkers that have been studied during cancer treatment are outlined as below.

• Troponin I

Cardiac troponins have been extensively studied and validated as a robust indicator of myocardial injury [70]. Elevation of troponin I (TnI) soon after chemotherapy predicts future development of systolic dysfunction and identifies patients at risk for future cardiac events [71]. Cardinale *et al.* showed that in a population treated with high-dose chemotherapy, troponin release patterns (early; within 72 h vs late; 1 month after therapy) identified patients at different levels of risk for future cardiac events. This group further showed that the presence of persistently elevated TnI was associated with more severe cardiotoxicity and a higher incidence of subsequent cardiac events [71]. Another study by the same group, looking at breast cancer patients treated with trastuzumab showed that cardiotoxicity occurred more frequently in patients with TnI elevation versus those without (62 vs 5%; $p < 0.001$) and that LVEF recovery was impaired in patients with a positive TnI versus those without (35 vs 100%; $p < 0.001$) [72]. In studying 78 breast cancer patients undergoing anthracycline and trastuzumab treatment, Ky *et al.* measured eight biomarkers: ultrasensitive TnI, high-sensitivity C-reactive protein (CRP), NT-proBNP,

GDF-15, myeloperoxidase (MPO), placental growth (PIGF), sFLt-1 and gal-3. A greater risk of cardiotoxicity was associated with interval changes in the TnI (HR: 1.38; 95% CI: 1.05–1.81; $p = 0.02$) and MPO (HR: 1.34; 95% CI: 1.00–1.80; $p = 0.048$) [72]. Currently, however, TnI is not in widespread use to assess for cardiotoxicity in part due to insufficient data defining the appropriate timing/frequency of measurement as well as the optimal cutoff value that would provide the best positive and negative predictive values. Further large scale studies are needed to answer these questions prior to incorporating TnI as part of a routine cardiotoxicity screening protocol.

• Other biomarkers

Studies have looked at the utility of other biomarkers such as CRP, NT-proBNP and those previously mentioned in Ky *et al.* in predicting cardiotoxicity but results thus far have been inconclusive or negative [73]. A large-scale study which is currently underway, the PREDICT study, is evaluating the effectiveness of using biomarkers to detect and identify cardiotoxicity in patients being treated with anthracyclines and will hopefully provide further insight into the clinical utility of biomarkers [74].

Figure 3. Cardiac MRI of a 44-year-old male who had acute myeloid leukemia as an adolescent and was treated with anthracycline and radiation therapy. Late gadolinium enhancement images were acquired on a 1.5 T magnet using a phase-sensitive inversion recovery fast gradient echo sequence. (A) The short axis image demonstrates hyper enhancement of the anterior and posterior right ventricular insertion sites (thin arrows) and mid-wall hyper enhancement of the inferior and inferolateral walls (thick arrows). Epicardial hyperenhancement of the anteroseptal wall is noted (asterisks), along with patchy right ventricular free wall and pericardial hyperenhancement (circle). (B) The long axis image of the left ventricle demonstrates epicardial enhancement of the basal anterior wall and patchy mid-wall/intermediate hyperenhancement of the basal to apical inferior wall.

Cardiotoxicity management strategies & cardioprotective agents

The effective management of chemotherapy-induced cardiotoxicity requires strategies aimed at treating baseline CVD risk factors, strategies aimed at preventing cardiotoxicity before or during cancer therapy and strategies aimed at treating subclinical or clinical evidence of cardiotoxicity. Despite the limited studies available investigating cardioprotective agents, it is clear that prevention along with early recognition and initiation of therapy provides the best chance of recovery from cardiotoxicity.

• Dexrazoxane

Dexrazoxane is a potent intracellular iron chelator and prevents the formation of anthracycline-iron complexes, consequently decreasing the formation of reactive oxygen species [75]. In addition to its iron chelating properties, dexrazoxane also inhibits formation of drug-induced Top2 α and Top2 β DNA cleavage complexes [76]. Lyu *et al.* showed that dexrazoxane binds the Top2's ATP-binding site thereby altering Top2's configuration to a closed-clamp form and prevent binding of anthracycline to the Top2 complex [76]. This is thought to be the main mechanism behind cardio-protection as other pure iron chelators have failed to show a benefit after anthracycline therapy [75]. A recent Cochrane meta-analysis that looked at pooled data from eight randomized control trials showed that dexrazoxane use in the setting of anthracycline therapy was associated with greater than 80% reduction in the incidence of clinical heart failure (relative risk: 0.18; 95% CI: 0.10–0.32; $p < 0.0001$) [77]. However, there was a trend towards a lower response rate in the dexrazoxane treated groups versus control, which was not statistically significant but does raise concerns about its effects on antitumor efficacy [77]. Another concern was reports from one study of increased secondary malignancies in children that received dexrazoxane as part of a Hodgkin's lymphoma regimen [78]. However, the above Cochrane review and a study by Salzer *et al.* did not show a significant difference in the occurrence of secondary tumors in children treated with and without dexrazoxane (RR: 1.16; 95% CI: 0.06–22.17; $p = 0.92$) [77,79]. At present, dexrazoxane is only FDA approved for use in advanced cancers (metastatic) and in adults who have received greater than 300 mg/m² of doxorubicin or other anthracycline dose equivalents and is used off-label in pediatric populations [80].

• Angiotensin converting enzymes inhibitors

Angiotensin-converting enzyme (ACE) inhibitors form the cornerstone for treatment of systolic heart failure with several large randomized controlled studies demonstrating a clear mortality benefit [81]. However, data on ACE inhibitors for primary and secondary prevention of cancer therapy induced cardiotoxicity remain scarce with only a few small human studies published to date. Nevertheless, findings thus far are encouraging and suggest a protective role for ACE inhibitors in cancer-induced cardiotoxicity. A study of patients randomized to enalapril or placebo following high-dose anthracycline therapy showed a significant reduction in LVEF (>10% to LVEF <50%) occurred in 43% of control patients at 12 months compared with none in the enalapril group [82]. There were also 30 cardiac events in the control group compared with only 1 in the enalapril group [82]. In another study of 120 patients with advanced breast cancer, among patients who developed heart failure, enalapril improved the NYHA functional class and reversed the LVEF decline (relative LVEF increase $\geq 15\%$) in seven of eight patient compared with only one of 33 untreated patients [83]. Finally, an observational study by Cardinale *et al.* in 221 patients with LVEF $\leq 45\%$ due to anthracycline cardiotoxicity showed that prompt initiation of enalapril with addition of carvedilol as tolerated led to normalization of LVEF in 42% of patients [12]. These findings have led to consensus advocating ACE inhibitor as first line agents in treating anthracycline induced cardiotoxicity. At present, there is no robust data for angiotensin receptor blockers but given the similar action on the renin angiotensin aldosterone system they should be considered in those with a contraindication to ACE inhibitors.

• Beta blockers

Beta blockers are the second main class of drugs shown in small trials to potentially decrease the risk of developing cancer therapy induced cardiomyopathy. However, the beneficial effects of this class have only been studied in limited fashion, with agents such as carvedilol and nebivolol. A study of 45 patients with breast cancer randomized to placebo versus prophylactic nebivolol 7 days prior to treatment with anthracyclines and continued for 6 months showed a lower LVEF in the placebo group compared with the nebivolol group [84]. The beneficial effects of carvedilol in the treatment of anthracycline induced

cardiotoxicity have been shown is several other studies [85–87]. Finally, the OVERCOME trial showed that treatment with carvedilol in combination with enalapril resulted in a lower incidence of the combined event of death or heart failure (6.7 vs 22%; $p = 0.036$) and of death, heart failure, or a final LVEF $<45\%$ (6.7 vs 24.4%; $p = 0.02$) compared with placebo [88]. These data suggest that initiation of combined therapy with ACE inhibitor and selective β -blockers at the earliest detection of cardiotoxicity may provide the best chance of reversing left ventricular dysfunction.

• Statins

Numerous studies have demonstrated the beneficial lipid lowering effects of statins and its associated reduction in morbidity and mortality. In addition, statins have also been shown to possess anti-inflammatory and antioxidant properties, the so-called pleiotropic effects. Given that a major mechanism of anthracycline mediated cardiotoxicity is secondary to oxidative stress and inflammation, one might postulate that the pleiotrophic effects of statins may protect against such cardiac injury. *In vitro* studies have shown that statins reduce anthracycline mediated cardiomyocyte cell death and impair Rac1 signaling thereby reducing Top2 β -mediated DNA damage [89,90]. In a study of men undergoing anthracycline therapy, use of daily atorvastatin 40 mg prior to therapy and continued for 6 months was associated with preservation of LVEF, LV systolic and diastolic parameters compared with controls [91]. The statin group also had no elevation in serum hsCRP levels compared with significant increase in the control group (3.84 ± 0.89 mg/dl vs 5.43 ± 1.78 mg/dl; $p < 0.0001$) [91]. These data emphasize the need for further human studies with larger sample sizes and sound research methodology to better elucidate if there is a cardioprotective effect of statins in this population.

As the populations of cancer survivors continue to grow, we will undoubtedly encounter more and more patients across various clinical settings presenting with cardiac complications of cancer therapy. Hence, there is a need for continued understanding of these disease processes so as to enable us to provide the best evidence based care to our patients. Given the relative complex, specialized and novel nature of this entity, the care of these patients is best formulated in collaboration with a cardiologist and oncologist. Employing a multidisciplinary approach early on will ensure timely implementation of cardioprotective therapy

and screening protocols if indicated. According to ASE/EAE recommendations, cardiology consultation should be sought during surveillance imaging if the LVEF is $<53\%$, GLS is below the limit of normal, and/or troponins are elevated so that risk-benefit ratio of continuing cancer therapy can be discussed with the patient's oncologist as well as consideration of initiation of cardioprotective therapies [7].

Future perspective

Over the past decade, the field of oncology has witnessed an exponential growth of novel anti-cancer drugs. This has resulted in remarkable strides in the fight against cancer with significant improvements to patient morbidity and mortality. As a result, with the increase in cancer survivors on an international scale, physicians are likely to encounter more patients with cardiotoxic manifestations of cancer therapy. However, these findings and recommendations on surveillance and treatment are based on relatively small studies, retrospective data and consensus statements based on expert opinion, emphasizing the need for continued understanding of this nascent field. Prospective, randomized trials are needed on a wider scale in high risk individuals – both those actively receiving therapy and survivors of 'high-risk' cancer therapy and/or radiation therapy – to evaluate the clinical efficacy of pharmacologic interventions. In addition, the evolution of advanced imaging modalities have made more accurate LVEF assessment possible with minimal or no exposure to radiation, along with noninvasive techniques to detect subclinical cardiotoxicity being made more readily available through echocardiography and CMR; as before, larger prospective trials are needed to evaluate the impact of abnormal findings – and subsequent intervention – on surveillance imaging. These are amongst the varied and numerous aims in the growing field of cardio-oncology, which holds significant potential for new and exciting discoveries in areas such as pathophysiology, diagnostic modalities (biomarkers and imaging) and pharmacologic interventions. Research opportunities at a basic science, translation and clinical level can potentially reveal insights into overlapping mechanisms of conventional cardiovascular disease states (i.e., CHF, coronary artery disease) and cardiotoxicity from both old and new and upcoming cancer agents.

Finally, and most importantly, these efforts are not an attempt to deter cancer therapy, but to promote further collaboration between both

EXECUTIVE SUMMARY

Cancer survivor epidemiology

- The population of cancer survivors in the USA is projected to increase to 19 million by 2024.
- Because of the prolonged survival rates of cancer survivors due to advances in chemotherapy and radiation treatments, cardiovascular disease (CVD) that is both inherent to the patients' baseline risk factor profile and CVD that can develop with certain treatments will be a short- and long-term concern that requires vigilant monitoring.
- As per the "multiple-hit" hypothesis, patients with pre-existing CVD risk factors undergoing chemotherapy are more likely to develop cardiotoxic manifestations due to both direct toxic effects as well as indirect detrimental effects with derangements in dietary and lifestyle factors.

Definitions of cardiotoxicity

- As per the 2014 American Society of Echocardiography/European Association of Cardiovascular Imaging expert consensus statement, the definition of cancer therapeutics-related cardiac dysfunction is either a decrease in the left ventricular ejection fraction (LVEF) of $>10\%$ and/or a value of $<53\%$ during treatment.
- Type 1 cardiotoxicity, associated with anthracycline use, is characterized by myocardial injury and is more likely to be irreversible, even with intervention or termination of the offending agent.
- Type 2 cardiotoxicity, associated with trastuzumab use, has a higher likelihood of recovery after discontinuation of the offending agent.

Chemotherapeutic agents associated with cardiotoxicity

- Anthracyclines are thought to induce cardiotoxicity via two major mechanisms: cytotoxicity and impaired mitochondrial function through oxidative stressors from iron and free radical generation; and disrupting the topoisomerase 2β enzyme which is responsible maintaining DNA transcription, replication and recombination by winding its double helix structure.
- Congestive heart failure is the most common manifestation of anthracycline induced cardiotoxicity and is dose dependent.
- Trastuzumab, a monoclonal antibody, is thought to cause cardiotoxicity by inhibiting the HER2/neu receptor, which prevents activation of the NRG-1/ErbB ligand-dependent signaling pathway, which may interfere with cardiac myocytes' ability to adapt to stress as well as DNA repair mechanisms. This risk of cardiotoxicity can be compounded with concurrent anthracycline use and is not dose dependent.
- VEGF signaling pathway tyrosine kinase inhibitors can cause cardiotoxicity by inhibiting myocardial angiogenesis and activating hypoxia-inducible genes (i.e., HIF- 1α), which impairs cardiac myocytes' ability to adapt to pathological stress, and can lead to myocardial dysfunction.
- Other known cardiotoxic clinical manifestations from chemotherapeutic agents include myocardial ischemia, hypertension, arrhythmias and/or QT prolongation, and arterial/venous thrombosis.

Screening for cardiotoxicity

- Currently, there are various expert consensus statements but no definitive screening guidelines for short- and long-term cardiotoxicity, due to a lack of sufficient evidence base to provide recommendations on screening and surveillance intervals.
- Attempts should be made prior, during, and after cancer treatment to optimize pre-existing CVD risk factors as best as possible, particularly if the patient will be exposed to potentially cardiotoxic therapy.
- The most optimal methods of determining LVEF by echocardiography, if available, include 2D-modified biplane Simpson's technique or 3D LVEF assessment.
- Myocardial deformation assessment by left ventricular global longitudinal strain measurement has been shown in early studies to be a useful tool in predicting prognosis and the development of cardiotoxicity.

EXECUTIVE SUMMARY**Screening for cardiotoxicity (cont.)**

- Cardiac MRI has replaced multigated radionuclide angiography (MUGA) to be the noninvasive reference standard for volumetric measurement of cardiac chamber size and ventricular function given its superior spatial and temporal resolution and lack of ionizing radiation. It should be considered if initial noninvasive imaging (i.e., echo, MUGA) suboptimal and may influence treatment strategies. However, cost and varying expertise in implementing imaging protocols may affect its availability and usage.
- Out of all the cardiac biomarkers, elevation of troponin I has been consistently been found in multiple small studies to be the most predictive of increased risk for cardiotoxicity during cancer treatment; however, optimal timing and frequency of checking levels and cutoff values have yet to be determined.
- Cardioprotective agents that have been shown in limited trials to reduce the incidence of cardiotoxicity include dexrazoxane (to prevent anthracycline-induced cardiomyopathy), angiotensin-converting enzyme inhibitors, and β -blockers.
- Cardiology consultation should be sought during cancer treatment if the LVEF <53%, global longitudinal strain is below the limit of normal, and/or serum troponins are elevated.

Conclusion

- The field of cardio-oncology has many opportunities at the basic science, clinical, and translational level to explore overlapping mechanisms of chemotherapy induced cardiotoxicity and conventional cardiovascular disease, potentially providing insight into novel mechanisms afflicting both cardiac and oncologic disease processes.
- Further large scale, prospective randomized trials are indicated to evaluate the efficacy of surveillance imaging strategies, biomarker utilization, as well as cardioprotective preventative strategies.
- The overall goal of the field is to not deter cancer therapy, but to optimally identify patients at risk for cardiotoxicity and implement cardioprotective strategies as early and effectively as possible so they can continue to undergo potentially lifesaving treatment for their cancer.

fields of cardiology and oncology to optimally identify patients at risk for cardiotoxicity and implement cardioprotective strategies as early and effectively as possible so they can continue to undergo potentially lifesaving treatment with minimized cardiac risk, and to also provide optimal surveillance to detect long-term cardiotoxic sequelae – some of which have yet to be discovered with the ongoing development of new chemotherapeutic agents.

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