HHS Public Access

Author manuscript

Clin Biochem. Author manuscript; available in PMC 2015 March 18.

Published in final edited form as:

Clin Biochem. 2015 March ; 48(0): 223–235. doi:10.1016/j.clinbiochem.2014.10.013.

Use of biomarkers for the assessment of chemotherapy-induced cardiac toxicity

Eric S. Christenson[a,*], **Theodore James**[a], **Vineet Agrawal**[a], and **Ben H. Park**[b]

[a]Johns Hopkins University, Department of Medicine, Baltimore, MD 21287, USA

[b]Johns Hopkins University, Department of Oncology, Baltimore, MD 21287, USA

Abstract

Objectives—To review the evidence for the use of various biomarkers in the detection of chemotherapy associated cardiac damage.

Design and methods—Pubmed.gov was queried using the search words chemotherapy and cardiac biomarkers with the filters of past 10 years, humans, and English language. An emphasis was placed on obtaining primary research articles looking at the utility of biomarkers for the detection of chemotherapy-mediated cardiac injury.

Results—Biomarkers may help identify patients undergoing treatment who are at high risk for cardiotoxicity and may assist in identification of a low risk cohort that does not necessitate continued intensive screening. cTn assays are the best studied biomarkers in this context and may represent a promising and potentially valuable modality for detecting cardiac toxicity in patients undergoing chemotherapy. Monitoring cTnI levels may provide information regarding the development of cardiac toxicity before left ventricular dysfunction becomes apparent on echocardiography or via clinical symptoms. A host of other biomarkers have been evaluated for their utility in the field of chemotherapy related cardiac toxicity with intermittent success; further trials are necessary to determine what role they may end up playing for prediction and prognostication in this setting.

Conclusions—Biomarkers represent an exciting potential complement or replacement for echocardiographic monitoring of chemotherapy related cardiac toxicity which may allow for earlier realization of the degree of cardiac damage occurring during treatment, creating the opportunity for more timely modulation of therapy.

Keywords

Cardiac toxicity; Chemotherapy; Anthracyclines; Troponin; Natriuretic peptides

*Corresponding author at: 601 North Caroline Street, Baltimore, MD 21287, USA. echris14@jhmi.edu (E.S. Christenson).

Author's contributions

EC, TJ, VA conducted the literature search and developed the tables. EC, TJ, VA, and BP all participated in writing and editing the paper.

Conflicts of interest

We declare that we have no conflicts of interest.

Introduction

Improved survival in many solid and hematologic malignancies is exposing more patients to the long-term effects of chemotherapy including cardiac toxicity [1]. With improved outcomes, increased emphasis has been placed on the side effects associated with treatment and several chemotherapeutic agents have gained notoriety for their untoward cardiovascular side effects such as arrhythmias, myocardial ischemia, hypertension, acute heart failure and late onset ventricular dysfunction [1–4]. In particular, late-onset heart failure with either reduced or preserved ejection frequently occurs years after chemotherapy has been completed and is associated with substantial morbidity and mortality [1].

Anthracyclines as well as several novel agents have the potential to cause severe cardiac toxicity which may hamper their optimal use in treatment of malignancy. Additionally, with an expanding pool of patients receiving chemotherapy, there are currently no good tools for differentiating progression of underlying cardiac disease from direct cardiotoxic effects of chemotherapeutic agents. Echocardiography is currently used to assess cardiac function prior to the initiation of chemotherapy and to monitor for the development of cardiac toxicity during therapy [5]. Unfortunately, echocardiography is an imperfect fit in this role as it is relatively insensitive for detecting early cardiac toxicity during treatment. This is because normal hearts have excellent reserve capacity, so even modest loss of left ventricular function is indicative of significant cardiovascular damage [6]. These issues in conjunction with the high cost of repeated imaging make the discovery and utilization of a biomarker guided approach a highly attractive option.

A number of chemotherapeutic agents associated with cardiac toxicity will be reviewed before discussing the utility of various biomarkers in the detection and monitoring of myocardial damage, and potential interventions that could be implemented either prophylactically or once cardiac injury is detected.

Methods

Pubmed.gov was queried using the search words chemotherapy and cardiac biomarkers with the filters of past 10 years, humans, and English language. These criteria yielded a total of 3186 articles which were then selected on the basis of their relevance to this article's topic and goals. Appropriate articles were then hand searched to identify additional relevant literature. An emphasis was placed on obtaining primary research articles looking at the utility of biomarkers for the detection of chemotherapy-mediated cardiac injury. Refer to Table 1 for a compilation of these studies.

Discussion

Chemotherapy induced cardiac toxicity is generally divided into two classes on the basis of its severity and reversibility. Type 1 is myocardial injury induced through damage to the microstructure of cardiac myocytes and results in cell death via necrosis or apoptosis [7]. This damage is generally considered irreversible [7]. In contrast, type 2 cardiotoxicity results in cardiac myocyte dysfunction with the notable absence of microstructural

disruption [7]. This impairment resolves with the completion of therapy and sometimes even during its continuation [7].

Chemotherapeutic agents

Anthracyclines—Anthracyclines are highly effective chemotherapeutic agents commonly used in breast cancer as well as hematologic tumors [2]. These drugs act through the intercalation of nucleic acids to interfere with cell replication, leading to potent antitumor effects [8]. In addition, anthracyclines generate free radicals through an iron-dependent, enzyme-mediated reductive process [8]. It is thought that this mechanism may also lead to cardiac tissue damage through the production of superoxide anion radicals [9,10].

In response to the extensive attention on chemotherapy induced cardiac damage, a recent meta-analysis showed that 6% of patients treated with anthracycline experience clinically overt cardiotoxicity, while 18% develop subclinical cardiotoxicity [11]. This is consistent with a 5-fold increased risk in congestive heart failure in patients treated with these agents [12].

Anthracycline-related cardiomyopathy appears to be dose dependent with increasing risk and severity of cardiomyopathy correlating with the cumulative dose [13–15]. However, it should be noted that myocardial damage can occur unpredictably; doses as low as 200 mg/m^2 can be associated with injury and the frequency increases as doses exceed 550 mg/m^2 [13]. This dose response curve becomes increasingly steep as doses increase and there appears to be a synergistic deleterious effect with radiation and/or trastuzumab co-administration [16].

Cyclophosphamide—Cyclophosphamide is a nitrogen mustard alkylating agent commonly used for the treatment of both neoplastic and autoimmune conditions. Although cyclosphosphamide has most often been associated with cardiomyopathy in settings where it is used in conjunction with anthracyclines, there is evidence to suggest that cyclophosphamide itself may rarely cause direct cardiac toxicity via hemorrhagic myocarditis [17,18]. Studies specifically investigating co-administration of cyclophosphamide and anthracycline have shown that the addition of cyclophosphamide leads to an earlier peak troponin level than anthracyclines alone; however inclusion of cyclophosphamide in therapy does not appear to alter absolute peak troponin levels or overall outcome [19]. Further supporting this claim, ejection fraction decreases noted following stem cell transplantation appear to be primarily associated with cumulative anthracycline toxicity as opposed to cyclophosphamide use [20]. N-terminal pro B-type natriuretic peptide (NT-proBNP) levels show transient elevations in the setting of cyclophosphamide use prior to stem cell transplantation for non-Hodgkin lymphoma and multiple myeloma which may be indicative of some temporary cardiac stunning or alternatively the concomitant use of large amounts of fluid during administration [21,22]. It has been noted that any symptoms that develop with cyclophosphamide use occur during drug administration, and usually resolve upon discontinuation [23].

Taxanes—Taxanes are a popular chemotherapeutic class that derive their antitumor effects through interference with the formation of microtubules necessary for cellular division [23].

Cardiac toxicity typically manifests with conduction disease, principally bradycardia, which is usually asymptomatic and does not require intervention [24]. This injury is thought to be secondary to damage to subcellular organelles [25].

5-Fluorouracil—5-Fluorouracil (5-FU) is an antimetabolite agent used in the treatment of a variety of neoplastic processes. The incidence of cardiotoxicity with this drug ranges widely from 1% to 68%, with manifestations including arrhythmias, pulmonary edema, acute myocardial infarction, and cardiogenic shock [23,26–29]. The exact mechanism of these sequelae is not entirely clear but is thought to relate to coronary vasospasm based on ultrasound and angiographic studies [29]. This wide variation likely relates to differing study populations and definitions regarding cardiac toxicity [26,27,30].

Biologic agents—The term targeted therapy is often perceived to indicate highly selective killing of tumor cells through their purported pathway specific mechanisms; unfortunately it is increasingly realized that this specificity for both pathway and cellular selectivity does not always achieve perfect fidelity. Several of these new biologic agents have been linked to potential cardiovascular consequences, most notably trastuzumab and sunitinib [1].

Trastuzumab—Trastuzumab is a HER2 inhibitor which is used principally in breast and gastric cancer cases that overexpress this receptor [31]. When used in the absence of concomitant anthracycline therapy, trastuzumab is associated with minimal reversible (type 2) cardiac toxicity which tends to resolve with appropriate congestive heart failure based management [32,33]. However if administered concomitantly or in rapid succession with anthracyclines, more devastating cardiovascular consequences can occur, with multiplication of not only their antitumor effects but also the risk of cardiomyopathy. The incidence of cardiac toxicity in this setting has been reported to be around 28%, although this risk has been less substantial in a large chart review by Russell et al. [34–36] One approach that shows promise is separating anthracycline dosing and the initiation of trastuzumab by at least 90 days which may help ameliorate some of these safety concerns [37, 38]. This principle is evidenced by a lower incidence of cardiac toxicity (4.3%) in the HERA cohort and has led to the recommendation that anthracyclines and trastuzumab not be used concomitantly in clinical practice to minimize their synergistic cardiac toxicity [37–39].

Animal studies have linked trastuzumab related toxicity to interference with HER2 mediated cardiac repair which leads to dilated cardiomyopathy and additional susceptibility to anthracycline based cardiac toxicity [34,40]. Through this mechanism, trastuzumab may prevent necessary myocyte repair following damage from anthracycline therapy, playing a synergistic role in its formation of cardiac damage [38]. This creates a treatment dilemma for physicians given the improved clinical outcomes for HER2 positive tumors when trastuzumab is included in the regimen [32]. This is especially poignant given the current recommendation of 1 year of therapy, associated with low recurrence rates but increased concern for cardiovascular events [41]. This issue is particularly important in older patients with co-morbidities who have an 18% risk of trastuzumab discontinuation despite its substantial benefits [42].

Multi-kinase inhibitors: sunitinib and sorafenib—Sunitinib is a tyrosine kinase inhibitor with a broad spectrum of activity shown to be effective in the management of renal cell carcinoma. This drug is unfortunately also associated with increased rates of adverse cardiovascular events which vary substantially from trial to trial with reported incidences from 4.1 to 33.8% [43–45]. Much of this discrepancy likely relates to differing definitions of cardiovascular events employed in these trials [43–45]. The mechanism of cardiac toxicity is thought to be from an off-target effect of sunitinib on ribosomal S6 kinase that results in increased apoptosis [46]. Additionally, there is some thought that its direct effect upon VEGFR1-3 signaling not only results in hypertension but limits the ability of cardiomyocytes to adapt in response to this increased pressure load invariably leading to congestive heart failure [44,46]. Regardless, these deleterious cardiac changes were transient and resolved with appropriate heart failure management, often allowing for the continuation of sunitinib [43].

Sorafenib is another multi-kinase inhibitor that has been associated with increased myocardial events (2.9% vs. 0.4% in placebo controls) [46]. In addition to its inhibition of VEGFR1-3, Flt3, KIT, and PDGFR receptor signaling which are thought to lead to loss of vascular integrity, the downstream effects of sorafenib upon RAF/BRAF are thought to increase oxidant-stress induced injury as well as cause apoptosis, resulting in type 1 myocardial injury [46].

Directed ABL inhibitors: imatinib, nilotinib, dasatinib—Imatinib acts through targeted inhibition of the BCR-ABL gene rearrangement and was truly revolutionary when it became available for the treatment of chronic myelogenous leukemia [47]. It has subsequently been discovered to have several off-target effects, some of which are beneficial and have been exploited for use in other malignancies, principally GIST tumors [48]. However these off target effects are not completely without consequence and some of its success has been soured by reports of left ventricular dysfunction mediated through induction of an endoplasmic reticulum regulated stress response with the ultimate activation of a cell-death pathway [47]. In animal studies, histologic changes have been ascribed to imatinib administration which increase in a dose response manner [49]. The clinical implications of this finding are controversial and since the initial alarm was raised, follow-up trials report only sporadic cases of heart failure that may or may not have been linked to imatinib use [50–52]. Cardiac biomarker monitoring in 55 GIST patients on imatinib showed only one with normal pretreatment cardiac function who developed an elevation in NT-proBNP levels [48]. On further inspection, investigators concluded that this case was likely related to mitral valve dysfunction with normal TnT levels [48]. Other newer directed ABL inhibitors such as nilotinib and dasatinib have not been extensively studied enough to know the true incidence of cardiac toxicity associated with them, but there is evidence to suggest that this class of medications is overall associated with an increased risk of exudative pericardial effusion [53].

Other biologic agents—Bevacizumab is associated with a small increase in the risk for left ventricular dysfunction [54,55]. This cardiac toxicity may relate to disruption of VEGF-mediated angiogenesis and endothelial maintenance thought to be important in protecting

cardiac myocytes from oxidative stress [56]. Alternatively the toxicity could be connected to its propensity for inducing hypertension with precipitation of underlying cardiac dysfunction [56].

Biomarkers of cardiac injury—Given the cardiovascular consequences noted with a variety of different chemotherapeutic agents, there is great interest in early detection of these side effects. At present there is no effective means of accurately detecting and predicting myocardial damage occurring with chemotherapy. Biomarkers have the potential to fill this void, allowing for the stratification of patients by risk distinguishing patient at increased susceptibility for side effects of therapy, in which lower doses are warranted, from patients for which more aggressive chemotherapeutic regimens can be entertained.

When exploring potential biomarkers for use in this setting, many markers and their associated assays have been evaluated based on their use in assessing cardiac dysfunction in other settings, notably ischemia and heart failure [57,58].

Stringent criteria are necessary for evaluating biomarkers given their power to affect prognostic information and alter treatment plans. As Dr. Hayes of the University of Michigan Health System eloquently states, “A bad tumor marker is as bad as a bad drug” [59]. In appraising markers, three Ms characterize the essential attributes of an effective biomarker: measurement, more information and management guidance. The first M refers to the ability to reliably ascertain levels of the desired biomarker [60]. Determining an appropriate context for interpreting data is invaluable; this necessitates the establishment of a population baseline as well as a threshold for which deviation from these values develops clinical significance. Given the potential variability of metabolic levels outside of medication and cardiotoxic effects, an understanding of the effect of gender, age, ethnicity, and comorbidities should be elucidated to create context on which these values can be interpreted for an individual patient [61]. In addition, it should be recognized that features extrinsic to levels found within the patient including collection and storage conditions may alter the fidelity of the ultimate concentrations obtained during testing [62,63].

The second essential feature of biomarkers involves clinical validity or the provision that the biomarker of interest reliably distinguishes patients at increased risk for an event from those in which the outcome of interest is less likely [62]. This utility should be measured in the context of current practice guidelines to evaluate the extent to which these new tests provide clinically valuable information (either in addition to or replacing) established best practices [60].

The third principle, and the most difficult criteria to fulfill, is the establishment of a positive impact that new assays have on the advancement of patient care [62,63]. This contribution again must be taken in the context of current clinical practice to determine its potential additive effect measured as a risk-benefit scenario; the positive effects as well as its potential to lead to harm through inappropriate triage for treatment or increased overall healthcare costs must be considered [62].

Troponin—Troponin (cTn) is probably the best characterized marker for evaluating chemotherapy induced cardiac injury. At present, most of this data has looked at anthracycline based therapy with uncertain broader applicability. Despite these reservations, an expert committee report to the FDA in 2004 concluded that troponin I (cTnI) and troponin T (cTnT) are sensitive, specific, and robust biomarkers of cardiac insult, allowing for the detection and quantification of cellular injury and death related to testing of new drugs [64].

Even before initiation of chemotherapy, patients presenting with hematologic malignancies appear to exhibit a detectable elevation of cTnI suggesting baseline cardiovascular strain and injury [65]. This suggests that the tumor itself may predispose cancer patients to cardiac damage from chemotherapeutic agents.

Troponin elevations have been shown to increase in magnitude in a step-wise fashion with escalating anthracycline doses administered in rat models; these biomarker indications of cardiac myocyte damage correlate with the degree of cardiac damage noted on histology [66, 67]. The clinical significance of this finding is supported by data showing that cTn elevations present during chemotherapy are associated with a significantly elevated risk of left ventricular dysfunction; this has been demonstrated in a number of patient populations including hematological malignancies and breast cancer [68–74]. With evidence that these elevations precede changes on echocardiography, measurement of cTn may provide valuable information to clinicians [75–77]. In addition to evaluating risk based solely on absolute cTn levels there exists evidence that monitoring the magnitude and kinetics of cTnI and cTnT elevations appears to correlate with the degree of left ventricular dysfunction present on subsequent echocardiography [78–80]. cTn also provides valuable information when there is an absence of detectable levels, particularly cTnI, helping to elucidate a group that may not need long term follow up for cardiovascular consequences [68,76,78,81].

A majority of data examining the link between cTn elevations, chemotherapy, and left ventricular dysfunction pertains to the use of high-dose anthracycline based chemotherapy for aggressive hematological malignancies or breast cancer. In this setting, cTnI levels have been noted to increase in approximately a third of patients [68]. These patients are at increased risk for cardiovascular consequences with persistent elevations of cTnI after cessation of high dose chemotherapy (HDC) showing an even greater propensity and magnitude of LVEF reduction compared to those with a transient rise [68,81,82]. Serial measurement of cTnT shows that levels peak at 23 days following administration of chemotherapy with an early peak noted in anthracycline regimens including cyclophosphamide without increase in absolute rise [19]. The percentage of patients exhibiting cTnI positivity tends to increase with the number and intensity of chemotherapy cycles the patient has undergone [68,83–85]. In patients receiving lower doses of anthracycline therapy, troponin levels show only an intermittent ability to predict poor cardiovascular outcomes [86–88].

The optimism for the use of troponin based assays for detecting cardiotoxicity has not been unanimous with some studies failing to detect elevations of troponin following anthracycline therapy or a correlation of elevations with clinical outcomes [35,89–95]. Given the low level

elevations that typically occur with anthracycline administration there is some concern that these changes may represent physiologic variation or unrelated cardiovascular disease as opposed to being indicative of true cardiac toxicity of therapy [96]. Of note, some of these negative trials may have resulted from the use of earlier generation troponin assays with inadequate signal, potential inappropriate cut offs and/or small sample size [35,89–94]. High sensitivity troponin assays may help improve stratification by providing a more sensitive assessment of subclinical depletion of cardiac physiologic reserve [97].

cTnI appears to have somewhat better predictive value than cTnT with higher sensitivity of detecting cardiac changes induced by anthracycline toxicity, particularly in the leukemia population [98,99]. This is speculated to be secondary to the smaller molecular weight and release kinetics of TnI that may allow for discordant early detection in anthracycline based cardiotoxicity [99].

While most studies looking at troponin elevations in chemotherapy have focused on the effects of anthracycline based therapy on cardiac performance, there exists evidence on the utility of cTn in identifying patients at risk for trastuzumab mediated cardiac toxicity [100]. In a 2010 study by Cardinale et al., cTn elevation during trastuzumab was associated with a 17.6 times increased risk of cardiotoxicity [100]. This rise typically occurs early in treatment, as opposed to the slowly increasing positivity noted with anthracycline therapy; this feature may provide additional warning of impending cardiac decompensation which is especially relevant given its proposed type 2 cardiotoxicity [100].

Overall, the results of clinical trials using cTn to predict cardiac toxicity are promising and warrant continued exploration. Longer follow-up may prove valuable in evaluating the predictive ability of cTn for long term consequences of anthracycline use. Timing may be key as many studies measure enzyme levels following the completion of therapy which may not accurately reflect the degree of myocardial injury occurring during chemotherapy or the long term cardiac toxicity of therapy [97]. More studies looking at optimal timing of biomarker assessment and the appropriate age and sex specific cut offs for enzyme elevations in this setting remain to be elucidated [97,101].

Natriuretic peptides—Natriuretic peptides are small peptides synthesized in the atria and ventricles [102]. They are thought to be released upon stretch of the atria and ventricles and induce natriuresis, vasodilation, and diuresis via cGMP mediated signaling pathways [102]. Natriuretic peptides have gained much of their acclaim in the arena of heart failure where they have proved valuable in the diagnosis and monitoring of patients with heart failure and/or cardiomyopathies. A number of trials have looked specifically at evaluating the predictive value of natriuretic peptides for chemotherapy induced left ventricular dysfunction.

Interestingly, natriuretic peptide level elevations even prior to the initiation of therapy as well as after one dose are predictive of subsequent development of cardiac toxicity in NHL and non-HDC breast cancer cohorts. This characteristic may help identify vulnerable populations with pre-existing subclinical disease in addition to patients sensitive to chemotherapy induced damage [87,103,104].

Natriuretic peptide levels have been shown to strongly correlate with the presence of heart failure in cancer patients in both adult and pediatric populations receiving anthracycline therapy [70,105]. These levels have been noted to rise prior to the development of heart failure causing optimism for their utility as a more sensitive indicator of impending clinical symptoms [106,107]. Making an argument for continued monitoring during therapy, persistent B-type natriuretic peptide (BNP) elevations following the administration of anthracyclines are more predictive of subsequent cardiac dysfunction than transient elevations [86,95,108,109]. In addition to the positive predictive value of elevated natriuretic peptide levels, a study looking at atrial natriuretic peptide (ANP) showed patients with levels below three times the upper limit of normal during administration of doxorubicin based chemotherapy had a low risk of subsequent cardiac sequelae [110]. Tempering some of this enthusiasm is evidence that while increased natriuretic peptide levels themselves predict left ventricular dysfunction, changes in levels do not appear to correlate with ejection fraction reduction [79,111]. Overall, natriuretic peptides' utility for chemotherapy mediated cardiac toxicity remains controversial with several studies reporting no prognostic value for BNP levels and echocardiography findings [35,75,81,112,113].

Part of this confusion may relate to the property that natriuretic peptide levels serve as reasonable surrogates for both left ventricular dysfunction and cumulative dose of anthracycline [88,114–119]. This clouds the picture as to whether these changes are early predictors of cardiac damage or relate to anthracycline dosing associated with both damage and natriuretic peptide levels [114,120].

Evaluating the ability of natriuretic peptides to monitor drug toxicity and its potential prevention, children presenting with ALL are noted to have NT-proBNP elevations at baseline which decrease with the initiation of therapy with further decreases seen with the addition of dexrazoxane to their chemotherapy regimen [107]. These levels are noted to continue to fall in the dexrazoxane group with a subsequent rise seen in the group receiving anthracycline monotherapy [107].

Which natriuretic peptide to use? In two small trials of 10 AML/MDS and 27 patients respectively, BNP was significantly associated with left ventricular changes while ANP showed no diagnostic changes [108,121]. In another small pilot study, NT-proBNP but not ANP was associated with QT prolongation [122]. These studies provide preliminary evidence that B type natriuretic peptides may be a better predictor of cardiovascular consequences for cancer patients receiving anthracyclines than ANP.

Cardiotoxic effects of malignancy in addition to treatment among children— One interesting finding discovered by cohort studies has been the idea of malignancy-associated damage to the myocardium either through direct infiltration or hemodynamic stress. This concept is supported by elevated NTproBNP levels in all childhood cancer survivors, even those not exposed to cardiotoxic therapy as well as elevated levels noted even prior to beginning chemotherapy [107,119]. NT-proBNP levels in the aforementioned group are lower than the levels in childhood cancer survivors treated with anthracyclines suggesting a role for both the primary neoplasm and therapy in precipitating cardiovascular

injury [123]. The applicability of these findings to the adult population has yet to be properly characterized.

High-sensitivity C reactive protein (hsCRP)—C-reactive protein is a nonspecific marker which has been assessed for its utility in predicting cardiac toxicity; however results have been extremely heterogeneous. One pilot study of 49 women treated with adjuvant trastuzumab showed a correlation between hs-CRP levels and later development of subsequent cardiomyopathy [35]. Another study looking at anthracycline-based therapy showed no correlation of hs-CRP with echocardiography findings [124].

Overall, hs-CRP levels tend to be higher in all survivors of childhood cancer whether or not they were exposed to cardiotoxic therapy. In a study by Lipshultz et al., left ventricular dysfunction was noted to correlate with hs-CRP levels in childhood cancer survivors not exposed to cardiotoxic therapy suggesting that the hs-CRP may be a surrogate for overall inflammation or tumor burden in addition to drug effects [119]. These studies support the previously mentioned concept that malignancy in addition to its therapy may have deleterious cardiovascular consequences.

Glycogen phosphorylase BB—Glycogen phosphorylase BB (GPBB) has been proposed as a novel biomarker for the detection of chemotherapy mediated cardiac damage [98]. In a study of patients who received HDC followed by stem cell transplantation there existed a subclass of patients with positive signal for GPBB without corresponding elevations in cTn or natriuretic peptides [125]. However without long term follow-up it is difficult to ascertain if this represents a more sensitive predictor of myocardial damage or aberrant elevations [98,125,126]. It is premature to comment on its utility and larger trials with long term follow up will be necessary to further define its potential role in this application [98].

Myeloperoxidase (MPO)—Myeloperoxidase (MPO) is a proatherogenic enzyme produced by neutrophils that leads to free radical production and lipid peroxidation [77]. MPO levels measured following anthracycline administration have been shown to correlate with subsequent development of cardiotoxicity in one study [77]. However more confirmatory trials are needed with long-term follow-up.

Total antioxidant status (TAOS)—Total antioxidant status is a sum of all measurable antioxidants within the blood which theoretically can be used to monitor anthracycline based therapy and its reported complications [88]. One small study of 29 children undergoing therapy for acute leukemia showed a significant drop in TAOS levels which correlated with increased doses of anthracycline [88]. As with the previously mentioned markers, these promising findings warrant further investigation with long-term clinical end points.

Circulating microRNAs—With more studies elucidating the exact mechanisms by which chemotherapeutic agents exert their cardiotoxic agents, circulating microRNAs have emerged as an attractive potential marker reflecting ongoing myocardial injury. MicroRNAs are short non-coding RNAs that are known to play an important role in maintaining homeostasis [127]. As such, they have been implicated in regulating multiple global cellular

processes such as oxidative stress response and cellular injury [128]. Preclinical studies have shown that doxorubicin administration is associated with substantially increased levels of mIR-146a, and it is thought that the mechanism of doxorubicin mediated cardiotoxicity is at least partially mediated by mIR-146a induced downregulation of ErbB4 and subsequent activation of apoptotic pathways [129]. Clinically, circulating levels of mIR-146a have been proposed as a predictive and prognostic indicator of multiple conditions such as sepsis, Sjogren's syndrome, and cancer [130–132]. However, future clinical studies are necessary to determine the validity of mIR-146a in the setting of chemotherapy-related cardiotoxicity. Studies have shown that mIR-146a levels are associated with specific conditions such as peripartum cardiomyopathy, but levels do not differ with other forms of non-inflammatory dilated cardiomyopathy when compared to healthy controls [133,134]. Thus, microRNA levels may be a potential biomarker specific to inflammatory or injury-mediated cardiotoxicity and heart failure.

Preventive strategies—Once evidence of cardiac toxicity is suspected through the use of biomarker, imaging, or clinical exam monitoring it becomes imperative to guide intervention to prevent further damage from occurring. Modulation of chemotherapy with dose and cycle reductions is one possible way of ameliorating cardiac toxicity but often comes at the expense of diminished antitumor effect. Another strategy aims to treat the current cardiac damage and/or prevent further injury through the administration of a variety of preventive agents outlined below.

Dexrazoxane—Dexrazoxane is a medication that has been investigated extensively for use in limiting anthracycline mediated cardiac injury with a reduction in the relative risk of clinical heart failure to 0.21 and subclinical cardiac toxicity to 0.33 [12]. This effect is postulated to occur through dexrazoxane's iron binding effects preventing it from forming free radical producing complexes with doxorubicin [135]. Of note, some of this effect appears to be gender specific with girls showing better cardiac preservation with dexrazoxane therapy than boys in a study examining the use of dexrazoxane plus doxorubicin in high risk children receiving treatment for ALL [136]. This cardioprotective effect can be monitored with cTnT levels whose rise is attenuated with the use of dexrazoxane in the setting of anthracycline use [135,137].

One of the trials that helped to confirm the efficacy of dexrazoxane for reducing cardiac toxicity also sparked controversy when its data raised concern for dexrazoxane decreasing the efficacy of anthracycline based therapy. This trial by Swain et al. revealed a reduction in the risk for decreased ejection fraction or congestive heart failure by a factor of 2.5 with the use of dexrazoxane in a breast cancer cohort, but sent shocks through the oncologic community when it also reported a decreased response to therapy going from 4 to 14% among the subgroup receiving dexrazoxane therapy, although this did not translate into a significant decrease in survival or time to progression [138]. Several subsequent trials and analyses have sought to further clarify this issue and have not replicated this finding [136,139].

Debate once again struck this cardioprotective therapy when post-hoc analysis showed increased formation of secondary malignancies among childhood cancer patients receiving

dexrazoxane therapy [140]. However these data immediately drew fire for the small number of incidences on which this claim rested (as few as one in the case of osteosarcoma) and has not been substantiated by subsequent trials [141].

A recent Cochrane review on the use of cardioprotective agents in anthracycline therapy determined that the use of dexrazoxane reduced the rate of subsequent heart failure by one third with no effect on survival, incidence of secondary malignancy, or tumor response rate [142]. This report concluded that this therapy should be considered in high risk patients [142].

Angiotensinogen converting enzyme inhibitor (ACE-I) therapy—The Renin–Angiotensin–Aldosterone (RAS) system is thought to play an important role in the development of anthracycline-mediated cardiotoxicity with an increase in cardiac angiotensin converting enzyme concentration noted in animal models following the initiation of anthracycline therapy [143]. Inhibition of this pathway is therefore thought to represent a rational mechanism for preventing this damage. In addition, many ACE-inhibitors (ACE-I) have antioxidant properties that prevent free radical mediated toxicity associated with anthracyclines [10,144].

Through their inhibition of the RAS system and free radical formation, ACE-I have shown efficacy in the prevention of contraction abnormalities and interstitial fibrosis following administration of anthracyclines [145,146]. Optimal dosing schedule has not been fully elucidated but ACE-I therapy appears to be effective given either simultaneously or a month following therapy to prevent cardiotoxicity [147, 148]. Studies have confirmed the effectiveness of this approach showing a reduction in cardiovascular outcomes and development of cardiomyopathy [149,150].

Using elevated cTn levels as a marker of risk for anthracycline mediated cardiac damage, Cardinale et al. were able to use enalapril to prevent the development of cardiomyopathy in a randomized controlled trial of 54 patients [82,151]. This trial also helped to demonstrate the strong negative predictive value of cTnI with none of the patients with normal cTnI values following chemotherapy experiencing cardiac events; this may represent a group where intensive cardiac protective therapy is unnecessary [82].

Beta blockers—Beta-blocker therapy has shown excellent efficacy in the treatment of ischemic and non-ischemic causes of heart failure. However, there remains a paucity of good data looking specifically at its potential role in chemotherapy-related cardiomyopathy. While all beta-blockers may have some efficacy, carvedilol and nebivolol represent rational choices in this setting given their additional antioxidant properties [152–155].

Current evidence including several case reports/series, two small randomized controlled trials and animal models have shown promising results but as of yet, no large human studies have been published [152,154,156–158]. These large trials would be immensely helpful in further characterizing the potential role for beta-blockers in this setting including individual drugs and dosing schema.

Liposomal based doxorubicin—Liposomal doxorubicin was designed in an attempt to decrease the risk of cardiac side effects present with traditional doxorubicin therapy. The idea behind developing a liposomal version of anthracyclines or other drugs is that these liposomes cannot leave the vascular system in places with tight capillary junctions such as the heart, depositing preferentially in areas where fenestrated capillaries are present or junctions are disrupted by inflammation or tumor growth [159]. Studies show that liposomal doxorubicin used in combination with cyclophosphamide for the treatment of breast cancer reduces the risk of cardiac toxicity when compared to traditional doxorubicin-based regimens [159,160].

Conclusion

There are a number of effective chemotherapeutic agents with the side effect of causing damage to the cardiovascular system. There is optimism that the use of biomarkers can help identify patients undergoing treatment who are at high risk for cardiotoxicity [161]. Also, these biomarkers can assist in identifying a low risk cohort that does not necessitate continued intensive screening, avoiding unnecessary cost and inconvenience to patients and the healthcare system. In particular, cTn assays represent a promising and potentially valuable modality for detecting cardiac toxicity in patients undergoing chemotherapy in a variety of clinical settings. Monitoring cTnI levels may provide earlier information regarding the development of cardiac toxicity allowing for proactive manipulation of regimens and cardioprotective strategies instead of being able to appreciate toxicity only after left ventricular dysfunction becomes apparent on echocardiography or via clinical symptoms. A host of other biomarkers have been evaluated for their utility in the field of chemotherapy related cardiac toxicity with intermittent success; further trials are necessary to determine what role they may end up playing for prediction and prognostication in this setting.

While biomarkers may ultimately complement or in some cases displace cardiac imaging for monitoring cardiac toxicity of chemotherapy, it should be stressed that current guidelines still recommend the assessment and monitoring of left ventricular function via echocardiography during anthracycline-containing chemotherapy [5]. Monitoring strategies include troponin, the natriuretic peptides and other biomarkers may turn out to be useful; however, a high bar must be set before evaluating and implementing their use given the high stakes present when managing chemotherapy.

References

1. Eschenhagen T, Force T, Ewer MS, de Keulenaer G, Suter TM, Anker SD, et al. Cardiovascular side effects of cancer therapies: a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2011; 13(1):1–10. [PubMed: 21169385]
2. Shan K, Lincoff AM, Young JB. Anthracycline-induced cardiotoxicity. Ann Intern Med. 1996; 125(1):47–58. [PubMed: 8644988]
3. Steinberg JS, Cohen AJ, Wasserman AG, Cohen P, Ross AM. Acute arrhythmogenicity of doxorubicin administration. Cancer. 1987; 60(6):1213–1218. [PubMed: 3621107]
4. Aleman BM, van den Belt-Dusebout AW, De Bruin ML, van ‘t Veer MB, Baaijens MH, de Boer JP, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. Blood. 2007; 109(5):1878–1886. [PubMed: 17119114]

5. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2012; 14(8):803–869. [PubMed: 22828712]
6. Ewer MS, Lenihan DJ. Left ventricular ejection fraction and cardiotoxicity: is our ear really to the ground? J Clin Oncol. 2008; 26(8):1201–1203. [PubMed: 18227525]
7. Ewer MS, Lippman SM. Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. J Clin Oncol. 2005; 23(13):2900–2902. [PubMed: 15860848]
8. Raj S, Franco VI, Lipshultz SE. Anthracycline-induced cardiotoxicity: a review of pathophysiology, diagnosis, and treatment. Curr Treat Options Cardiovasc Med. 2014; 16(6):315. [PubMed: 24748018]
9. Doroshow JH. Effect of anthracycline antibiotics on oxygen radical formation in rat heart. Cancer Res. 1983; 43(2):460–472. [PubMed: 6293697]
10. Abd, El-Aziz MA.; Othman, AI.; Amer, M.; El-Missiry, MA. Potential protective role of angiotensin-converting enzyme inhibitors captopril and enalapril against adriamycin-induced acute cardiac and hepatic toxicity in rats. J Appl Toxicol. 2001; 21(6):469–473. [PubMed: 11746193]
11. Lotrionte M, Biondi-Zoccai G, Abbate A, Lanzetta G, D'Ascenzo F, Malavasi V, et al. Review and meta-analysis of incidence and clinical predictors of anthracycline cardiotoxicity. Am J Cardiol. 2013; 112(12):1980–1984. [PubMed: 24075281]
12. Smith LA, Cornelius VR, Plummer CJ, Levitt G, Verrill M, Canney P, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. BMC Cancer. 2010; 10:337. [PubMed: 20587042]
13. Friedman MA, Bozdech MJ, Billingham ME, Rider AK. Doxorubicin cardiotoxicity. Serial endomyocardial biopsies and systolic time intervals. JAMA. 1978; 240(15):1603–1606. [PubMed: 691145]
14. Steinherz LJ, Steinherz PG, Tan CT, Heller G, Murphy ML. Cardiac toxicity 4 to 20 years after completing anthracycline therapy. JAMA. 1991; 266(12):1672–1677. [PubMed: 1886191]
15. Volkova M, Russell R 3rd. Anthracycline cardiotoxicity: prevalence, pathogenesis and treatment. Curr Cardiol Rev. 2011; 7(4):214–220. [PubMed: 22758622]
16. Bristow MR, Mason JW, Billingham ME, Daniels JR. Dose-effect and structure-function relationships in doxorubicin cardiomyopathy. Am Heart J. 1981; 102(4):709–718. [PubMed: 7282516]
17. Gottdiener JS, Appelbaum FR, Ferrans VJ, Deisseroth A, Ziegler J. Cardiotoxicity associated with high-dose cyclophosphamide therapy. Arch Intern Med. 1981; 141(6):758–763. [PubMed: 7235784]
18. Auner HW, Tinchon C, Brezinschek RI, Eibl M, Sormann S, Maizen C, et al. Monitoring of cardiac function by serum cardiac troponin T levels, ventricular repolarisation indices, and echocardiography after conditioning with fractionated total body irradiation and high-dose cyclophosphamide. Eur J Haematol. 2002; 69(1):1–6. [PubMed: 12270055]
19. Auner HW, Tinchon C, Linkesch W, Tiran A, Quehenberger F, Link H, et al. Prolonged monitoring of troponin T for the detection of anthracycline cardiotoxicity in adults with hematological malignancies. Ann Hematol. 2003; 82(4):218–222. [PubMed: 12679885]
20. Fujimaki K, Maruta A, Yoshida M, Sakai R, Tanabe J, Koharazawa H, et al. Severe cardiac toxicity in hematological stem cell transplantation: predictive value of reduced left ventricular ejection fraction. Bone Marrow Transplant. 2001; 27(3):307–310. [PubMed: 11277179]
21. Zver S, Zadnik V, Cernelc P, Kozelj M. Cardiac toxicity of high-dose cyclophosphamide and melphalan in patients with multiple myeloma treated with tandem autologous hematopoietic stem cell transplantation. Int J Hematol. 2008; 88(2):227–236. [PubMed: 18548196]
22. Kuittinen T, Jantunen E, Vanninen E, Mussalo H, Vuolteenaho O, Ala-Kopsala M, et al. Cardiac effects within 3 months of BEAC high-dose therapy in non-Hodgkin's lymphoma patients undergoing autologous stem cell transplantation. Eur J Haematol. 2006; 77(2):120–127. [PubMed: 16856907]

23. Jones RL, Ewer MS. Cardiac and cardiovascular toxicity of nonanthracycline anticancer drugs. Expert Rev Anticancer Ther. 2006; 6(9):1249–1269. [PubMed: 17020459]
24. Rowinsky EK, McGuire WP, Guarnieri T, Fisherman JS, Christian MC, Donehower RC. Cardiac disturbances during the administration of taxol. J Clin Oncol. 1991; 9(9):1704–1712. [PubMed: 1678781]
25. Albini A, Pennesi G, Donatelli F, Cammarota R, De Flora S, Noonan DM. Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio-oncological prevention. J Natl Cancer Inst. 2010; 102(1):14–25. [PubMed: 20007921]
26. Schober C, Papageorgiou E, Harstrick A, Bokemeyer C, Mugge A, Stahl M, et al. Cardiotoxicity of 5-fluorouracil in combination with folinic acid in patients with gastrointestinal cancer. Cancer. 1993; 72(7):2242–2247. [PubMed: 8374883]
27. Tsibiribi P, Descotes J, Lombard-Bohas C, Barel C, Bui-Xuan B, Belkhiria M, et al. Cardiotoxicity of 5-fluorouracil in 1350 patients with no prior history of heart disease. Bull Cancer. 2006; 93(3):E27–E30. [PubMed: 16567310]
28. Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. J Am Coll Cardiol. 2009; 53(24):2231–2247. [PubMed: 19520246]
29. Sorrentino MF, Kim J, Foderaro AE, Truesdell AG. 5-fluorouracil induced cardiotoxicity: review of the literature. Cardiol J. 2012; 19(5):453–458. [PubMed: 23042307]
30. Labianca R, Beretta G, Clerici M, Fraschini P, Luporini G. Cardiac toxicity of 5-fluorouracil: a study on 1083 patients. Tumori. 1982; 68(6):505–510. [PubMed: 7168016]
31. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010; 376(9742):687–697. [PubMed: 20728210]
32. Suter TM, Cook-Bruns N, Barton C. Cardiotoxicity associated with trastuzumab (Herceptin) therapy in the treatment of metastatic breast cancer. Breast. 2004; 13(3):173–183. [PubMed: 15177418]
33. Ewer MS, Vooletich MT, Durand JB, Woods ML, Davis JR, Valero V, et al. Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. J Clin Oncol. 2005; 23(31):7820–7826. [PubMed: 16258084]
34. Crone SA, Zhao YY, Fan L, Gu Y, Minamisawa S, Liu Y, et al. ErbB2 is essential in the prevention of dilated cardiomyopathy. Nat Med. 2002; 8(5):459–465. [PubMed: 11984589]
35. Onitilo AA, Engel JM, Stankowski RV, Liang H, Berg RL, Doi SA. High-sensitivity C-reactive protein (hs-CRP) as a biomarker for trastuzumab-induced cardiotoxicity in HER2-positive early-stage breast cancer: a pilot study. Breast Cancer Res Treat. 2012; 134(1):291–298. [PubMed: 22476854]
36. Russell SD, Blackwell KL, Lawrence J, Pippen JE Jr. Roe MT, Wood F, et al. Independent adjudication of symptomatic heart failure with the use of doxorubicin and cyclo-phosphamide followed by trastuzumab adjuvant therapy:acombined review of cardiac data from the National Surgical Adjuvant breast and Bowel Project B-31 and the North Central Cancer Treatment Group N9831 clinical trials. J Clin Oncol. 2010; 28(21):3416–3421. [PubMed: 20530275]
37. Smith I, Procter M, Gelber RD, Guillaume S, Feyereislova A, Dowsett M, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet. 2007; 369(9555):29–36. [PubMed: 17208639]
38. Ewer SM, Ewer MS. Cardiotoxicity profile of trastuzumab. Drug Saf. 2008; 31(6):459–467. [PubMed: 18484781]
39. Balduzzi S, Mantarro S, Guarneri V, Tagliabue L, Pistotti V, Moja L, et al. Trastuzumab-containing regimens for metastatic breast cancer. Cochrane Database Syst Rev. 2014:6. [CD006242].
40. Ozcelik C, Erdmann B, Pilz B, Wettschureck N, Britsch S, Hubner N, et al. Conditional mutation of the ErbB2 (HER2) receptor in cardiomyocytes leads to dilated cardio-myopathy. Proc Natl Acad Sci U S A. 2002; 99(13):8880–8885. [PubMed: 12072561]

41. Pivot X, Romieu G, Debled M, Pierga JY, Kerbrat P, Bachelot T, et al. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. Lancet Oncol. 2013; 14(8):741–748. [PubMed: 23764181]
42. Vaz-Luis I, Keating NL, Lin NU, Lii H, Winer EP, Freedman RA. Duration and toxicity of adjuvant trastuzumab in older patients with early-stage breast cancer: a population-based study. J Clin Oncol. 2014; 32(9):927–934. [PubMed: 24516021]
43. Schmidinger M, Zielinski CC, Vogl UM, Bojic A, Bojic M, Schukro C, et al. Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. J Clin Oncol. 2008; 26(32):5204–5212. [PubMed: 18838713]
44. Chu TF, Rupnick MA, Kerkela R, Dallabrida SM, Zurakowski D, Nguyen L, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. Lancet. 2007; 370(9604):2011–2019. [PubMed: 18083403]
45. Richards CJ, Je Y, Schutz FA, Heng DY, Dallabrida SM, Moslehi JJ, et al. Incidence and risk of congestive heart failure in patients with renal and nonrenal cell carcinoma treated with sunitinib. J Clin Oncol. 2011; 29(25):3450–3456. [PubMed: 21810682]
46. Force T, Krause DS, Van Etten RA. Molecular mechanisms of cardiotoxicity of tyrosine kinase inhibition. Nat Rev Cancer. 2007; 7(5):332–344. [PubMed: 17457301]
47. Kerkela R, Grazette L, Yacobi R, Iliescu C, Patten R, Beahm C, et al. Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. Nat Med. 2006; 12(8):908–916. [PubMed: 16862153]
48. Perik PJ, Rikhof B, de Jong FA, Verweij J, Gietema JA, van der Graaf WT. Results of plasma N-terminal pro B-type natriuretic peptide and cardiac troponin monitoring in GIST patients do not support the existence of imatinib-induced cardiotoxicity. Ann Oncol. 2008; 19(2):359–361. [PubMed: 17962203]
49. Herman EH, Knapton A, Rosen E, Thompson K, Rosenzweig B, Estis J, et al. A multi-faceted evaluation of imatinib-induced cardiotoxicity in the rat. Toxicol Pathol. 2011; 39(7):1091–1106. [PubMed: 21937741]
50. Ribeiro AL, Marcolino MS, Bittencourt HN, Barbosa MM, Nunes Mdo C, Xavier VF, et al. An evaluation of the cardiotoxicity of imatinib mesylate. Leuk Res. 2008; 32(12):1809–1814. [PubMed: 18495246]
51. Gambacorti-Passerini C, Tornaghi L, Franceschino A, Piazza R, Corneo G, Pogliani E. In reply to ‘Cardiotoxicity of the cancer therapeutic agent imatinib mesylate’. Nat Med. 2007; 13(1):13–14. [author reply 5–6]. [PubMed: 17206117]
52. Park YH, Park HJ, Kim BS, Ha E, Jung KH, Yoon SH, et al. BNP as a marker of the heart failure in the treatment of imatinib mesylate. Cancer Lett. 2006; 243(1):16–22. [PubMed: 16388897]
53. Kelly K, Swords R, Mahalingam D, Padmanabhan S, Giles FJ. Serosal inflammation (pleural and pericardial effusions) related to tyrosine kinase inhibitors. Target Oncol. 2009; 4(2):99–105. [PubMed: 19381453]
54. Gressett SM, Shah SR. Intricacies of bevacizumab-induced toxicities and their management. Ann Pharmacother. 2009; 43(3):490–501. [PubMed: 19261963]
55. Hawkes EA, Okines AF, Plummer C, Cunningham D. Cardiotoxicity in patients treated with bevacizumab is potentially reversible. J Clin Oncol. 2011; 29(18):e560–e562. [PubMed: 21606423]
56. Khawaja MZ, Cafferkey C, Rajani R, Redwood S, Cunningham D. Cardiac complications and manifestations of chemotherapy for cancer. Heart. 2014; 100(14):1133–1140. [PubMed: 24326899]
57. Morrow DA, Cannon CP, Jesse RL, Newby LK, Ravkilde J, Storrow AB, et al. National Academy Of Clinical Biochemistry Laboratory Medicine Practice Guidelines: clinical characteristics and utilization of biochemical markers in acute coronary syndromes. Circulation. 2007; 115(13):e356–e375. [PubMed: 17384331]
58. Yancy CW, Jessup M, Bozlurt B, Butler J, Casey DE Jr. Drazner MH, et al. 2013 ACCF/ AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013; 62(16):e147–e239. [PubMed: 23747642]

59. Hayes DF. OMICS-based personalized oncology: if it is worth doing, it is worth doing well! BMC Med. 2013; 11:221. [PubMed: 24228698]
60. Morrow DA, de Lemos JA. Benchmarks for the assessment of novel cardiovascular biomarkers. Circulation. 2007; 115(8):949–952. [PubMed: 17325253]
61. Apple FS, Collinson PO. Biomarkers ITFoCAoC. Analytical characteristics of high-sensitivity cardiac troponin assays. Clin Chem. 2012; 58(1):54–61. [PubMed: 21965555]
62. Henry NL, Hayes DF. Cancer biomarkers. Mol Oncol. 2012; 6(2):140–146. [PubMed: 22356776]
63. Febbo PG, Ladanyi M, Aldape KD, De Marzo AM, Hammond ME, Hayes DF, et al. NCCN Task Force report: evaluating the clinical utility of tumor markers in oncology. J Natl Compr Canc Netw. 2011; 9(Suppl. 5):S1–S32. [quiz S3].
64. Wallace KB, Hausner E, Herman E, Holt GD, MacGregor JT, Metz AL, et al. Serum troponins as biomarkers of drug-induced cardiac toxicity. Toxicol Pathol. 2004; 32(1):106–121. [PubMed: 14713555]
65. Missov E, Calzolari C, Davy JM, Leclercq F, Rossi M, Pau B. Cardiac troponin I in patients with hematologic malignancies. Coron Artery Dis. 1997; 8(8–9):537–541. [PubMed: 9431482]
66. Herman EH, Lipshultz SE, Rifai N, et al. Use of cardiac troponin T levels as an indicator of doxorubicin-induced cardiotoxicity. Cancer Res. 1998; 58(2):195–197. [PubMed: 9443390]
67. Herman EH, Lipshultz SE, Rifai N, Zhang J, Papoian T, Yu ZX, et al. Correlation between serum levels of cardiac troponin-T and the severity of the chronic cardiomyopathy induced by doxorubicin. J Clin Oncol. 1999; 17(7):2237–2243. [PubMed: 10561281]
68. Cardinale D, Sandri MT, Colombo A, Colombo N, Boeri M, Lamantia G, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. Circulation. 2004; 109(22):2749–2754. [PubMed: 15148277]
69. Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Tan TC, et al. Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab. Circ Cardiovasc Imaging. 2012; 5(5):596–603. [PubMed: 22744937]
70. Lee HS, Son CB, Shin SH, Kim YS. Clinical correlation between brain natriuretic peptide and anthracycline-induced cardiac toxicity. Cancer Res Treat Off J Korean Cancer Assoc. 2008; 40(3): 121–126.
71. Mavinkurve-Groothuis AM, Marcus KA, Pourier M, Loonen J, Feuth T, Hoogerbrugge PM, et al. Myocardial 2D strain echocardiography and cardiac biomarkers in children during and shortly after anthracycline therapy for acute lymphoblastic leukaemia (ALL): a prospective study. Eur Heart J Cardiovasc Imaging. 2013; 14(6):562–569. [PubMed: 23109647]
72. Lipshultz SE, Rifai N, Sallan SE, Lipsitz SR, Dalton V, Sacks DB, et al. Predictive value of cardiac troponin T in pediatric patients at risk for myocardial injury. Circulation. 1997; 96(8): 2641–2648. [PubMed: 9355905]
73. Specchia G, Buquicchio C, Pansini N, Serio F, Liso V, Pastore D, et al. Monitoring of cardiac function n the basis of serum troponin I levels in patients with acute leukemia treated with anthracyclines. J Lab Clin Med. 2005; 145(4):212–220. [PubMed: 15962840]
74. Kilickap S, Barista I, Akgul E, Aytemir K, Aksoyek S, Aksoy S, et al. cTnT can be a useful marker for early detection of anthracycline cardiotoxicity. Ann Oncol. 2005; 16(5):798–804. [PubMed: 15774486]
75. Ruggiero A, De Rosa G, Rizzo D, Leo A, Maurizi P, De Nisco A, et al. Myocardial performance index and biochemical markers for early detection of doxorubicin-induced cardiotoxicity in children with acute lymphoblastic leukaemia. Int J Clin Oncol. 2013; 18(5):927–933. [PubMed: 22911020]
76. Dolci A, Dominici R, Cardinale D, Sandri MT, Panteghini M. Biochemical markers for prediction of chemotherapy-induced cardiotoxicity: systematic review of the literature and recommendations for use. Am J Clin Pathol. 2008; 130(5):688–695. [PubMed: 18854260]
77. Ky B, Putt M, Sawaya H, French B, Januzzi JL Jr. Sebag IA, et al. Early increases in multiple biomarkers predict subsequent cardiotoxicity in patients with breast cancer treated with doxorubicin, taxanes, and trastuzumab. J Am Coll Cardiol. 2014; 63(8):809–816. [PubMed: 24291281]

78. Cardinale D, Sandri MT, Martinoni A, Borghini E, Civelli M, Lamantia G, et al. Myo-cardial injury revealed by plasma troponin I in breast cancer treated with high-dose chemotherapy. Ann Oncol. 2002; 13(5):710–715. [PubMed: 12075738]

79. Garrone O, Crosetto N, Lo Nigro C, Catzeddu T, Vivenza D, Monteverde M, et al. Prediction of anthracycline cardiotoxicity after chemotherapy by biomarkers kinetic analysis. Cardiovasc Toxicol. 2012; 12(2):135–142. [PubMed: 22189487]

80. Mornos C, Petrescu L. Early detection of anthracycline-mediated cardiotoxicity: the value of considering both global longitudinal left ventricular strain and twist. Can J Physiol Pharmacol. 2013; 91(8):601–607. [PubMed: 23889668]

81. Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Cohen V, et al. Early detection and prediction of cardiotoxicity in chemotherapy-treated patients. Am J Cardiol. 2011; 107(9):1375–1380. [PubMed: 21371685]

82. Cardinale D, Colombo A, Sandri MT, Lamantia G, Colombo N, Civelli M, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. Circulation. 2006; 114(23):2474–2481. [PubMed: 17101852]

83. Cardinale D, Sandri MT, Martinoni A, Tricca A, Civelli M, Lamantia G, et al. Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. J Am Coll Cardiol. 2000; 36(2):517–522. [PubMed: 10933366]

84. Sandri MT, Cardinale D, Zorzino L, Passerini R, Lentati P, Martinoni A, et al. Minor increases in plasma troponin I predict decreased left ventricular ejection fraction after high-dose chemotherapy. Clin Chem. 2003; 49(2):248–252. [PubMed: 12560347]

85. Drafts BC, Twomley KM, D'Agostino R Jr. Lawrence J, Avis N, Ellis LR, et al. Low to moderate dose anthracycline-based chemotherapy is associated with early non-invasive imaging evidence of subclinical cardiovascular disease. JACC Cardiovasc Imaging. 2013; 6(8):877–885. [PubMed: 23643285]

86. Romano S, Fratini S, Ricevuto E, Procaccini V, Stifano G, Mancini M, et al. Serial measurements of NT-proBNP are predictive of not-high-dose anthracycline cardiotoxicity in breast cancer patients. Br J Cancer. 2011; 105(11):1663–1668. [PubMed: 22068815]

87. Feola M, Garrone O, Occelli M, Francini A, Biggi A, Visconti G, et al. Cardiotoxicity after anthracycline chemotherapy in breast carcinoma: effects on left ventricular ejection fraction, troponin I and brain natriuretic peptide. Int J Cardiol. 2011; 148(2):194–198. [PubMed: 19945181]

88. Erkus B, Demirtas S, Yarpuzlu AA, Can M, Genc Y, Karaca L. Early prediction of anthracycline induced cardiotoxicity. Acta Paediatr. 2007; 96(4):506–509. [PubMed: 17391467]

89. Fink FM, Genser N, Fink C, Falk M, Mair J, Maurer-Dengg K, et al. Cardiac troponin T and creatine kinase MB mass concentrations in children receiving anthracycline chemotherapy. Med Pediatr Oncol. 1995; 25(3):185–189. [PubMed: 7623727]

90. Kismet E, Varan A, Ayabakan C, Alehan D, Portakal O, Buyukpamukcu M. Serum troponin T levels and echocardiographic evaluation in children treated with doxorubicin. Pediatr Blood Cancer. 2004; 42(3):220–224. [PubMed: 14752858]

91. Dodos F, Halbsguth T, Erdmann E, Hoppe UC. Usefulness of myocardial performance index and biochemical markers for early detection of anthracycline-induced cardiotoxicity in adults. Clin Res Cardiol. 2008; 97(5):318–326. [PubMed: 18193371]

92. Grover S, Leong DP, Chakrabarty A, Joerg L, Kotasek D, Cheong K, et al. Left and right ventricular effects of anthracycline and trastuzumab chemotherapy: a prospective study using novel cardiac imaging and biochemical markers. Int J Cardiol. 2013; 168(6):5465–5467. [PubMed: 24090744]

93. Koseoglu V, Berberoglu S, Karademir S, Kismet E, Yurttutan N, Demirkaya E, et al. Cardiac troponin I: is it a marker to detect cardiotoxicity in children treated with doxorubicin? Turk J Pediatr. 2005; 47(1):17–22. [PubMed: 15884624]

94. Kremer LC, Bastiaansen BA, Offringa M, Lam J, van Straalen JP, de Winter RJ, et al. Troponin T in the first 24 hours after the administration of chemotherapy and the detection of myocardial damage in children. Eur J Cancer. 2002; 38(5):686–689. [PubMed: 11916551]

95. Soker M, Kervancioglu M. Plasma concentrations of NT-pro-BNP and cardiac troponin-I in relation to doxorubicin-induced cardiomyopathy and cardiac function in childhood malignancy. Saudi Med J. 2005; 26(8):1197–1202. [PubMed: 16127512]

96. Berridge BR, Pettit S, Walker DB, Jaffe AS, Schultze AE, Herman E, et al. A translational approach to detecting drug-induced cardiac injury with cardiac troponins: consensus and recommendations from the Cardiac Troponins Biomarker Working Group of the Health and Environmental Sciences Institute. Am Heart J. 2009; 158(1):21–29. [PubMed: 19540388]

97. Dhesy-Thind S, Kumar V, Snider-McNair A, Shortt C, Mukherjee SD, Ellis P, et al. Cardiac and inflammation biomarker profile after initiation of adjuvant trastuzumab therapy. Clin Chem. 2013; 59(1):327–329. [PubMed: 22997283]

98. Horacek JM, Tichy M, Pudil R, Jebavy L. Glycogen phosphorylase BB could be a new circulating biomarker for detection of anthracycline cardiotoxicity. Ann Oncol. 2008; 19(9):1656–1657. [PubMed: 18622008]

99. Horacek JM, Pudil R, Tichy M, Jebavy L, Strasova A, Ulrychova M, et al. Cardiac tro-ponin I seems to be superior to cardiac troponin T in the early detection of cardiac injury associated with anthracycline treatment. Onkologie. 2008; 31(10):559–560. [PubMed: 18854658]

100. Cardinale D, Colombo A, Torrisi R, Sandri MT, Civelli M, Salvatici M, et al. Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of tropo-nin I evaluation. J Clin Oncol. 2010; 28(25):3910–3916. [PubMed: 20679614]

101. Shortt C, Mansour M, Dhesy-Thind S, Hotte S, Leong D, Worster A, et al. Myocardial injury in cancer patients – are there differences between women and men? AACC Ann Meet. 2014:S222. [B-353].

102. D'Alessandro R, Masarone D, Buono A, Gravino R, Rea A, Salerno G, et al. Natriuretic peptides: molecular biology, pathophysiology and clinical implications for the cardiologist. Future Cardiol. 2013; 9(4):519–534. [PubMed: 23834693]

103. Gimeno E, Gomez M, Gonzalez JR, Comin J, Alvarez-Larran A, Sanchez-Gonzalez B, et al. NT-proBNP: a cardiac biomarker to assess prognosis in non-Hodgkin lymphoma. Leuk Res. 2011; 35(6):715–720. [PubMed: 21333352]

104. Geiger S, Stemmler HJ, Suhl P, Stieber P, Lange V, Baur D, et al. Anthracycline-induced cardiotoxicity: cardiac monitoring by continuous wave-Doppler ultrasound cardiac output monitoring and correlation to echocardiography. Onkologie. 2012; 35(5):241–246. [PubMed: 22868502]

105. Aggarwal S, Pettersen MD, Bhambhani K, Gurczynski J, Thomas R, L'Ecuyer T. B-type natriuretic peptide as a marker for cardiac dysfunction in anthracycline-treated children. Pediatr Blood Cancer. 2007; 49(6):812–816. [PubMed: 17171687]

106. Okumura H, Iuchi K, Yoshida T, Nakamura S, Takeshima M, Takamatsu H, et al. Brain natriuretic peptide is a predictor of anthracycline-induced cardiotoxicity. Acta Haematol. 2000; 104(4):158–163. [PubMed: 11279304]

107. Lipshultz SE, Miller TL, Scully RE, Lipsitz SR, Rifai N, Silverman LB, et al. Changes in cardiac biomarkers during doxorubicin treatment of pediatric patients with high-risk acute lymphoblastic leukemia: associations with long-term echocardiographic outcomes. J Clin Oncol. 2012; 30(10): 1042–1049. [PubMed: 22370326]

108. Suzuki T, Hayashi D, Yamazaki T, Mizuno T, Kanda Y, Komuro I, et al. Elevated B-type natriuretic peptide levels after anthracycline administration. Am Heart J. 1998; 136(2):362–363. [PubMed: 9704703]

109. Sandri MT, Salvatici M, Cardinale D, Zorzino L, Passerini R, Lentati P, et al. N-terminal pro-B-type natriuretic peptide after high-dose chemotherapy: a marker predictive of cardiac dysfunction? Clin Chem. 2005; 51(8):1405–1410. [PubMed: 15932966]

110. Bauch M, Ester A, Kimura B, Victorica BE, Kedar A, Phillips MI. Atrial natriuretic peptide as a marker for doxorubicin-induced cardiotoxic effects. Cancer. 1992; 69(6):1492–1497. [PubMed: 1531780]

111. Daugaard G, Lassen U, Bie P, Pedersen EB, Jensen KT, Abildgaard U, et al. Natriuretic peptides in the monitoring of anthracycline induced reduction in left ventricular ejection fraction. Eur J Heart Fail. 2005; 7(1):87–93. [PubMed: 15642537]

112. Meinardi MT, van Veldhuisen DJ, Gietema JA, Dolsma WV, Boomsma F, van den Berg MP, et al. Prospective evaluation of early cardiac damage induced by epirubicin-containing adjuvant chemotherapy and locoregional radiotherapy in breast cancer patients. J Clin Oncol. 2001; 19(10):2746–2753. [PubMed: 11352968]

113. Poutanen T, Tikanoja T, Riikonen P, Silvast A, Perkkio M. Long-term prospective follow-up study of cardiac function after cardiotoxic therapy for malignancy in children. J Clin Oncol. 2003; 21(12):2349–2356. [PubMed: 12805337]

114. Hayakawa H, Komada Y, Hirayama M, Hori H, Ito M, Sakurai M. Plasma levels of natriuretic peptides in relation to doxorubicin-induced cardiotoxicity and cardiac function in children with cancer. Med Pediatr Oncol. 2001; 37(1):4–9. [PubMed: 11466716]

115. Pichon MF, Cvitkovic F, Hacene K, Delaunay J, Lokiec F, Collignon MA, et al. Drug-induced cardiotoxicity studied by longitudinal B-type natriuretic peptide assays and radionuclide ventriculography. In Vivo. 2005; 19(3):567–576. [PubMed: 15875778]

116. Nousiainen T, Jantunen E, Vanninen E, Remes J, Vuolteenaho O, Hartikainen J. Natriuretic peptides as markers of cardiotoxicity during doxorubicin treatment for non-Hodgkin's lymphoma. Eur J Haematol. 1999; 62(2):135–141. [PubMed: 10052718]

117. Kouloubinis A, Kaklamanis L, Ziras N, Sofroniadou S, Makaritsis K, Adamopoulos S, et al. ProANP and NT-proBNP levels to prospectively assess cardiac function in breast cancer patients treated with cardiotoxic chemotherapy. Int J Cardiol. 2007; 122(3):195–201. [PubMed: 17289172]

118. Sherief LM, Kamal AG, Khalek EA, Kamal NM, Soliman AA, Esh AM. Biomarkers and early detection of late onset anthracycline-induced cardiotoxicity in children. Hematology. 2012; 17(3):151–156. [PubMed: 22664114]

119. Lipshultz SE, Landy DC, Lopez-Mitnik G, Lipsitz SR, Hinkle AS, Constine LS, et al. Cardiovascular status of childhood cancer survivors exposed and unexposed to cardiotoxic therapy. J Clin Oncol. 2012; 30(10):1050–1057. [PubMed: 22393080]

120. Ekstein S, Nir A, Rein AJ, Perles Z, Bar-Oz B, Salpeter L, et al. N-terminal-proB-type natriuretic peptide as a marker for acute anthracycline cardiotoxicity in children. J Pediatr Hematol Oncol. 2007; 29(7):440–444. [PubMed: 17609620]

121. Nousiainen T, Jantunen E, Vanninen E, Remes J, Puustinen J, Rantala A, et al. Acute neurohumoral and cardiovascular effects of idarubicin in leukemia patients. Eur J Haematol. 1998; 61(5):347–353. [PubMed: 9855251]

122. Broeyer FJ, Osanto S, Ritsema van Eck HJ, van Steijn AQ, Ballieux BE, Schoemaker RC, et al. Evaluation of biomarkers for cardiotoxicity of anthracyclin-based chemotherapy. J Cancer Res Clin Oncol. 2008; 134(9):961–968. [PubMed: 18343950]

123. Mladosievicova B, Urbanova D, Radvanska E, Slavkovsky P, Simkova I. Role of NT-proBNP in detection of myocardial damage in childhood leukemia survivors treated with and without anthracyclines. J Exp Clin Cancer Res. 2012; 31:86. [PubMed: 23057994]

124. Morris PG, Chen C, Steingart R, Fleisher M, Lin N, Moy B, et al. Troponin I and C-reactive protein are commonly detected in patients with breast cancer treated with dose-dense chemotherapy incorporating trastuzumab and lapatinib. Clin Cancer Res. 2011; 17(10):3490–3499. [PubMed: 21372222]

125. Horacek JM, Tichy M, Jebavy L, Ulrychova M, Pudil R. Glycogen phosphorylase BB as a marker of cardiac toxicity during high-dose chemotherapy followed by hematopoietic cell transplantation. Ann Oncol. 2007; 18(12):2041. [PubMed: 17974554]

126. Horacek JM, Tichy M, Jebavy L, Pudil R, Ulrychova M, Maly J. Use of multiple biomarkers for evaluation of anthracycline-induced cardiotoxicity in patients with acute myeloid leukemia. Exp Oncol. 2008; 30(2):157–159. [PubMed: 18566582]

127. Fichtlscherer S, Zeiher AM, Dimmeler S. Circulating microRNAs: biomarkers or mediators of cardiovascular diseases? Arterioscler Thromb Vasc Biol. 2011; 31(11):2383–2390. [PubMed: 22011751]

128. Mendell JT, Olson EN. MicroRNAs in stress signaling and human disease. Cell. 2012; 148(6): 1172–1187. [PubMed: 22424228]

129. Horie T, Ono K, Nishi H, Nagao K, Kinoshita M, Watanabe S, et al. Acute doxorubicin cardiotoxicity is associated with miR-146a-induced inhibition of the neuregulin-ErbB pathway. Cardiovasc Res. 2010; 87(4):656–664. [PubMed: 20495188]
130. Wang JF, Yu ML, Yu G, Bian JJ, Deng XM, Wan XJ, et al. Serum miR-146a and miR-223 as potential new biomarkers for sepsis. Biochem Biophys Res Commun. 2010; 394(1):184–188. [PubMed: 20188071]
131. Pauley KM, Stewart CM, Gauna AE, Dupre LC, Kuklani R, Chan AL, et al. Altered miR-146a expression in Sjogren's syndrome and its functional role in innate immunity. Eur J Immunol. 2011; 41(7):2029–2039. [PubMed: 21469088]
132. Brase JC, Wuttig D, Kuner R, Sultmann H. Serum microRNAs as non-invasive biomarkers for cancer. Mol Cancer. 2010; 9:306. [PubMed: 21110877]
133. Haghikia A, Podewski E, Libhaber E, Labidi S, Fischer D, Roentgen P, et al. Phenotyping and outcome on contemporary management in a German cohort of patients with peripartum cardiomyopathy. Basic Res Cardiol. 2013; 108(4):366. [PubMed: 23812247]
134. Fan KL, Zhang HF, Shen J, Zhang Q, Li XL. Circulating microRNAs levels in Chinese heart failure patients caused by dilated cardiomyopathy. Indian Heart J. 2013; 65(1):12–16. [PubMed: 23438607]
135. Lipshultz SE, Rifai N, Dalton VM, Levy DE, Silverman LB, Lipsitz SR, et al. The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. N Engl J Med. 2004; 351(2):145–153. [PubMed: 15247354]
136. Lipshultz SE, Scully RE, Lipsitz SR, Sallan SE, Silverman LB, Miller TL, et al. Assessment of dexrazoxane as a cardioprotectant in doxorubicin-treated children with high-risk acute lymphoblastic leukaemia: long-term follow-up of a prospective, randomised, multicentre trial. Lancet Oncol. 2010; 11(10):950–961. [PubMed: 20850381]
137. Herman EH, Zhang J, Rifai N, Lipshultz SE, Hasinoff BB, Chadwick DP, et al. The use of serum levels of cardiac troponin T to compare the protective activity of dexrazoxane against doxorubicin- and mitoxantrone-induced cardiotoxicity. Cancer Chemother Pharmacol. 2001; 48(4):297–304. [PubMed: 11710630]
138. Swain SM, Whaley FS, Gerber MC, Weisberg S, York M, Spicer D, et al. Cardioprotection with dexrazoxane for doxorubicin-containing therapy in advanced breast cancer. J Clin Oncol. 1997; 15(4):1318–1332. [PubMed: 9193323]
139. Speyer JL, Green MD, Sanger J, Zeleniuch-Jacquotte A, Kramer E, Rey M, et al. A prospective randomized trial of ICRF-187 for prevention of cumulative doxorubicin-induced cardiac toxicity in women with breast cancer. Cancer Treat Rev. 1990; 17(2–3):161–163. [PubMed: 2125531]
140. Tebbi CK, London WB, Friedman D, Villaluna D, De Alarcon PA, Constine LS, et al. Dexrazoxane-associated risk for acute myeloid leukemia/myelodysplastic syndrome and other secondary malignancies in pediatric Hodgkin's disease. J Clin Oncol. 2007; 25(5):493–500. [PubMed: 17290056]
141. Barry EV, Vrooman LM, Dahlberg SE, Neuberg DS, Asselin BL, Athale UH, et al. Absence of secondary malignant neoplasms in children with high-risk acute lymphoblastic leukemia treated with dexrazoxane. J Clin Oncol. 2008; 26(7):1106–1111. [PubMed: 18309945]
142. van Dalen EC, Caron HN, Dickinson HO, Kremer LC. Cardioprotective interventions for cancer patients receiving anthracyclines. Cochrane Database Syst Rev. 2011:6. [CD003917].
143. Okumura K, Jin D, Takai S, Miyazaki M. Beneficial effects of angiotensin-converting enzyme inhibition in adriamycin-induced cardiomyopathy in hamsters. Jpn J Pharmacol. 2002; 88(2): 183–188. [PubMed: 11928719]
144. Cadeddu C, Piras A, Mantovani G, Deidda M, Dessi M, Madeddu C, et al. Protective effects of the angiotensin II receptor blocker telmisartan on epirubicin-induced inflammation, oxidative stress, and early ventricular impairment. Am Heart J. 2010; 160(3):487. e1–7. [PubMed: 20826257]
145. Tokudome T, Mizushige K, Noma T, Manabe K, Murakami K, Tsuji T, et al. Prevention of doxorubicin (adriamycin)-induced cardiomyopathy by simultaneous administration of angiotensin-converting enzyme inhibitor assessed by acoustic densitometry. J Cardiovasc Pharmacol. 2000; 36(3):361–368. [PubMed: 10975594]

146. Sacco G, Bigioni M, Evangelista S, Goso C, Manzini S, Maggi CA. Cardioprotective effects of zofenopril, a new angiotensin-converting enzyme inhibitor, on doxorubicin-induced cardiotoxicity in the rat. Eur J Pharmacol. 2001; 414(1):71–78. [PubMed: 11230997]

147. al-Shabanah O, Mansour M, el-Kashef H, al-Bekairi A. Captopril ameliorates myocardial and hematological toxicities induced by adriamycin. Biochem Mol Biol Int. 1998; 45(2):419–427. [PubMed: 9678264]

148. Vaynblat M, Shah HR, Bhaskaran D, Ramdev G, Davis WJ 3rd, Cunningham JN Jr. et al. Simultaneous angiotensin converting enzyme inhibition moderates ventricular dysfunction caused by doxorubicin. Eur J Heart Fail. 2002; 4(5):583–586. [PubMed: 12413500]

149. Jensen BV, Nielsen SL, Skovsgaard T. Treatment with angiotensin-converting-enzyme inhibitor for epirubicin-induced dilated cardiomyopathy. Lancet. 1996; 347(8997):297–299. [PubMed: 8569365]

150. Nakamae H, Tsumura K, Terada Y, Nakane T, Nakamae M, Ohta K, et al. Notable effects of angiotensin II receptor blocker, valsartan, on acute cardiotoxic changes after standard chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone. Cancer. 2005; 104(11):2492–2498. [PubMed: 16247790]

151. Colombo A, Sandri MT, Salvatici M, Cipolla CM, Cardinale D. Cardiac complications of chemotherapy: role of biomarkers. Curr Treat Options Cardiovasc Med. 2014; 16(6):313. [PubMed: 24771223]

152. Fazio S, Palmieri EA, Ferravante B, Bone F, Biondi B, Sacca L. Doxorubicin-induced cardiomyopathy treated with carvedilol. Clin Cardiol. 1998; 21(10):777–779. [PubMed: 9789703]

153. Yue TL, McKenna PJ, Ruffolo RR Jr. Feuerstein G. Carvedilol, a new beta-adrenoceptor antagonist and vasodilator antihypertensive drug, inhibits superoxide release from human neutrophils. Eur J Pharmacol. 1992; 214(2–3):277–280. [PubMed: 1355437]

154. Matsui H, Morishima I, Numaguchi Y, Toki Y, Okumura K, Hayakawa T. Protective effects of carvedilol against doxorubicin-induced cardiomyopathy in rats. Life Sci. 1999; 65(12):1265–1274. [PubMed: 10503942]

155. Munzel T, Gori T. Nebivolol: the somewhat-different beta-adrenergic receptor blocker. J Am Coll Cardiol. 2009; 54(16):1491–1499. [PubMed: 19815121]

156. Mukai Y, Yoshida T, Nakaike R, Mukai N, Iwato K, Kyo T, et al. Five cases of anthracycline-induced cardiomyopathy effectively treated with carvedilol. Intern Med. 2004; 43(11):1087–1088. [PubMed: 15609710]

157. Kalay N, Basar E, Ozdogru I, Er O, Cetinkaya Y, Dogan A, et al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. J Am Coll Cardiol. 2006; 48(11):2258–2262. [PubMed: 17161256]

158. Kaya MG, Ozkan M, Gunebakmaz O, Akkaya H, Kaya EG, Akpek M, et al. Protective effects of nebivolol against anthracycline-induced cardiomyopathy: a randomized control study. Int J Cardiol. 2013; 167(5):2306–2310. [PubMed: 22727976]

159. Batist G, Ramakrishnan G, Rao CS, Chandrasekharan A, Gutheil J, Guthrie T, et al. Reduced cardiotoxicity and preserved antitumor efficacy of liposome-encapsulated doxorubicin and cyclophosphamide compared with conventional doxorubicin and cyclophosphamide in a randomized, multicenter trial of metastatic breast cancer. J Clin Oncol. 2001; 19(5):1444–1454. [PubMed: 11230490]

160. O'Brien ME, Wigler N, Inbar M, Rosso R, Grischke E, Santoro A, et al. Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCI (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. Ann Oncol. 2004; 15(3):440–449. [PubMed: 14998846]

161. Lenihan DJ. Cardiac biomarkers, cardiotoxicity, and active collaboration: is this the final frontier or the wave we should catch? J Am Coll Cardiol. 2014; 63(8):817–818. [PubMed: 24291278]

Table 1

Studies evaluating the use of biomarkers to predict chemotherapy-induced cardiac toxicity.

	Troponin-I	
Papers demonstrating correlation between increase in biomarker and cardiotoxicity		
Cardinale et al. [83]	50 patients received EPI–CYC, 41 received taxotere–EPI–CYC, 48 received Ifosfamide–CARB–ETO 16 received taxotere–Ifosfamide–CARB–ETO, 49 received CYC.	All patients with decrease in LVEF of greater than 30% had TnI elevation greater than 0.5 ng/mL
Cardinale et al. [78]	51 patients received EPI–CYC (EC), 85 received taxotere–EPI–CYC (TEC), 43 patients who had previously been treated with anthracyclines received Ifosfamide–CARB–ETO (ICE) while 32 other patients previously treated with anthracyclines received taxotere–ifosfamide–CARB–ETO (TICE). All subsequently received radiotherapy.	The percentage of patients with TnI positivity was 53% in EC, 31% in TEC, 28% in ICE and 16% in TICE. A strong correlation was found between the magnitude of TnI rise and reduction in EF.
Cardinale et al. [68]	703 patients enrolled in a number of different regimens including: EPI–CYC; taxotere–EPI–CYC; ifosfamide–CARB–ETO; taxotere–isofamide–CARB–ETO; carmustine–ETO–cytarabine–melphalan; ETO–solumedrol–cytarabine–platinum; mitoxantrone; melphalan; idarubicin; sequential; CYC.	Correlation between elevated TnI and reduction in ejection fraction was even more likely in individuals with elevated Tn's at multiple time points during and after chemotherapy.
Cardinale et al. [100]	251 patients received TZT with or without other chemotherapy (197 had prior exposure to anthracyclines).	TnI identifies patients at risk for developing cardiotoxicity (including decrease in LVEF) who are unlikely to recover following completion of therapy.
Drafts et al. [85]	37 patients received DOX and 16 received daunorubicin.	TnI trended upward with therapy. 26% showed positivity by the end of 6 months, BNP fell during therapy.
Ky et al. [77]	78 patients received DOX–CYC every 3 weeks for 4 cycles, followed by PAC–TZT weekly for 12 weeks, followed by TZT every 3 weeks totaling a full year of therapy.	Increases in TnI and MPO levels were associated with the development of cardiac dysfunction.
Lee et al. [70]	67 patients received DOX, 15 received daunorubicin, 1 received EPI, 1 received idarubicin, 1 received DOX and EPI, 1 received DOX and idarubicin.	TnI and BNP concentrations correlated with anthracycline cumulative dose and LVEF. Heart failure was more common if BNP levels reached 100 pg/mL at least once.
Lipshultz et al. [107]	100 patients received DOX, 105 received DOX and dexrazoxane.	TnI and NT-proBNP levels during the first 90 days of treatment predicted the development of cardiac dysfunction 4 years later.
Morris et al. [124]	95 patients initially received DOX–CYC (DC) followed by PAC–TZT–lapatinib for 3 months with continuation of TZT–lapatinib for 1 year.	TnI rise preceded maximal decline in LV function, CRP did not correlate with cardiotoxicity.
Sandri et al. [84]	79 patients received TEC, 49 received CYC–MTX–ETO–idarubicin (SEQ), 26 received TICE, 17 received ICE, 8 received EC.	52 (32%) of patients with a positive TnI had a decrease in LVEF. No LV dysfunction was noted in the group with negative TnI.
Sawaya et al. [81]	39 patients received DOX–taxanes, 4 received EPI–taxanes; 10 received anthracycline containing chemotherapy prior to	TnI elevation at 3 months was predictive of the development of LV

	Troponin-I	
	enrollment.	dysfunction at 6 months.
Sawaya et al. [69]	82 patients received DOX or EPI for 3 months followed by weekly PAC–TZT for 3 months followed by 9 more months of TZT.	TnI and peak systolic myocardial strain predicted cardiotoxicity, no significant associations were observed for LVEF, NT-proBNP or ST-2, and the development of heart failure.
Specchia et al. [73]	Anthracycline containing chemotherapy with median doses of daunorubicin 300 mg/m^2, idarubicin 51 mg/m^2, and mitoxantrone 47 mg/m^2	Echocardiography findings showed transient decrease in EF correlated with increased TnI levels
Papers failing to demonstrate correlation between increase in biomarker and cardiotoxicity		
Grover et al. [92]	46 patients received three to six 21 day cycles of EPI, DOX, and/or TZT with or without taxanes.	TnI and CRP increased with therapy but did not correlate with subsequent LV dysfunction.
Soker et al. [95]	31 patients received DOX based therapy.	NT-proBNP levels were significantly more elevated in patients with LV dysfunction, cTnI remained undetectable throughout the study.
Zver et al. [21]	30 patients received VCR–EPI–dexamethasone followed by CYC–melphalan followed by autologous hematopoietic stem cell transplantation.	Increased levels of BNP and ET-1 were associated with worsening LV diastolic dysfunction. TnI remained within the normal range.
	Troponin-T	
Papers demonstrating correlation between increase in biomarker and cardiotoxicity		
Auner et al. [18]	2 patients received DOX, 28 received pegylated liposomal DOX, 3 received daunorubicin, 43 received idarubicin, 58 received Mitoxantrone.	Patients with positive TnT levels correlated with greater decrease in LVEF.
Geiger et al. [104]	40 patients received DOX, 6 received mitoxantrone–daunorubicin, 2 received mitoxantrone, 1 received liposomal DOX, 1 received liposomal DOX.	NT-proBNP levels increased more in patients who subsequently developed reduced EF, TnT levels increased following chemotherapy and were also associated with reduced EF.
Kilickap et al. [74]	29 patients received DOX, 5 received idarubicin, 4 received daunorubicin, 3 received EPI.	Positive TnT levels were associated with LV diastolic dysfunction in younger patients.
Mavinkurve-Groothuis et al. [71]	60 patients received 120 mg/m^2 of anthracyclines and were then stratified to low (n = 20), moderate (n = 30) or high risk (n = 10) based on response with moderate risk receiving an additional 180 mg/m^2 of anthracycline and high risk receiving either an additional 120 mg/m^2 anthracycline +18 mg/m^2 idarubicin +52.5 mg/m^2 mitoxantrone or consideration of bone marrow transplantation.	TnT elevations predicted some LV dysfunction, NT-proBNP was not predictive of cardiac toxicity.
Mornos et al. [80]	100 patients received anthracycline containing therapy.	Changes in TnT levels predicted the development of cardiac toxicity while changes in NT-proBNP did not show significant predictive value.
	Troponin-I	
Papers failing to demonstrate		

	Troponin-I	
correlation between increase in biomarker and cardiotoxicity		
Kremer et al. [94]	20 patients received DOX, 4 received daunorubicin, 9 received EPI, 5 received mitoxantrone.	Measurement of TnT within the first 24 h of chemotherapy did not predict subsequent development of cardiac toxicity.
Dodos et al. [91]	100 patients received anthracycline containing chemotherapy, 53 received DOX, 29 received EPI, 15 received daunorubicin, 2 received mitoxantrone, and 1 received idarubicin.	TnT and BNP did not predict subsequent development of cardiac dysfunction.
	B-type naturetic peptide	
Papers demonstrating correlation between increase in biomarker and cardiotoxicity		
	Anthracycline containing regimens	
Hayakawa et al. [114]	34 patients received DOX-based chemotherapy more than 1 month prior.	Both ANP and BNP levels correlated with both the cumulative dose of anthracycline and LV systolic dysfunction.
Lipshultz et al. [107]	100 patients received DOX, 105 received DOX and dexrazoxane.	TnT levels rose during treatment in the DOX group and to a lesser extent the group with dexrazoxane coadministration, NT-proBNP levels were initially elevated, fell in both groups although to a lesser extent in the group without dexrazone, NT-proBNP rose again post-treatment in the DOX group but continued to fall in the dexrazosin coadministration group. hsCRP was not significantly different between groups. TnI and NTproBNP levels during the first 90 days of treatment predicted the development of cardiac dysfunction 4 years later.
Sandri et al. [109]	52 patients received HDC	Persistently elevated NT-proBNP levels strongly associated with the development of systolic and diastolic dysfunction following HDC.
Nakamae et al. [150]	40 patients received CYC–DOX–VCR–prednisolone (CHOP therapy).	CHOP induced transient increases in the LV end-diastolic diameter on echocardiogram and in the plasma BNP and ANP. Valsartan therapy prevented elevation in BNP and LV end-diastolic diameter, but not ANP.
Pichon et al. [115]	50 patients received anthracycline based therapy, 17 patients were pre-treated with anthracycline-based therapy followed by TZT and taxanes or vinorelbine.	BNP concentrations correlated with anthracycline cumulative dose and LVEF.
Lee et al. [70]	67 patients received DOX, 15 received daunorubicin, 1 received EPI, 1 received idarubicin, 1 received DOX and EPI, 1 received DOX and idarubicin.	BNP and TnI concentrations correlated with cumulative anthracycline dose and LVEF. Heart failure was more common if BNP levels reached 100 pg/mL at least once.
Romano et al. [86]	34 patients received liposomal DOX–docetaxel and 37 received EPI–5-FU–CYC.	Persistently elevated NT-proBNP levels were associated with subsequent impairment of LV function.

	Troponin-I	
Feola et al. [87]	53 patients received six 21 day cycles of CYC–EPI–5-FU.	BNP levels correlated with LV systolic dysfunction
Kouloubinis et al. [117]	26 patients received six 21 day cycles of EPI–paclitaxel, 14 received six 21 day cycles of mitoxantrone–docetaxel.	proANP and NT-proBNP levels correlated with LV dysfunction.
Gimeno et al. [103]	35 patients received modified-CHOP regimen with or without rituximab.	Patients with initially elevated NT-proBNP levels had a significantly higher risk of heart failure progression and death from all causes in comparison to those with lower levels.
Mladosievicova et al. [123]	69 patients who had previously received DOX, daunorubicin, or EPI based therapy or non-anthracycline therapy were compared to 44 health controls.	NT-proBNP elevations were more common in childhood cancer survivors exposed to anthracyclines compared to unexposed survivors.
Geiger et al. [104]	40 patients received DOX, 6 received mitoxantrone–daunorubicin, 2 received mitoxantrone, 1 received liposomal DOX.	NT-proBNP levels increased more in patients who subsequently developed reduced EF, TnT levels increased following chemotherapy and were also associated with reduced EF.
Sherief et al. [118]	50 patients who had previously received anthracycline based chemotherapy.	NT-proBNP levels correlated with the total anthracycline dose previously received.
Lipshultz et al. [119]	102 patients received anthracycline based therapy vs. other protocols not containing anthracyclines.	Increased NT-proBNP levels were associated with decreased LV function.
Aggarwal et al. [105]	63 patients previously received anthracycline based chemotherapy at least 1 year prior to enrollment.	Elevated BNP levels were associated with cardiac dysfunction on echocardiography.
Soker et al. [95]	31 patients received DOX based therapy.	NT-proBNP levels were significantly more elevated in patients with LV dysfunction, cTnI levels remained undetectable throughout the study.
Zver et al. [21]	30 patients received VCR–EPI–dexamethasone followed by CYC–melphalan followed by autologous hematopoietic stem cell transplantation.	Increased levels of BNP and ET-1 were associated with worsening LV diastolic dysfunction. TnI remained within the normal range.
Nakamae et al. [150]	40 patients received CYC–DOX–VCR–prednisolone (CHOP therapy).	CHOP induced transient increases in the LV end-diastolic diameter on echocardiogram and in the plasma BNP and ANP. Valsartan therapy prevented elevations in BNP and LV end-diastolic diameter, but not ANP.
Feola et al. [87]	53 patients received six 21 day cycles of CYC–EPI–5-FU.	BNP levels correlated with left ventricular systolic dysfunction in this patient population.
Kuittinen et al. [22]	30 patients received carmustine–ETO–cytarabine–CYC–MESNA followed by stem cell transplantation.	LV dysfunction correlated with NT-proANP and NT-proBNP levels.
Romano et al. [86]	34 patients received Liposomal DOX–docetaxel and 37 received EPI–5-FU–CYC.	Persistently elevated NT-proBNP levels were associated with subsequent impairment of LV function.
Pichon et al. [115]	50 patients received anthracycline based therapy, 17 patients were pre-treated with anthracycline-based therapy followed by TZT and taxanes or vinorelbine	BNP concentrations correlated with anthracycline cumulative dose and LVEF.
Ribeiro et al. [50]	103 patients received imatinib.	4 patients receiving imatinib had elevated BNP with one showing depressed LVEF, however this small number of patients precluded

	Troponin-I	
		the comparison of their features with the whole study sample.
	Troponin-I	
Papers failing to demonstrate correlation between increase in biomarker and cardiotoxicity		
Meinardi et al. [112]	21 patients received five cycles of 5-FU–EPI–CYC (FEC), 19 received four cycles of FEC followed by high-dose chemotherapy consisting of CYC–thiotepa–carboplatin. Both groups subsequently underwent locoregional radiotherapy.	No statistically significant correlation was found between BNP levels and prediction of LVEF dysfunction.
Garrone et al. [79]	50 patients received six 21 day cycles of CYC–EPI–5-FU.	Kinetics of Tn rise correlated with LVEF reduction. There was no correlation between BNP and change in LVEF.
Mavinkurve-Groothuis et al. [71]	60 patients received 120 mg/m^2 of anthracyclines and were then stratified to low (n = 20), moderate (n = 30) or high risk (n = 10) based on response with moderate risk receiving an additional 180 mg/m^2 of anthracycline and high risk receiving either an additional 120 mg/m^2 anthracycline +18 mg/m^2 idarubicin +52.5 mg/m^2 mitoxantrone or consideration of bone marrow transplantation.	TnT elevations predicted LV dysfunction, NT-proBNP levels were not predictive.
Drafts et al. [85]	37 patients received DOX and 16 received daunorubicin.	TnI trended upward with 26% showing positivity by the end of 6 months, BNP levels fell during therapy.
Mornos et al. [80]	100 patients received anthracycline containing therapy.	Changes in TnT levels predicted the development of cardiac toxicity while changes in NT-proBNP did not show significant predictive value.
Poutanen et al. [113]	39 patients received anthracycline based therapy with or without radiotherapy 5 to 7 years prior to evaluation.	NT-proANP is a useful method to evaluate cardiac function in cancer survivors, BNP levels did not correlate with cardiac function.
Daugaard et al. [111]	66 patients received EPI, 41 received DOX. 13 patients additionally received radiotherapy of the left chest wall.	Neither changes in NT proANP nor BNP correlated with a change in EF.
Sawaya et al. [69]	82 patients received DOX or EPI for 3 months followed by weekly PAC–TZT for 3 months followed by 9 more months of TZT.	TnI and peak systolic myocardial strain predicted cardiotoxicity, no significant associations observed for LVEF, NT-proBNP, or ST-2 and the development of heart failure.
Dodos et al. [91]	100 patients received anthracycline containing chemotherapy, 53 received DOX, 29 received EPI, 15 received daunorubicin, 2 received mitoxantrone, and 1 received idarubicin.	TnT and BNP did not predict subsequent development of cardiac dysfunction
	Atrial naturetic peptide	
Papers demonstrating correlation between increase in biomarker and cardiotoxicity		
Hayakawa et al. [114]	34 patients received DOX-based chemotherapy more than 1 month prior.	ANP and BNP levels correlated with both the cumulative dose of anthracycline and LV systolic function.

	Troponin-I	
Nakamae et al. [150]	40 patients received CYC–DOX–VCR–prednisolone (CHOP therapy).	CHOP induced transient increases in the LV end-diastolic diameter on echocardiogram and in the plasma BNP and ANP. Valsartan therapy prevented elevation in BNP and LV end-diastolic diameter, but not ANP.
Poutanen et al. [113]	39 patients received anthracycline based therapy with or without radiotherapy 5 to 7 years prior to evaluation.	NT-proANP levels corresponded with cardiac function in cancer survivors, BNP levels did not correlate with cardiac function.
Kouloubinis et al. [117]	26 patients received six 21 day cycles of EPI–PAC, 14 received six 21 day cycles of mitoxantrone and docetaxel.	NT-proANP and NT-proBNP levels correlated with LV dysfunction.
Kuittinen et al. [22]	30 patients received carmustine–ETO–cytarabine–CYC–MESNA followed by stem cell transplantation.	LV dysfunction was associated with NT-proANP and NT-proBNP levels.
Papers failing to demonstrate correlation between increase in biomarker and cardiotoxicity		
Daugaard et al. [111]	66 patients received EPI, 41 received DOX. 13 patients additionally received radiotherapy of the left chest wall.	Neither changes in NT-ANP nor BNP correlated were predictive of a change in EF.
	C-reactive protein	
Papers demonstrating correlation between increase in biomarker and cardiotoxicity		
Onitilo et al. [35]	49 patients received adjuvant TZT therapy (24 had prior exposure to anthracycline).	hs-CRP correlated with subsequent reduction in LVEF.
Papers failing to demonstrate correlation between increase in biomarker and cardiotoxicity		
Lipshultz et al. [107]	100 patients received DOX, 105 received DOX–dexrazoxane.	TnT levels rose during treatment in the DOX and to a lesser extent in the group with dexrazoxane coadministration, NT-proBNP levels were initially elevated, fell in both groups although to a lesser extent in the group without dexrazone, NT-proBNP rose again post-treatment in the DOX group but continued to fall in the dexrazosin coadministration group. Increases in hsCRP were not associated with changes on echocardiography. TnI and NTproBNP levels during the first 90 days of treatment predicted the development of cardiac dysfunction 4 years later.
Morris et al. [124]	95 patients enrolled initially receiving DOX–CYC (DC) followed by PAC–TZT–lapatinib for 3 months with continuation of TZT-lapatinib for 1 year.	TnI rise preceded maximal decline in left ventricular function, CRP did not correlate with cardiotoxicity

	Troponin-I	
	Troponin-I	
Grover et al. [92]	46 patients received three to six 21 day cycles of EPI, DOX and/or TZT with or without taxanes.	TnI and CRP increased with therapy but did not correlate with subsequent LV dysfunction.
	Myeloperoxidase	
Papers demonstrating correlation between increase in biomarker and cardiotoxicity		
Ky et al. [77]	78 patients received DOX–CYC every 3 weeks for 4 cycles, followed by PAC–TZT weekly for 12 weeks, followed by TZT every 3 weeks totaling a full year of therapy.	Increases in TnI and MPO levels were associated with the development of cardiac dysfunction.
	Endothelin-1	
Papers demonstrating correlation between increase in biomarker and cardiotoxicity		
Zver et al. [21]	30 patients received VCR–EPI–dexamethasone followed by CYC– melphalan followed by autologous hematopoietic stem cell transplantation.	Increased levels of BNP and ET-1 were associated with worsening LV diastolic dysfunction. TnI levels remained within the normal range.
	ST-2	
Papers failing to demonstrate correlation between increase in biomarker and cardiotoxicity		
Sawaya et al. [69]	82 patients received DOX or EPI for 3 months followed by weekly PAC–TZT for 3 months followed by 9 more months of TZT.	TnI and peak systolic myocardial strain predicted cardiotoxicity, no significant associations observed for LVEF, NT-proBNP, or ST-2 and the development of heart failure.

Abbreviations used within the table. *Biomarkers:* Tn = troponin, TnI = cardiac troponin I, TnT = cardiac troponin T, BNP = B-type natriuretic peptide, ANP = atrial natriuretic peptide, NT-proBNP = N-Terminal pro B-type natriuretic peptide, NT-proANP = N-terminal pro atrial natriuretic peptide, CRP = C-reactive protein, hsCRP = high sensitivity C-reactive protein, ET-1 = endothelin-1, MPO = myeloperoxidase. *Chemotherapy:* 5-FU = 5-fluorouracil, CARB = carboplatin, CYC = cyclophosphamide, DOX = doxorubicin, EPI = epirubicin, ETO = etoposide, HDC = high dose chemotherapy, MTX = methotrexate, ONC = oncovorin, PAC = paclitaxel, TZT = trastuzumab, VCR = vincristine. *Cardiovascular parameters:* EF = ejection fraction, LVEF = left ventricular ejection fraction, LV = Left ventricle.

Search criteria: chemotherapy and cardiac biomarkers over the past 10 years, in humans, available in English. Hand-searching of articles was performed to locate additional studies. Inclusion criteria: studies containing greater than 30 patients evaluating the use of biomarkers to detect cardiac toxicity in the setting of chemotherapy.