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The Role of Biomarkers in Detection of Cardio-toxicity

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Abstract The goal of this paper is to review the current literature on the role of biomarkers in the detection and management of patients with cardio-oncologic disease. The role of biomarker surveillance in patients with known cardiac disease, as a result of chemotherapy or with the potential to develop cardio-toxicity, will be discussed. In addition, the studies surrounding sub-clinical cardiac toxicity monitoring during therapy, identification of high-risk patients prior to therapy, and tailoring oncologic therapies to potential biomarker risk profiles are reviewed. Based on evidence, to date, troponin and natriuretic peptides have the greatest potential to detect sub-clinical cardiac dysfunction and even tailor therapy to prevent progression based on biomarker profiles. Finally, future directions for potential utilization of novel biomarkers for the improvement of care of patients in the field of cardio-oncology are discussed.

Keywords Cardio-toxicity · Detection · Cardio-oncology · Biomarkers · Heart failure

This article is part of the Topical Collection on *Cardio-oncology*

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Introduction

The field of oncology has made significant progress over the past decade with advancement of targeted therapies for multiple malignancies. These novel agents have been successful in improvement of survival and quality of life in many patients with cancer. However, many of these agents have known adverse cardiovascular effects, which have led to the burgeoning field of cardio-oncology: the cardiovascular care of cancer patients. The conventional monitoring strategies for these effects have been limited to periodic clinical and imaging assessments. These often leave those engaged in surveillance only able to detect cardio-toxic effects when a functional impairment has already occurred.

Biomarkers are a part of the cornerstone of the initial evaluation and management of patients at risk and with known cardiovascular disease. The role of biomarkers in cardio-oncology may be multi-dimensional. Biomarkers can play a role in identification of high-risk patients for cardiovascular adverse events prior to initiation of therapy. Additionally, they may complement imaging during active therapy to detect sub-clinical disease. Finally, the potential for tailoring oncologic therapy or preventive cardiovascular therapy partly based on cardiac biomarker profiles would be an idealistic role for the future.

What Is Cardio-toxicity and Who Is at Risk?

The possible adverse cardiovascular effects from cancer treatment are broad. In 2013, the National Cancer Institute and the National Heart, Lung and Blood Institute created a framework for defining cancer treatment-related cardio-toxicity [1]. Cardio-toxicity includes, but is not limited to, ventricular dysfunction, heart failure (HF), arrhythmias, coronary artery

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disease/acute coronary syndrome (ACS), hypertension, and thromboembolic events [2]. The exact prevalence of these conditions in the context of cancer therapy is not clear. While likely an oversimplified classification which does not adequately represent the complex effects of multiple chemotherapeutic agents, two major types of cardiac injury have been proposed: type 1 chemotherapy-induced cardio-toxicity (direct myocyte death) and type 2 chemotherapy-induced cardio-toxicity (reversible myocyte dysfunction). Agents associated with type 1 cardio-toxicity (i.e., anthracyclines) have been thought to be associated with propensity to cause long-term effects, thus driving the need to develop more refined diagnostic tools to gauge lifetime risk. On the other hand, chemotherapy associated with type 2 cardio-toxicity (i.e., trastuzumab) typically is not thought to be associated with long-term cardio-toxicity.

With respect to risk factors for development of cardio-toxicity, it is established that cumulative dose of chemotherapeutic agents, amount of irradiation, and age are independently associated with a higher risk of developing cardiotoxicity [3]. Risk factors such as diabetes and alcohol consumption have been shown to increase the risk of cardio-toxicity in patients on anthracycline therapy [4]. Comorbidities including coronary artery disease, hypertension, obesity, and tobacco use are also associated with increased risk of left ventricular (LV) dysfunction and symptomatic HF in breast cancer patients on therapy with the monoclonal antibody trastuzumab [5]. These pre-existing comorbidities, prior to a diagnosis of cancer, increase the risk of development of cardiovascular disease. Some authors argue for a "multiple-hit" hypothesis, where adjuvant chemotherapy causes a direct cardio-toxic effect while lifestyle risk factors cause indirect effects, synergistically increasing the risk of CVD [6].

Anthracyclines and radiation therapy were first identified as causing cardiovascular complications [7••]. Adverse cardiovascular effects include arrhythmias, cardiac dysfunction, myocarditis, and pericarditis. HER2 inhibitors (i.e., trastuzumab), vascular endothelial growth factor (VEGF) signaling inhibitors, and multi-targeted tyrosine kinase inhibitors have all shown varying incidences and severity of cardio-toxic effects [7••, 8]. As the number of anti-cancer therapies increase, increased vigilance for surveillance and detection of both known and unanticipated cardiac adverse effects is warranted.

The timing of cardio-toxicity may be acute, sub-acute, or years after exposure to oncologic therapies. LV dysfunction or clinical HF is one of the more commonly recognized and routinely measured adverse effects of chemotherapies. Current strategies often rely on routine echocardiography to evaluate for new or progressive LV dysfunction. Biomarkers may provide insight into cardiac injury at early stages of the disease. Risk factor scores to predict development of HF in patients taking trastuzumab include typical comorbidities (age, coronary artery disease, atrial fibrillation/flutter, hypertension, etc.) as predictors of the 3-year risk for development of HF [5]. These risk score have not assessed biomarkers as a part of the prediction profile. In addition to prediction prior to initiation of therapy, there may be a role for cardio-toxicity surveillance during therapy. The question remains: What outcome will be measured? Small studies have utilized echocardiographic parameters such as LV ejection fraction (LVEF), strain, and fractional shortening [29]. The third area where there is a significant need to be filled is the long-term detection after therapy for development of CVD. Despite the rising body of literature in this field, the potential length of time after cancer therapy and development of cardio-toxicity—and the ideal duration of cardio-toxicity surveillance for each chemotherapeutic agent—is unclear.

The Role of Biomarkers

A biomarker is a measurable substance whose presence is an indicator of physiology, pathophysiology, or response to therapy. The ideal biomarker has either high sensitivity or specificity. It should be measureable and reproducible with a cost-effective assay. Ideally, the use of biomarkers would be able to improve clinical outcomes for patients at risk for, or with known cardio-toxicity [9••].

Troponin

Cardiac troponin (cTn) is a protein complex integral to myocardial contraction. Detectable serum levels of cTn are an indicator of heart muscle damage. Measurement and interpretation of troponin are part of the diagnosis of acute myocardial infarction (AMI) and workup of possible cardiac chest pain [10]. Although not specific to myocardial infarction, detectable troponin is extremely sensitive in the diagnosis of AMI. High-sensitive troponin assays have demonstrated the ability to improve time to diagnosis of AMI as well as predict CVD in those without symptoms or known CVD [11, 12]. Measureable levels using contemporary or high-sensitive troponin assays are indicative of underlying cardiac damage in ACS and other pathologic conditions including HF, pulmonary embolism, and arrhythmias.

Multiple studies have established the validity of cTn in detecting cardiovascular disease in patients receiving oncologic therapy, specifically addressing surveillance during therapy. One analysis of 703 patients with cancer (primarily breast cancer) measured cTn immediately after chemotherapy and 1 month later [13]. These patients were followed for development of adverse cardiovascular event, defined as cardiac death, acute pulmonary edema, overt HF, LVEF reduction by ≥25%, or life-threatening arrhythmia. Individuals who

had early elevations and persistent cTn elevation (≥0.08 ng/mL) had the greatest incidence of adverse event (84 versus 37%) as compared to the group which were initially positive and became negative. This study identified patients at risk 3 years after initial therapy. A smaller cohort (204) of patients with aggressive malignancies had cTn measured after every single cycle of high-dose chemotherapy [14]. In the subjects (31.8%) who had elevated cTn (≥0.5 ng/ml), LVEF reduction was more marked with cancer therapy and remained reduced through 9 months of follow-up. These two studies demonstrate the value of contemporary cTn measurement for surveillance in patients receiving high-dose chemotherapy as a sensitive and reliable marker of minor myocardial damage, often preceding LV dysfunction.

High-sensitive cTn assays are currently in widespread use in Europe and will eventually be incorporated in the USA as part of routine clinical care [15]. As a part of an analysis of patients with non-Hodgkin's lymphoma receiving the anthracycline epirubicin, high-sensitive troponin and echocardiography with strain was performed during therapy. Levels that were greater than 0.004 ng/mL or a decrease in global longitudinal strain on echocardiography predicted post-chemotherapy LVEF reduction. Furthermore, a study of 18 patients with non-Hodgkin's lymphoma and breast cancer demonstrated that patients with an elevated baseline high-sensitive cTn was associated with an increased incidence of LVEF decline with doxorubicin therapy [16•]. Although these studies are small, they suggest that utilization of high-sensitive cTn assays may identify patients at elevated risk for cardio-toxicity prior to and during therapy. Recently, a brief report of two cases was published, demonstrating fulminant myocarditis which developed in patients with melanoma taking immune checkpoint inhibitors [17]. This is a rare, but potentially fatal, complication, and the authors of this brief report recommended weekly measurement of troponin during weeks 1–3 for patients receiving combination immunotherapy.

Survivors of childhood cancers represent a growing group of patients studied to screen for late adverse cardiac effects from chemotherapy agents. Multiple studies have shown that in childhood cancer survivors who were treated with anthracycline therapy, cTn and hs-cTn were not elevated in patients who developed cardiac dysfunction on imaging [18–20]. These studies demonstrate that troponin may not be a sensitive marker for late onset sub-clinical cardio-toxicity.

Natriuretic Peptides

Natriuretic peptides (NPs) have an important role in the diagnosis, risk stratification, and long-term management of patients with congestive HF. Low values in patients with dyspnea have excellent negative predictive value for the rule-out of acute decompensated HF [21, 22]. The release of NPs from cardiac myocytes is indicative of underlying pressure overload and myocardial wall stretch. The potential attractiveness of NPs, as a marker for cardio-toxicity, is their ability to showcase underlying hemodynamic stress, possibly prior to clinical decompensation.

A single-center study of 109 cancer patients who received anthracycline-based chemotherapy had surveillance echocardiography and B-type natriuretic peptide (BNP) monitoring. During follow-up, 10.1% of patients experienced a cardiac event (LV dysfunction, symptomatic HF, arrhythmia, sudden cardiac death, or ACS) and all had at least one BNP > 100 pg/mL prior to event [23•]. This study demonstrated the potential utility of using point-of-care periodic BNP measurements during therapy to complement imaging in detection of cardiotoxicity. Similarly, in children who receive doxorubicin therapy, BNP monitoring during treatment identified those who developed cardiomyopathy [24]. In another small study, BNP was measured immediately after radiation therapy in 43 subjects with left-sided breast cancer. Study protocol arranged for BNP to be measured prior to therapy and serially through 12 months after therapy [25]. Patients were followed up for a median time of 87 months. None of these patients developed HF, although small elevations in BNP were detected after radiation therapy (RT), which may indicate an early marker of myocyte stress. A small number of subjects (4) experienced cardiovascular events, and all had BNP values rise and remain higher than basal values. BNP may have value as a marker of early RT-related CVD, especially those at elevated risk for CAD.

When the precursor to BNP (pre-proBNP) is released from myocytes, it is cleaved into BNP and the biologically inactive N-terminal fragment, NT-proBNP, another commonly used biomarker in HF management. Another small study assessed the role of NT-proBNP and its association with LV dysfunction after high-dose chemotherapy in patients with aggressive malignancy [26]. This study demonstrated worsening systolic and diastolic function in patients whose NT-proBNP levels remained elevated (mean 1163 ng/L) 72 h after infusion therapy. Another study used NT-proBNP to screen for heart disease in patients with cancer presenting with dyspnea [27]. They determined that a cutoff of 100 pg/mL had useful sensitivity but low specificity, as it was elevated in patients with CAD, atrial fibrillation, LV dysfunction, LVH, and valvular heart disease. Both BNP and NT-proBNP have demonstrated the potential to serve as biomarkers to indicate sub-clinical cardiac dysfunction in the context of cardio-toxicity. Given the multitude of studies performed examining cTn and NPs in the context of cardio-toxicity detection, Table 1 summarizes the larger trials published thus far.

Table 1 Troponin and NPs as Biomarkers and Current Evidence for Cardio-Toxicity

Study	Biomarker	Timing	Therapy	Outcome	Utility
Troponin					
Cardinale et al. [28]	Troponin I	Baseline	Trastuzumab	LVEF decline >10% from baseline, associated with a decline below 50%, asymptomatic	Positive
Fallah-Rad N et al. [29]	Troponin T	During therapy	Trastuzumab	LVEF decline at least 10%, below 55%, symptomatic	Neutral
Morris et al. [30]	Troponin T	During therapy	Doxorubicin and cyclophosphamide ≥ Paclitaxel and Lapatinib	LVEF decline >10 to <50%, asymptomatic	Positive
Sawaya et al. [31]	High-sensitivity cardiac troponin I	Baseline and during therapy	Anthracyclines and trastuzumab	LVEF reduction ≥5 to <55% with HF symptoms or asymptomatic reduction of the LVEF of ≥10 to <55%	Positive
Ky et al. [32]	Troponin I and myeloperoxidase	During therapy	Doxorubicin and trastuzumab	Decline in LVEF of at least 10 to <50%, asymptomatic	Positive
Putt M et al. [33]	High-sensitivity troponin I, myeloperoxidase and GDF-15	Baseline and during therapy	Doxorubicin and trastuzumab	Reduction in LVEF of ≥5 to <55% with HF symptoms or an asymptomatic reduction in LVEF of ≥10 to <55%	Positive
Natriuretic peptides					
Romano et al. [34]	NT-proBNP	Baseline and during therapy	Doxorubicin and docetaxel or epirubicin with fluorouracil and cyclophosphamide	LVEF decrease ≥20% and/or an increase in LVESV of ≥15%, asymptomatic	Positive
Kittiwarawut A et al. [35]	NT-proBNP	Baseline and during	Doxorubicin and cyclophosphamide	Grade I–V, ranging from asymptomatic LVEF reduction to death	Positive
Lenihan DJ et al. [23•]	BNP	Baseline and during	Anthracycline	Asymptomatic LV dysfunction >15%, symptomatic HF, symptomatic arrhythmia, sudden cardiac death, or ACS	Positive
Sandri, et al. [26]	NT-proBNP	Before and during	Various regimens	LVEF and diastolic parameters, asymptomatic	Positive

Myeloperoxidase

Myeloperoxidase (MPO) is a biomarker aside from troponin and natriuretic peptides that has shown some promise in terms of cardio-toxicity detection. MPO is a peptide secreted by leukocytes and functions to catalyze oxidative reactions. It is mechanistically linked to atherosclerosis by being a part of the pathway provoking lipid peroxidation and LDL conversion to lipid-laden foam cells. Multiple studies have demonstrated its prognostic value in patients with ACS and heart failure [36]. In the study by Ky et al., 78 patients with breast cancer who underwent doxorubicin and trastuzumab therapy had multiple biomarkers measured at baseline and 3 months into therapy [32]. The outcome studied was defined as either a reduction in LVEF of ≥5 to <55% with symptoms of HF or an asymptomatic reduction of LVEF of ≥10 to <55%. The authors determined that each standard deviation (355.6 pmol/L) increase in MPO was associated with a 40% increased risk of cardio-toxicity. Similar results were found with troponin measurements via Siemens Ultrasensitive assay. Therefore, early increases in cTn and MPO offer additive information about the risk of cardio-toxicity in patients undergoing doxorubicin and trastuzumab therapy.

Current Recommendations for Biomarker Utilization

Given the increasing amount of evidence in the field of cardio-oncology, major societies have created consensus statements and position papers regarding cardio-toxicity. Specifically, there are recommendations made regarding surveillance during treatment. The American Society of Echocardiography (ASE) 2014 consensus statement states that elevated troponins in patients receiving potentially cardio-toxic chemotherapy may be a sensitive measurement for the early detection of toxicity, and NPs may be less consistent in the early identification of cardio-toxicity [37••]. The ASE document also emphasizes the limitations including uncertainty of timing of biomarker measurement and optimal cutoffs. When either chemotherapy regimens associated with type I toxicity or

trastuzumab (associated with type II toxicity) are initiated, the ASE recommends baseline serum cTn measurement and to use this level in conjunction with global longitudinal strain and LVEF to initiate cardiology consultation.

The European Society of Cardiology consensus states the use of cardiac biomarkers during chemotherapy may be considered in order to detect early cardiac injury, and the same assay should be used for screening throughout the treatment pathway [38]. This statement also acknowledges there is insufficient evidence to establish the significance of subtle rises of detectable biomarkers or the variations with different assays. They also state there is insufficient evidence to reliably predict clinically relevant late consequences of cancer therapy with biomarkers. It is important to keep in mind both societies have put together consensus statements on this topic but are unable to create complete guidelines at this time. This is a reflection of the relatively small number of subjects and few studies focusing on biomarkers and cardio-oncology. The incorporation of routine troponin testing in the outpatient setting would require a full system in place, which incorporates a system-level understanding of the role of testing. We include a generalized pathway to illustrate the complementary role of biomarkers for surveillance during chemotherapy (Fig. 1). However, it is critical to avoid overly aggressive workup and mis-diagnosis of patients who are either being risk-assessed or undergoing routine monitoring for cardio-toxicity.

However, in the cancer survivor population, evidence showing benefit with biomarker surveillance is lacking, particularly those with childhood cancers. In the 2015 International Late Effects of Childhood Cancer Guideline Harmonization Group report, a review of the evidence surrounding biomarker surveillance in survivors of childhood cancer found Level B evidence of troponin T and I, and NPs testing to be of poor diagnostic value for detection of asymptomatic cardiomyopathy, nor did it find any evidence that screening with biomarkers was cost-effective. Thus, use of biomarkers in this population was not recommended as the only strategy for cardiomyopathy surveillance, regardless of their risk of developing long-term cardiotoxicity based on anthracycline and/or radiation dose exposure. The report did state that it could be reasonable to use biomarkers in conjunction with imaging studies where symptomatic cardiomyopathy was strongly suspected, or in survivors with borderline cardiac function during primary surveillance [39••]. In addition, the evidence surrounding long-term biomarker surveillance in survivors of adult cancer is especially lacking and warrants further study.

Novel Biomarkers and Mechanisms

Given the potential for biomarkers to reveal underlying neurohormonal mechanisms for cardio-toxicity, one study sought to

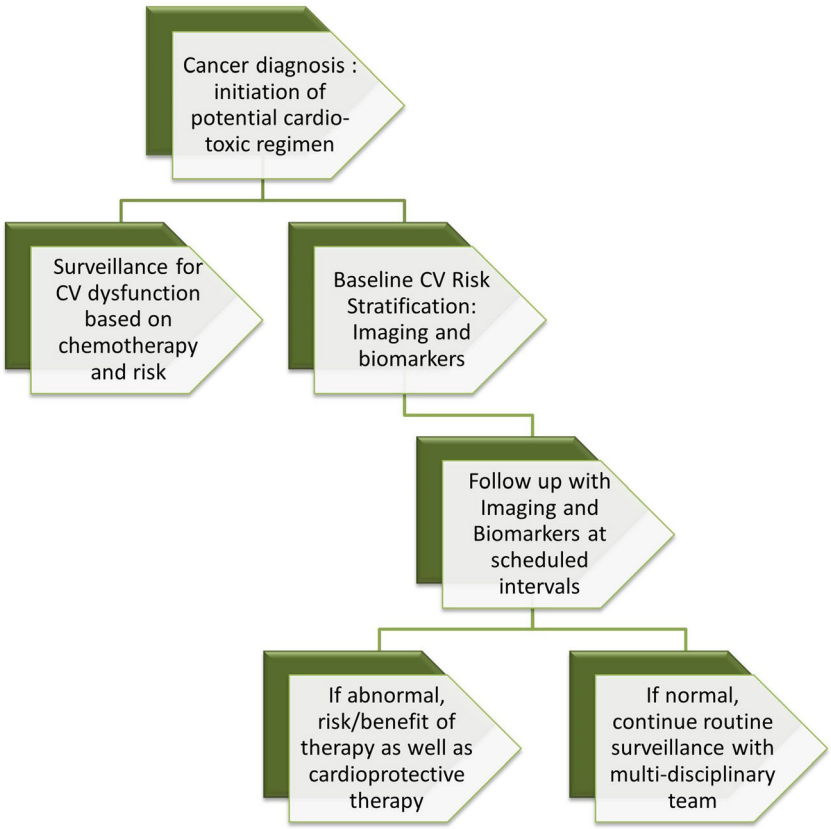

Fig. 1 Generalized pathway for initiation and surveillance of cardio-toxicity with multi-disciplinary approach utilizing biomarkers and routine imaging

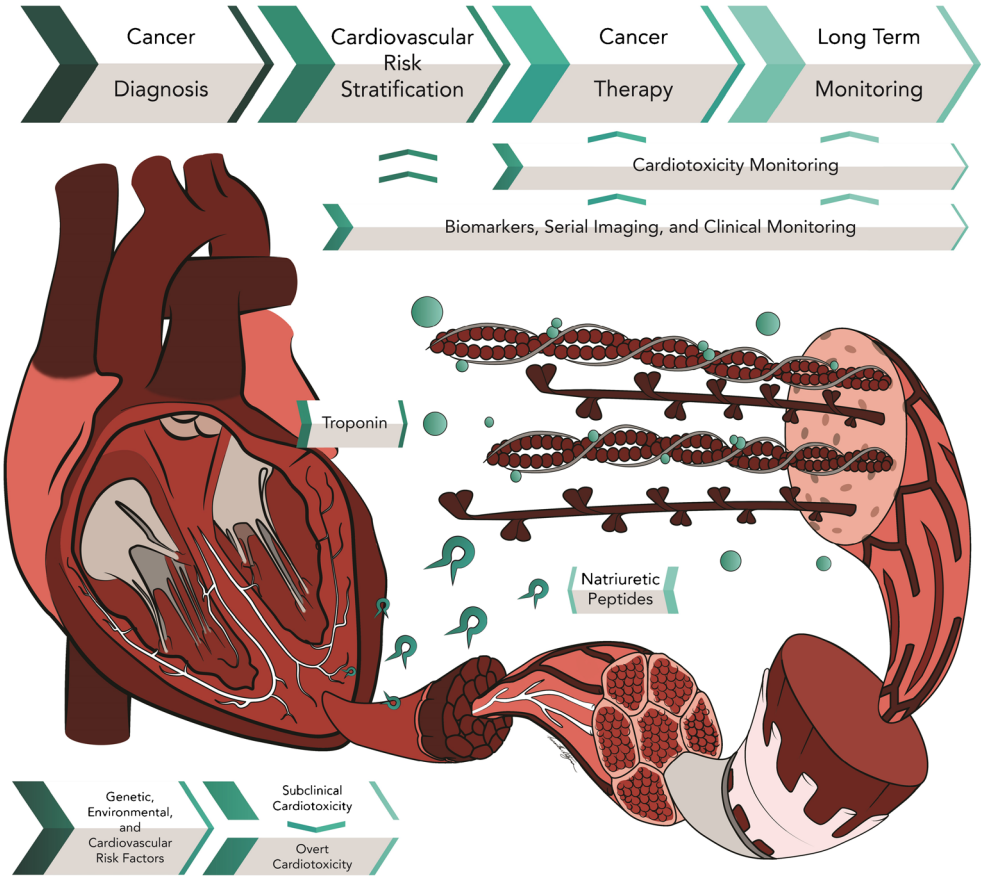

Fig. 2 A Scheme for the role of biomarkers in cardio-toxicity detection

determine the relationship between multiple biomarkers in patients with cancer and mortality [40]. In this analysis of 555 cancer patients (most commonly breast, followed by lung cancer), there were 186 (34%) deaths. Multiple biomarkers were measured prior to any potentially cardio-toxic therapy. The analysis studied natriuretic peptides specifically NT-proBNP and mid-regional pro-atrial natriuretic peptide. It also studied baseline inflammatory markers (interleukin-6 and C-reactive protein), stress markers (mid-regional pro-adrenomedullin and copeptin), and vasoconstrictors (C-terminal proendothelin-1). All markers were found to have an association with mortality, independent of age, gender, tumor entity/stage, and presence of cardiac comorbidities. This analysis demonstrated that patients with cancer have baseline elevated levels of multiple marker reflecting underlying hemodynamic stress and neurohormonal activation, even prior to potentially cardio-toxic therapy. Therefore, future studies considering utilization of them to monitor disease progression should take into consideration their baseline-elevated levels in patient with cancer.

Another possible role for biomarkers is to elucidate insight into the mechanisms of cardio-toxic damage. RT is associated with myocardial, valvular, pericardial, and vascular toxic effects [41]. In 25 subjects with breast or lung cancer who underwent pelvic or thoracic radiation therapy, hs-cTn, NT-proBNP, and galectin-3 (a mediator of cardiac fibrosis) were measured before and after RT. Levels of all three biomarkers were unaffected by RT, suggesting the mechanism of injury related to RT may be different than chemotherapy-mediated damage.

Management

Data is limited but growing regarding management of patients who experience cardio-toxicity as a result of cancer therapy. Specifically, HF therapies should be in line with current guideline-directed therapy [42]. Studies have studied preventative HF therapies in patients at risk for development of LV dysfunction. In a small study of 25 subjects, carvedilol was initiated before anthracycline therapy and this improved systolic (LVEF%) and diastolic parameters (E/A ratios) as compared to placebo [43]. Similar small studies with anthracycline toxicity have been performed studying HF therapies (enalapril, spironolactone, metoprolol, and candesartan) with positive results in the prevention of LV dysfunction [44–46]. In a biomarker-tailored approach, one prospective trial of 473 patients with cancer, who demonstrated an elevation of cTn after high-dose chemotherapy (various regimens), was prescribed with enalapril for 1 year [47]. The incidence of LV dysfunction was significantly lower in patients receiving ACE inhibitor therapy (43 versus 0%; $P < 0.001$). This study demonstrated the

potential to classify patients as high risk for development of HF during therapy using biomarker profiling and early treatment to prevent progression. The management of other cardiovascular complications (arrhythmias, CAD, valvular disease, etc.) has not been specifically studied in the context of cardio-oncology.

Conclusion

The field of prediction, detection, and management of cardiotoxicity will continue to grow as strategies incorporating biomarkers and imaging are more refined. Cardio-oncology programs in centers that provide care to cancer patients should be considered to help establish protocols for optimal care for these patients (Fig. 2) [48]. Troponin and natriuretic peptides are the best established markers for cardio-toxicity thus far during cancer treatment, although current evidence does not demonstrate a role for its use in surveillance for survivors of childhood cancer without evidence or symptoms of cardiac disease. Novel biomarkers will continue to help elucidate mechanistic insights into the cause of disease and possibly provide future therapeutic targets moving forward. The field of cardio-oncology will work to balance the reduction of both short- and long-term adverse cardiovascular events and optimal cancer therapy, while striving to prolong quantity and improve quality of life.

Compliance with Ethical Standards

Conflict of Interest Kevin S. Shah and Eric H. Yang declare that they have no conflict of interest. Alan S. Maisel has received compensation from Critical Diagnostics and Alere for service as a consultant and has received non-financial research support from Roche and Abbott Laboratories. Gregg C. Fonarow has received compensation from Medtronic, Amgen, Novartis, ZS Pharma, St. Jude Medical, and Janssen for service as a consultant and has received financial support through grants from the National Institutes of Health (NIH).

Human and Animal Rights and Informed Consent This article does not contain any studies with animal subjects performed by any of the authors but does contain studies with human subjects performed by Drs. Maisel and Fonarow.

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