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ALTERNATIVE BIOMARKERS FOR COMBINED BIOLOGY

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Synopsis

The combined use of traditional and novel anti-neoplastic agents has significantly increased survival of patients suffering from various malignancies. However, chemotherapy-related cardiac dysfunction (CRCDD) has challenged clinicians to hesitate in using cardiotoxic agents such as anthracycline and several protein kinase inhibitors. As early detection of CRCDD and the timely cessation of cardiotoxic agents became a strategy to avoid CRCDD, cardiac troponin and natriuretic peptide are widely measured to monitor cardiotoxicity, yet there are inconsistencies in their predictability of CRCDD. Consequently, alternative biomarkers have been extensively researched for potential use as more sensitive and accurate biomarkers. In this review, the mechanisms of CRCDD and previous studies on traditional and novel biomarkers for CRCDD were examined to enlighten future direction of investigation in this combined biology.

Keywords

Chemotherapy-related cardiac dysfunction; heart failure; malignancy; biomarkers

Introduction

Chemotherapy-related cardiac dysfunction (CRCDD) has challenged clinicians in choosing the best cardiotoxic agents such as anthracycline and several protein kinase inhibitors to treat cancers. As the recommended total cumulative dose of doxorubicin (500–550 mg/m²) originated from statistical rather than pathophysiological principles,¹ patients who may

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tolerate a higher dose of drug are deprived of the chance of appropriate treatment owing to this empirical dose-limitation recommendation. Screening patients at risk of CRCD has mainly been dependent on the left ventricular ejection fraction (LVEF). Despite consensus statements from several groups,² there are multiple definitions for reduced LVEF. In fact, LVEF turned out to lack sensitivity to detect subclinical decline of ventricular function with chemotherapy treatment.^{3, 4} Therefore, endeavors have been made to find novel biomarkers capable of detecting early subclinical changes in various cardiovascular diseases.^{5, 6}

Over the decades, there have been many studies investigating the relationship between biomarkers and CRCD (Table 1). However, many of these studies are single center observations, and well-designed studies with good statistical power are rare. The majority of these studies involved clinically available biomarkers of myocardial necrosis (e.g., cardiac troponin) or myocardial stress (e.g., natriuretic peptides). Studies have consistently reported an increase in cardiac troponin or natriuretic peptide in patients treated with anthracycline or anti-HER-2 monoclonal antibodies (Table 1). Probably because of difficulties in follow-up, particularly in pediatric populations, these studies were designed as a cross-sectional analysis where the biomarkers were supposed to predict development of cardiac dysfunction when there were significant correlations between changes of biomarkers level in serum and changes in cardiac function (i.e., LVEF).^{7, 8, 9, 10} However, correlations between changes of serum biomarker levels and reduced cardiac function do not necessarily imply the ability of biomarkers to predict cardiac dysfunction due to a lack in temporal causality.

There are other studies on the acute or subacute toxicity of anthracycline with evaluations within a few days to months after administration of the agents, where the increase in troponin was assumed to predict reduced LVEF.^{11–13} Elevated natriuretic peptides in patients also seemed to predict development of CRCD,^{14, 15} but natriuretic peptides would often normalize in subsequent cycles of chemotherapy.¹⁶ Although the usefulness of cardiac troponin and natriuretic peptides in predicting cardiac dysfunction was proposed in short-term studies, the development of cardiac dysfunction was often judged based on the presence of left ventricular diastolic dysfunction or alteration of myocardial strain rather than LVEF, because reductions of LVEF were not prominent in many short-term studies.^{14, 17} Oncologists' efforts to reduce the administration of cardiotoxic agents and subtle reductions in LVEF may be reasons many clinical studies failed to demonstrate predictability of the biomarkers.

On the other hand, as normalization of both elevated biomarkers and cardiac function were frequently observed during short-term observation, longer observation studies were required. Despite still contradictory results, elevated cardiac troponin or natriuretic peptide appeared to predict development of cardiac dysfunction or clinical heart failure during observation periods of more than three months after completion of chemotherapy.^{18–22} Elevated cardiac troponin predicted cardiac remodeling such as left ventricular dilatation and wall thinning nine months after chemotherapy as well as functional deterioration.²³ In the largest study to date, Cardinale et al., showed that plasma cardiac troponin I (cTnI) measured at various time points was predictive of subsequent cardiotoxicity with high positive and negative predictive values in a study of 703 patients with diverse malignancies. In addition, patients with sustained elevation of cTnI had a greater reduction of left ventricular dysfunction than those

whose cTnI levels normalized during follow-up. Death and symptomatic heart failure were more prevalent in patients with sustained elevation of cTnI as well.^{19, 24} High-sensitivity or ultrasensitive cardiac troponin assays drew attention in recent studies as they are known to detect as small an amount of myocardial necrosis as corresponding to 10 ng/L of cardiac troponin or less.²⁵ Ultrasensitive cTnI, along with the measurement of left ventricular systolic strain, predicted the development of CRCD in 81 patients who were treated with anthracycline followed by trastuzumab and taxanes where LVEF dropped from $64 \pm 5\%$ to $59 \pm 6\%$ ($p < 0.0001$) during 15 months of observation.²⁰

The elevation of natriuretic peptides also preceded cardiac dysfunction and clinical heart failure and correlated with cumulative doses of anthracycline, suggesting predictability for development of CRCD.^{26–31} In a Japanese study, natriuretic peptide increased prior to the development of clinical or subclinical heart failure, which was detected by radionuclide angiography. The authors suggested B-type natriuretic peptide (BNP) as a sensitive indicator of daunorubicin induced cardiomyopathy.³² However, because reduction of LVEF was not prominent in all of the long-term studies, other indicators of cardiac dysfunction such as LV diastolic dysfunction or myocardial strain were adopted for end-points like in the short-term observation studies discussed above.^{33–35}

Criticism Against Cardiac Troponin and Natriuretic Peptides

Several studies have raised questions about the usefulness of traditional biomarkers of cardiac dysfunction in predicting CRCD. Pavo et al., evaluated amino-terminal proBNP (NT-proBNP), mid-regional pro-atrial natriuretic peptide (MR-proANP), mid-regional pro-adrenomedullin (MRproADM), C-terminal pro-endothelin-1 (CT-proET-1), copeptin, high sensitivity cardiac troponin T (hs-cTnT), interleukin 6 (IL-6), high-sensitivity C-reactive protein (hs-CRP), serum amyloid A (SAA), haptoglobin and fibronectin in 555 patients with various malignancies and without evidence of cardiac disease. In the study, prior to anti-neoplastic chemotherapy, multiple vasoactive peptides and hs-cTnT were elevated and significantly correlated with systemic pro-inflammatory markers IL-6 and CRP. All of the biomarkers were elevated as the stage of the malignancy progressed. The presence of NT-proBNP, MR-proANP, MRproADM, hs-cTnT, and copeptin were associated with all-cause mortality. The findings in the study may defy the traditional notion that elevated troponin or natriuretic peptides are predictive of CRCD because the biomarkers were elevated *before* chemotherapy. According to the results, higher troponin or natriuretic peptides appear to indicate the patients in more severe status of malignancy and require more aggressive chemotherapy rather than discontinuation of chemotherapy.³⁶ Blaes et al., also reported that patients with reduced LVEF four weeks after completion of chemotherapy had higher levels of hs-cTnT at baseline before chemotherapy, which suggests there are certain patients with latent cardiac dysfunction, which may be aggravated by chemotherapy more rapidly.¹³

The majority of studies examined reported that natriuretic peptide levels are predictive of both short- and long-term cardiac dysfunction. Of note, serum natriuretic peptide increased during the early phase of chemotherapy and gradually decreased after cessation of chemotherapy.³⁷ Furthermore, patients with persistently elevated natriuretic peptide seem more susceptible to future ventricular dysfunction.²⁹ However, as chemotherapy is usually

accompanied by intravenous hydration during administration to reduce systemic toxicity, it is possible that elevated natriuretic peptide might result from acute volume or pressure overload on the ventricles rather than cardiotoxicity by chemotherapy agents.³⁸ For example, in a placebo-controlled study by Reijers et al., when either trastuzumab or placebo in normal saline was infused into healthy volunteers, serum NT-proBNP was found to be elevated after four days in both groups.³⁹ Another example comes from a study of patients with multiple myeloma who underwent chemotherapy containing cyclophosphamide.¹⁴ The administration of cyclophosphamide is frequently complicated by hemorrhagic cystitis as well as cardiac injury and requires large amounts of hydration before and during treatment. In this study, serum BNP concentrations significantly increased while cTnI was within normal range. Although there was no reduction in left ventricular ejection fraction, left ventricular diastolic dysfunction developed. Interestingly, functional mitral regurgitation developed in 40% of patients, suggesting overloaded intravascular volume, although the authors did not provide information on hydration or the weight change of enrolled patients.

In a study by Dugaard et al., natriuretic peptide showed significant correlation with LVEF when LVEF was < 50% but no correlation when LVEF ≥ 50%. Change in serum natriuretic peptide level was not correlated with change in LVEF either. These results suggest that the release of natriuretic peptide does not increase without impaired cardiac dysfunction and, therefore, elevation of natriuretic peptide may follow reduced LVEF rather than precede it.⁴⁰ Conversely, as natriuretic peptides are usually measured during hospitalization, elevated natriuretic peptide may indicate latent left ventricular dysfunction that becomes prominent with hydration with or without chemotherapy.⁴¹ Therefore, whether elevated natriuretic peptide indicates toxicity of a chemotherapy agent *per se* rather than a latent cardiac dysfunction before chemotherapy that deteriorates into prominent cardiac dysfunction during chemotherapy must be clarified.

Candidate Alternative Biomarkers for Chemotherapy-Related Cardiac Dysfunction

With the usefulness of cardiac troponin and natriuretic peptides called into question, various other cardiac biomarkers validated for ischemic heart disease or heart failure have been investigated for utility in the field of cardio-oncology.⁵ These potential biomarkers include peptides, hormones, and cytokines and are representative of various potential mechanisms of cardiotoxicity (e.g., oxidative stress, fibroblast proliferation or ischemia). For example, serum levels of myeloperoxidase (MPO), an enzyme produced by polymorphonuclear leukocytes with a proposed role in oxidative stress, were found to increase with worsening cardiac function and clinical outcomes,^{42, 43} while growth differentiation factor 15 (GDF-15), which belongs to a superfamily of transforming growth factor β cytokines and seems to be stimulated by oxidative stress, inflammation or injury, was elevated in cancer survivors treated with anthracycline.^{44, 8} Other potential biomarkers involved in oxidative stress or inflammatory pathways include erythrocyte superoxide dismutase (SOD) and resistin, which increases in response to inflammatory stimuli.^{45, 46} On the other hand, potential biomarkers representing fibroblast proliferation and cardiac hypertrophy include placental growth factor (PIGF), soluble fms-like tyrosine kinase receptor 1 (sFlt-1), and

galectin-3 (Gal3),^{47, 48, 49} while glycogen phosphorylase BB (GPBB) was suggested as a potential biomarker in acute coronary syndrome because it is released during the early ischemic phase.^{50, 51, 52}

In perhaps the most important study to date, Ky et al., studied multiple biomarkers in 78 breast cancer patients who were treated with doxorubicin followed by trastuzumab.²¹ They investigated multiple biomarkers in patients with breast cancers, in which each biomarker represented a specific pathway of CRCD: cardiomyocyte injury (high sensitivity cTnI); inflammation (hsCRP and GDF-15); neuro-hormonal activation (NT-proBNP); oxidative stress (MPO); anti-angiogenesis and vascular remodeling (PIGF and sFlt-1); and fibrosis (Gal3).²¹ Among the evaluated biomarkers, hs-cTnI and MPO were associated with cardiotoxicity while the others showed no association.^{21, 53} In particular, the interval increase in serum levels of the two biomarkers during the early phase after chemotherapy predicted cardiotoxicity. Combining troponin and MPO is proposed to produce better utility in predicting subsequent cardiotoxicity as the functional axis of the biomarkers was orthogonal.

However, in a conflicting study by Putt et al., GDF15 and PIGF, as well as MPO, did show significant association with cardiotoxicity at both the same visit and subsequent visits. Although the number of enrolled patients was relatively small, the study was designed to have enough power to detect significant hazards.⁵³ Interestingly, hs-cTnI and natriuretic peptides did not show significant association with cardiotoxicity, which the authors attributed to missing data.

Another potential biomarker of cardiotoxicity, ischemia-modified albumin (IMA), is produced when human serum albumin passes through ischemic tissue and undergoes modification at the N-terminus. The reactive oxygen species produced in ischemic tissue appear to play a role in this process.⁵⁴ Since IMA can be detected during the early stages of myocardial ischemia before apparent myocardial necrosis, it has been suggested as a biomarker of myocardial ischemia; and, as oxidative stress is a leading mechanism of doxorubicin induced cardiac injury, the ability of IMA to predict doxorubicin induced cardiomyopathy was investigated. In a study with 152 breast cancer patients, an increase of IMA showed significant correlation with reduction in LVEF and had a greater area under the curve in Receiver Operator Characteristic curves than those of cardiac troponin or CK-MB. Furthermore, combined measurement of IMA, troponin and CK-MB had 92% sensitivity and 83% specificity for detection of cardiac injury at 12 months post chemotherapy.⁵⁵

Finally, taking a different approach and moving away from biomarkers altogether, Garrone et al., suggested that the degree of change in LVEF or rate of reduction in hemoglobin concentration held greater predictive value of further reduction of left ventricular systolic function than the measurement of one or two cardiac biomarkers such as cardiac troponin or natriuretic peptide. In a study of 50 early breast cancer patients with three years of follow-up, the reduction of LVEF to below 53% or declining hemoglobin blood concentration > 0.33 g/dL/month during chemotherapy increased the odds of subsequent cardiotoxicity by 37.3 and 18 respectively, with specificity of 93.3% and 80%, sensitivity of 90.9% and 81.2%. The authors supposed the anthracycline had myelotoxicity to reduce hemoglobin

concentration as well as cardiotoxicity. In any case, measuring and comparing the change in metabolomic parameters such as hemoglobin may shift the focus of investigation from biomarkers to inherent diathesis of individuals.⁵⁶

Under-refined Study Designs may Undermine Credibility in Previous Cardiac Biomarker Studies

In many studies dealing with CRCD, relatively low rates of adverse cardiac events, inadequate numbers and high drop-out rates resulted in diminished statistical power to prove usefulness of potential biomarkers. Notably, clinicians' efforts to reduce the administration of cardio-toxic agents to their patients might have helped to preserve cardiac function and potentially lead to statistically underpowered studies with inconsistent results. With current clinical guidelines somewhat conservative in defining CRCD (i.e., reduction of LVEF > 10% or development of clinical heart failure)², investigators had difficulty in demonstrating the predictability of potential biomarkers.^{57, 58} Inconsistent timing of blood sampling among cohort studies or groups in a cohort might have also played a role in contradictory results in the biomarker studies. In particular, many chemotherapy protocols have changed to a one-day hospital stay where frequent blood sampling for serial assessment of the biomarkers becomes implausible.⁵⁷

In general principle, the usefulness of cardiac biomarkers in predicting cardiotoxicity must be demonstrated by their elevation in blood prior to prominent reduction in LVEF during follow-up. However, many studies instead concluded that significant correlations among the blood levels of cardiac biomarkers, invasively or non-invasively measured left ventricular function and cumulative anthracycline dose meant that the cardiac biomarkers were useful predictors of reduced cardiac function. But correlations among the parameters at a certain time point do not guarantee the predictability of the biomarkers, only their correlation at the time point measured.⁵⁹ These interfering factors must be sorted out during study design to ensure that predictability can be reliably discerned.

Proteomics/Genomics Under Investigation to Search for Novel Biomarkers

As another alternative to using cardiac troponin or natriuretic peptides, several authors have looked for biomarkers in the patient's genome or proteome. For example, quantifying the intercalation of anthracycline molecules into DNA to form doxorubicin-DNA adducts has been suggested as a potential preclinical marker of doxorubicin induced myocardial injury. Depurination of dGMP and dAMP occurs in parallel with increasing ADM concentration, enabling the quantification of the formed DNA adducts even at low doses of doxorubicin.⁶⁰ It is conceivable that analysis from more accessible tissue (e.g., skeletal muscle lymph nodes) surrogating doxorubicin-exposed myocardium may make this diagnostic approach feasible in the near future, but its predictive value remains to be determined.

Drug-induced damage to organs can constantly change circulating blood proteomes, which may contain high amounts of previously undiscovered potential biomarkers. Detection of these low molecular weight peptide fragments may have specificity for the disease based on the unique microenvironment of damaged organs. As the most common analytical platform,

serum proteomic pattern diagnostics can be utilized to produce a pattern of proteomic signatures. This method showed 98% negative predictive value and 69.4% positive predictive value in an animal study in which saline or doxorubicin with or without dexrazoane was administered. Rats administered with a weaker cardiotoxin, mitoxanthrone, were also classified as diseased, showing good classification accuracy of the method.⁶¹ On the other hand, because different drugs with different toxicity can induce similar metabolomic alterations, in studies of biomarkers based on metabolomics you must be able to distinguish between cardiotoxicity and other end-organ toxicities.⁶² Meanwhile, S100A1, a member of the S100 protein family, is mainly expressed in cardiac muscle. This protein is known to be a regulator of myocardial contractility by way of Ca^{2+} -induced Ca^{2+} release.⁶³ In rats treated with trastuzumab or lapatinib, cardiac troponin I in serum was elevated, while S100A1 level in serum was significantly reduced. Therefore, the authors suggested that measurement of S100A1 might be used as a detector of cardiotoxicity.⁶⁴

Genomic biomarkers are a new area of exploration for the detection and prediction of cardiotoxicity. Toxicogenomic analysis was suggested as a potential tool to evaluate toxicity mechanism of various chemicals and may be used to detect early pathology induced by the chemicals. This approach previously identified genes such as kidney injury molecule 1 (Kim1), lipocalin 2 (Lcn2) and secreted phosphoprotein 1 (Spp1) in rats, which are now acknowledged as promising genomic biomarkers of acute nephrotoxicity in humans.⁶⁵ Hearts from rats administered with cardiotoxic agents (including doxorubicin) up-regulated expression of 36 genes that were related to inflammation and degeneration of myocardium. Contrary to cardiac troponin, which is rapidly normalized after completion of chemotherapy, up-regulated genes showed sustained elevation profiles that are advantageous to detect long-term cardiovascular complications at early stage toxicity screening. Intriguingly, five out of 36 up-regulated genes predicted cardiac dysfunction, even before the development of histopathological changes with high specificity.⁶⁶ Todorova et al., investigated genomic biomarkers from both hearts and peripheral blood cells from doxorubicin-exposed rats. As obtaining cardiomyocytes from patients is not always possible, they hypothesized that genomic biomarkers from peripheral blood cells could surrogate for cardiomyocytes. They found 2,411 genes are dysregulated both in heart and peripheral blood cells from doxorubicin treated rats and suggested 188 molecules among the genes as potential biomarkers, which were known to be associated with decreased transcription and expression of RNA. Interestingly, the analysis of dysregulated genes expressed in both hearts and peripheral blood cells revealed the oxidative stress-related pathway is a main pathway in doxorubicin toxicity.⁶⁷ Doxorubicin seems to induce premature senescence of cardiac progenitor cells and reduced regenerative capacity; consequentially it provides a basis of doxorubicin induced cardiomyopathy.⁶⁸ With cardiomyocytes treated with doxorubicin or other anthracyclines, dozens of unique protein features involving dysregulation of protein folding, translational regulation and cytoskeleton regulation were overexpressed and suggested as potential biomarkers.^{69–72} Similar to anthracycline, trastuzumab also upregulated or downregulated the expression of genes related to oxidative stress and apoptosis in mice.⁷³ However, generalization to clinical practice warrants much caution because very little about genomic biomarkers in this topic has been studied in human subjects.

MicroRNAs are endogenous 19–25 nucleotide-long, regulatory RNA molecules. Their functions were once thought to be limited to the developmental phase of some lower forms of life, but they now are acknowledged to play a role in post-transcriptional regulation of mRNAs in a diverse range of physiological processes as well as in the developmental stage.⁷⁴ Four weekly administration of doxorubicin in rats revealed dysregulation of 25 miRNAs among 370 measurable miRNAs from excised rat hearts. Five of these dysregulated microRNAs (miR208b, miR215, miR216b, miR34c and miR367) were thought to be potential cardiac biomarkers as they showed consistent dose-dependent alteration in amounts of administered doxorubicin. Interestingly, alteration of miRNAs occurred in the absence of histopathological change, suggesting miRNAs is the most sensitive cardiac biomarker, indicating the earliest cardiac lesions induced by doxorubicin. Another group of investigators evaluated 1179 unique miRNAs in mice. In the study, the number of differentially expressed miRNA increased as cumulative doses of doxorubicin increased. Among them, miR-34a, related to apoptosis signals, was upregulated at low cumulative doses of doxorubicin and suggested it was a potential biomarker.⁷⁵ Although roles of up-regulated miRNAs are still obscure, they can target certain mRNA transcriptions to mediate a homeostatic response to toxic stimulation by doxorubicin.⁷⁶ When cardiomyocytes from human pluripotent stems cells were treated with doxorubicin, dozens of miRNAs were differently expressed in the cells.⁷⁷ However, dysregulated miRNAs of interest still had discrepancies among the type of study, species of animals and methods of administration of doxorubicin.^{76, 78, 79} Disappointingly, when Oliveira-Cavalho et al. investigated 59 patients with breast cancer who underwent a first round of chemotherapy with doxorubicin, cyclophosphamide and paclitaxel, the level of miR208a in serum did not increase in all patients, while cardiac troponin increased and LVEF decreased in patients with cardiotoxicity.⁸⁰

Non-blood Biomarkers: Combining with New Imaging Modalities

In part because of the controversial results from biomarker studies and in part because of the low sensitivity/specificity of LVEF in predicting CRCD, new imaging modalities have been examined to find a substitute for LVEF. In a systematic review of 1,504 patients who underwent chemotherapy for cancers, decrease in global longitudinal strain consistently detected early change of ventricular function prior to reduction in left ventricular ejection fraction. Longitudinal strain reduction between 9 and 19% using 2D speckle tracking methods or longitudinal strain rate reduction between 9 and 20% using tissue Doppler based methods were observed during or immediately after chemotherapy in the absence of a reduction of LVEF. In 452 patients with known clinical cardiotoxicity, early reduction of global longitudinal strain was associated with subsequent reduction of LVEF or development of clinical heart failure.⁸¹ Furthermore, a strain image-guided cardioprotective strategy appears to significantly save medical costs compared with a LVEF-guided strategy, justifying routine evaluation of strain echocardiography for patients at high risk of CRCD.⁸² However, as the degree of myocardial deformation varies depending on age, sex, pressure/volume load and machine vendors, there is no universal agreement on normal strain, or strain rate values, that could guide preemptive treatment for CRCD. The absence of consensus is a critical hindrance for strain imaging application in clinical practice.⁸³

Novel scintigraphic methods were investigated to detect early functional change during doxorubicin administration. Nuclear cardiology technology may visualize tissue-level pathophysiology at an earlier stage when appropriate tracers are used. Sympathetic neuronal imaging with a wide variety of SPECT and PET tracers, In-111 antimyosin which is a specific marker of myocyte injury and necrosis, Tc-99m annexin V which visualized apoptosis and programmed cell death, fatty acid scintigraphy which visualizes fatty acid retention in the lipid pool of the cytosol which can be impaired by cardiotoxic agents, 61 and direct imaging of In-111 trastuzumab to study trastuzumab targeting of the myocardium have been considered.^{84, 85}

Induction of apoptosis is assumed as a mechanism of anthracycline related cardiotoxicity. Caspase3 may be an indicator of cardiomyocytes apoptosis because it is a catalytic enzyme functioning in the terminal step of apoptosis. When a synthesized caspase-3 substrate (18F-labeled tetrapeptidic caspase substrate) tagged with a radioisotope was administered in mice treated with doxorubicin, increased uptake of the substrate represented overexpression of caspase-3 activity, which was detected with microPET. It is possible to use 18F-CP18 as a biomarker of doxorubicin cardiotoxicity.⁸⁶

Finally, cardiac magnetic resonance image (CMR) is a promising method to detect early change of CRCD. Serial CMR evaluation of both ventricles, using the latissimus dorsi muscle for the area of comparison, revealed myocardial edema before apparent decrease of LVEF in 46 patients. LVEF decreased in 5% of patients at 4 months and in 26% of patients at 12 months, while right ventricular ejection fraction decreased in 23% and 34% at the same points. During observation, NTproBNP did not increase and hs-cTnT increased within normal range. Therefore, myocardial edema, evaluated by cardiac MR, appears to be a useful method to detect early change in CRCD.⁸⁷ Decrease in regional ventricular tissue velocity, which was evaluated with cardiac MR, predicted reduction of LVEF at 6 months of follow-up in patients treated with trastuzumab, while troponin and brain natriuretic peptide did not change.⁸⁸ Combined use of positron emission tomography/magnetic resonance likely allows the acquisition of complimentary data on cardiac structure and function⁸⁹ and limits exposure to radiation.⁹⁰

Conclusions

Although the mechanism of CRCD still requires further investigation, the combined use of traditional and novel anti-neoplastic agents has significantly reduced both morbidity and mortality of patients suffering from malignancies. Troponin and natriuretic peptide, which are widely used biomarkers in the field of ischemic heart disease and heart failure, have been evaluated for potential utility in the early detection of CRCD. Unfortunately, there are considerable controversies on their utility because a significant number of studies failed to demonstrate the predictability of those biomarkers for short- and long-term cardiotoxicity, while a lot of other studies succeeded in doing just that. Owing to an inconclusive utility of traditional biomarkers in cardio-oncology, alternative biomarkers have been investigated to replace traditional ones, including various peptides, hormones, cytokines, proteomics, microRNA, genomics and various combinations of them. Clearly, the endeavor to find

alternative biomarkers in this field is not yet satisfactory and continued research will undoubtedly enlighten future directions of investigation.

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Key Points

1. Chemotherapy-related cardiac dysfunction has been a problem as the development of effective anti-neoplastic agents has decreased mortality rates and increased the number of cancer survivors.
2. To avoid chemotherapy-related cardiac dysfunction, early detection and timely discontinuation of cardiotoxic drugs has become a standard treatment strategy.
3. Traditional biomarkers, such as troponin for ischemic heart disease and natriuretic peptide for heart failure, are commonly measured to detect early signs of chemotherapy-related cardiac dysfunction, but those biomarkers' predictability in CRCD is not consistent among studies.
4. Alternative biomarkers have been investigated because of the need for more sensitive, accurate and reliable biomarkers.
5. Proteomics and genomics are under investigation in translational research and can be potential reliable biomarkers.
6. A combination of different methods, for example, the combined use of biomarkers and new imaging modalities, may improve the accuracy in screening patients at high risk of CRCD.

Table 1

Cardiac biomarker studies for chemotherapy related cardiac dysfunction

Author (published year)	Study designs/ Duration of observation	Biomarkers	Study Subjects	Results	Comments
No or very short interval from biomarker measurement to cardiac function evaluation					
Bauch M (1992) ⁹¹	Cross sectional	ANP	16 pediatric patients.	ANP useful.	More cardiac events in patients with increased ANP.
Missov E (1997) ⁹²	Cross sectional	hs-TnI, CKMB, myoglobin	30 patients with ANT vs. 25 ANT-naïve patients vs. 60 healthy controls	cTnI useful.	↑cTnI in only doxorubicin-treated patients. No LVEF.
Nousiainen T (1999) ⁹³	Cross sectional	ANP, NTproANP, BNP	30 patients with lymphoma.	Not useful.	NP was correlated with LVEF. NP was slower than LVEF.
Hayakawa H (2001) ⁹⁴	Cross sectional	ANP, BNP	34 childhood cancer survivors vs. healthy controls.	ANP, BNP useful.	ANP and BNP increased in patients and were correlated with LVEF.
Nousiainen T (2002) ⁹⁵	Cross sectional	ANP, NTproBNP, BNP	30 patients with lymphoma.	ANP, NTproBNP, BNP useful.	NP had no correlation with LV systolic function, but had correlation with LV diastolic function.
Poutanen T (2003) ⁹⁶	Cross sectional	NTproANP	39 childhood cancer survivors.	NTproANP useful.	NTproANP was correlated with cumulative ANT dose. No predictability suggested.
Kismet E (2004) ⁹⁷	Cross sectional	cTnT	24 patients with solid tumor.	cTnT Not useful	No ↑cTnT during follow-up. No correlation between cTnT, cumulative dose of doxorubicin and cardiac functions.
Köseoğlu V (2005) ⁹⁸	Cross sectional	cTnI	22 pediatric patients with solid tumor.	cTnI not useful	No correlation between cTnI, cumulative dose of doxorubicin and echocardiographic parameters.
Perik PJ (2006) ⁹⁹	Cross sectional	NTproBNP	15 patients with breast cancer.	NTproBNP useful	↑NTproBNP in patients with cardiotoxicity more than those without.
Aggarwal S (2007) ¹⁰⁰	Cross sectional	BNP	63 pediatric patients.	BNP useful	BNP associated with LV dysfunction other than LVEF.
Jones LW (2007) ¹⁰¹	Cross sectional	BNP	26 post-chemotherapy patients vs. 10 matched controls.	BNP useful	↑BNP in patients. Correlation between BNP and LVEF.
Krawczuk-Rybak M (2011) ³⁷	Cross sectional	proBNP	44 pediatric patients with hematologic	BNP useful	↑proBNP in patients.

Author (published year)	Study designs/ Duration of observation	Biomarkers	Study Subjects	Results	Comments
			malignancies vs. control groups.		
D'Errico MP (2011) ¹⁰²	Cross sectional	NTproBNP, cTnI	30 breast cancer patients with irradiation therapy vs. 30 without irradiation therapy.	NTproBNP useful, cTnI Not useful	↑NTproBNP in patient with RT.
Guler E (2011) ¹⁰³	Cross sectional	Total nitrite level	29 pediatric patients vs. matched controls.	Nitrite level ↑	↑Nitrite level in patients.
Tragiannidis A (2012) ¹⁰⁴	Cross sectional	BNP	20 children with hematologic malignancies	BNP useful	↑BNP & ↓LVEF after intensive chemotherapy
Sherief LM (2012) ¹⁰⁵	Cross sectional	cTnT, NTproBNP	50 acute leukemia survivors.	NTproBNP useful	↑NTproBNP in patients.
Pongprot Y (2012) ⁷	Cross sectional	NTproBNP, cTnT, CKMB	30 pediatric patients.	NTproBNP useful.	higher NTproBNP in LV dysfunction.
Mladostevicova B (2012) ¹⁰⁶	Cross sectional	NTproBNP	36 pediatric patients with ANT, 33 without ANT, 44 healthy controls.	NTproBNP useful	↑NTproBNP in patients with ANT exposure.
Arslian D (2013) ⁸	Cross sectional	GDF15, cTnI, myocardial strain	38 pediatric patients vs. 32 matched controls	GDF15 useful. cTnI not useful.	↑GDF15 in patients.
Ylänen K (2015) ¹⁰⁷	Cross sectional	NTproBNP, cTnT, hs-cTnT, cTnI, cTnAAbs	76 childhood cancer survivors.	NTproBNP & cTnAAbs useful.	↑NTproBNP and ↑cTnAAbs in patients with cardiac dysfunction. No ↑hs-cTnT.
Pourier MS (2015) ¹⁰⁸	Cross sectional	hs-cTnT, NTproBNP	64 childhood cancer survivors.	Hs-cTnT not useful	No ↑hs-cTnT.
endur MA (2015) ⁹	Cross sectional	hs-CRP, NTproBNP	164 patients.	NTproBNP useful	NTproBNP associated with LVEF loss.
van Bortel W (2015) ¹⁰⁹	Cross sectional	NT-proBNP, TNF-α, galectin-3, IL-6, cTnI, ST2, sFlt-1	55 patients with breast cancer.	NTproBNP useful	Correlation between NTproBNP and LVEF.
Oliveira-Carvalho V (2015) ⁸⁰	Cross sectional	cTnT, miR208a	59 breast cancer patients.	cTnT useful, miR208a not useful.	↑cTnT, No ↑miR208.
Caram ME (2015) ¹⁰	Cross sectional	BNP, cTnT, NTproBNP, urine NTproBNP	269 breast cancer patients.	NTproBNP useful	Correlation between NTproBNP and LV systolic dysfunction.
Short interval from biomarker measurement to cardiac function evaluation) < 3 months.					
Kremer L C (2002) ¹¹⁰	24 hours	cTnT	38 pediatric patients.	cTnT Not useful	Measurement of cTnT within 24 hours had low sensitivity for the identification of following cardiotoxicity.

Author (published year)	Study designs/ Duration of observation	Biomarkers	Study Subjects	Results	Comments
Sandri MT (2003) ¹¹	72 hours	cTnI	179 patients with solid or hematologic malignancies.	cTnI useful	↑cTnI predicted ↓LVEF.
Speechia G (2005) ¹¹	1 month	cTnI, myoglobin, CPK, LDH	79 with hematologic malignancies.	cTnI useful	cTnI was correlated with LVEF.
Polena S (2005) ¹¹²	48 hours	cTnI	38 patients	NOT useful	No change in cTnI, LVEF.
Kuitinen T (2006) ¹⁶	3 months	NTproANP, NTproBNP	30 adults patients with NHL	Probably, not useful	NP transiently increased but normalized within 3 months.
Mercuro G (2007) ¹⁷	7 days	BNP, cTnI, myoglobin, CKMB, IL-6, glutathione peroxidase, ROS	16 patients with solid tumor.	ROS useful.	Level of ROS predicted reduction of myocardial strain. (No reduction of LVEF)
Zver S (2008) ¹⁴	3 months.	cTnI, BNP, Endothelin-1	30 patients with multiple myeloma.	BNP useful	↑BNP associated with LV diastolic dysfunction, No LVEF.
Goel S (2011) ¹¹³	24 hours	NTproBNP, cTnI	36 patients	NTproBNP ↑	↑NTproBNP in 39% of patients. No LVEF.
Roziakova L (2012) ¹²	1 month	NTproBNP, hs-cTnT	37 patients with hematologic malignancies.	NTproBNP, hs-cTnT useful	Persistent ↑NTproBNP, hs-cTnT was associated with subsequent LV dysfunction.
Roziakova L (2012) ¹⁴	1–2 months	NTproBNP, cTnT	21 patients with hematologic malignancies for hematopoietic stem cell transplantation	NTproBNP, cTnT useful	↑NTproBNP, ↑cTnT in treated patients.
Kittiwarawut A (2013) ¹⁵	3 months	NTproBNP, cTnT, CKMB	52 breast cancer patients.	NTproBNP useful	↑NTproBNP was associated with subsequent ↓LVEF.
Blaes AH (2015) ¹³	1 month	hs-cTnT, NTproBNP, cTnT, cTnI, CKMB	18 breast or NHL patients	hs-cTnT useful	Baseline hs-cTnT before chemotherapy was associated with reduced LV systolic function 4 week after chemotherapy
Long interval from biomarker measurement to cardiac function evaluation) > 3 months.					
Lipshultz SE (1997) ²³	9 months	cTnT	15 children with ALL.	cTnT useful	↑cTnT predicted LV dilatation and wall thinning after 9 months.
Okumura H (2000) ³²	7 months.	BNP, ANP	13 patients with acute leukemia.	BNP useful	↑BNP before development of subclinical or clinical HF.
Mathew P (2001) ¹¹⁵	9 months.	cTnI	15 pediatric patients.	Not useful	No cTnI, No LVEF during follow-up.

Author (published year)	Study designs/ Duration of observation	Biomarkers	Study Subjects	Results	Comments
Meinardi MT (2001) ¹¹⁶	1 year	N-ANP and BNP	40 breast cancer patients.	N-ANP, BNP Not useful	N-ANP, BNP increased but no correlation between NP and LVEF.
Auner HW (2003) ¹⁸	3–12 months	cTnT	78 patients with hematologic malignancies.	cTnT useful	Positive cTnT predicted delayed LV systolic dysfunction.
Kilickap S (2005) ³³	4–6 months.	cTnT	41 patients.	cTnT useful	↑cTnT, but No LVEF during follow-up. cTnT was correlated with LV diastolic dysfunction.
Pichon MF (2005) ²⁶	2–3 years	BNP	12 breast cancer patients.	BNP useful	↑BNP in patients developing heart failure during follow-up. BNP was correlated with LVEF and cumulative dose of anthracycline.
Daugaard G (2005) ⁴⁰	1 year	N-ANP, BNP	107 patients.	N-ANP, BNP Not useful	Correlation between NP and LVEF, but no correlation between NP and LVEF.
Ekstein S (2007) ¹¹⁷	4–6 months.	NTproBNP	23 pediatric patients vs. 54 control.	Not useful	↑NTproBNP only after 1st cycle. No cardiac function.
Dodos F (2008) ³⁸	6 months.	BNP, cTnT	100 patients	Not useful	No BNP, No cTnT during follow-up.
Horacek JM (2007) ²⁷	6 months.	NTproBNP, cTnT	26 patients with acute leukemia	NTproBNP useful, cTnT Not useful	NTproBNP was correlated with LV systolic and diastolic dysfunction. cTnT did not increase during follow-up.
Horacek JM (2008) ³²	6 months.	myoglobin, CK-MB, cTnT, cTnI, H-FABP, GPBB.	12 patients with acute leukemia.	GPBB useful	↑GPBB in 16.7%, ↑cTnI/cTnT in 8.3% of patients. No information on LV function.
Lee HS (2008) ¹¹⁸	6 months to 2 years	BNP	86 patients with hematologic malignancies.	BNP useful	Various cardiac events developed, but there was no LV dysfunction developed.
Feola M (2011) ²⁸	2 years	cTnI, BNP	53 patients with breast cancer.	BNP useful, cTnI not useful	Baseline BNP significantly associated with reduced LVEF at second year.
Cardinale D (2010) ¹⁹	34 months	cTnI	251 patients with breast cancer.	cTnI useful	Positive cTnI at baseline predicted reduced LVEF.
Horacek JM (2010) ¹⁹	4–6 months	GPBB, H-FABP, cTnT, cTnI, CKMB, myoglobin	47 adults with acute leukemia.	GPBB useful	↑GPBB in 21.7%, cTnI/cTnT increased 8.3% of patients. No information on LV function.

Author (published year)	Study designs/ Duration of observation	Biomarkers	Study Subjects	Results	Comments
Sawaya H (2011) ³⁴	6 months.	NTproBNP, hs-cTnI	43 patients with breast cancers	hs-cTnI useful, NTproBNP not useful	hs-cTnI and longitudinal strain at 3 months predicted cardiotoxicity at 6 months.
Romano S (2011) ²⁹	12 months.	NTproBNP	71 patients (No/transient $\uparrow$ NTproBNP vs. persistent $\uparrow$ NTproBNP)	NTproBNP useful	NTproBNP predicted LV dysfunction at 3-, 6- and 12-month follow-up.
Morris PG (2011) ³⁹	18 months	cTnI, CRP	95 patients with breast cancer.	cTnI not useful	$\uparrow$ cTnI preceded decline in LVEF, but did not predict reduction of LVEF.
Garrone O (2012) ³⁶	40 months.	Hemoglobin, cTnI, BNP, catecholamines	50 patients with early breast cancer.	hemoglobin useful	LVEF and Hemoglobin predicted reduced LVEF or clinical heart failure at 40months.
Onitilo AA (2012) ¹²⁰	3–4 months	BNP, hsCRP, cTnI	54 patients with breast cancer.	hsCRP useful. BNP and cTnI not useful	hsCRP predicted reduction of LVEF with high negative predictive value.
Sawaya H (2012) ²⁰	15 months	NTproBNP, ultrasensitive-cTnI, ST2	81 breast cancer	ultrasensitive-cTnI useful, NTproBNP and ST2 Not useful	hs-cTnI and longitudinal strain predicted reduced LVEF or clinical HF.
Mavinkurve-Groothuis AM (2013) ³⁵	1 year	NTproBNP, cTnT	60 pediatric patients with acute leukemia vs. 60 age matched healthy controls.	NTproBNP, cTnT Not useful.	NT proBNP, cTnT did not predict LV dysfunction evaluated by strain analysis. (No LV fractional shortening)
Ky B (2014) ²¹	15 months	ultrasensitive-cTnI, hsCRP, NTproBNP, GDF15, MPO, PIGF, sFlt-1, Galectin-3	78 patients with breast cancer.	ultrasensitive-cTnI, MPO useful	$\uparrow$ ultrasensitive-cTnI and $\uparrow$ MPO associated with subsequent $\downarrow$ LVEF or clinical HF.
Katsurada K (2014) ²²	15 months	hs-cTnT	19 patients with breast cancer.	hs-cTnT useful	$\uparrow$ hs-cTnT at 6 months predicted LVEF at 15 months.
Putt M (2015) ⁵³	15 months	hs-cTnI, hsCRP, NT-proBNP, GDF15, MPO, PIGF, sFlt-1, galectin-3	78 patients with breast cancer.	MPO, PIGF, GDF15 useful	$\uparrow$ MPO, PIGF, GDF15 was associated with cardiotoxicity at subsequent visits.
De Iulius F (2016) ³⁰	1 year	NTproBNP	100 patients with breast cancer.	NTproBNP useful	$\uparrow$ NTproBNP before evident LVEF.
Lenihan DJ (2016) ³¹	6–12 months	cTnI, BNP	109 patients	BNP useful	$\uparrow$ BNP in patients with cardiac events.

Abbreviations: ANP, atrial natriuretic peptide; *hs-TnI*, high sensitive troponin I; *CKMB*, creatinine kinase-MB type isoenzyme; *NTproBNP*, Amino terminal pro B-type natriuretic peptide; *cTnI*, cardiac troponin I; *cTnT*, cardiac troponin T; *ANP*, atrial natriuretic peptide; *BNP*, B-type natriuretic peptide; *NTproANP*, amino terminal pro Atrial natriuretic peptide; *LV*, left ventricular; *GDF15*, growth differentiation factor-15; *cTnAAbs*, cardiac troponin specific autoantibodies; *hs-CRP*, high sensitive C reactive protein; *TNF- α* , tumor necrosis factor- α ; *ST2*, soluble form of interleukin-1 receptor; *sFlt-1*, soluble fms-like tyrosine kinase receptor 1; *miR208a*, microRNA 208a; *ROS*, reactive oxygen species; *N-ANP*; *H-FABP*, heart type fatty acid binding protein; *GPBB*, Glycogen phosphorylase BB; *MPO*, myeloperoxidase; *PIGF*, placental derived growth factor.