HHS Public Access

Author manuscript

Heart. Author manuscript; available in PMC 2017 March 01.

Published in final edited form as:

Heart. 2016 March ; 102(6): 425–430. doi:10.1136/heartjnl-2015-307894.

Roadmap for biomarkers of cancer therapy cardiotoxicity

Anthony F Yu[1] and **Bonnie Ky**[2,3]

[1]Department of Medicine, Cardiology Service, Memorial Sloan Kettering Cancer Center, New York, New York, USA

[2]Division of Cardiovascular Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA

[3]Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA

Abstract

Contemporary cancer treatment uses multiple modalities such as chemotherapy, targeted therapy and radiotherapy. These therapies, often used in combination, are associated with an increased risk of cardiotoxicity, specifically cardiomyopathy and heart failure. Cardiologists and oncologists are faced with the challenge of maximising the clinical benefit from cancer therapy while minimising the risk of early and late-onset cardiotoxicity. The current paradigm for cardiotoxicity detection and management relies primarily upon the assessment of left ventricular ejection fraction (LVEF). However, LVEF alone is limited in both diagnostic and prognostic ability. There is growing enthusiasm over the identification of newer biomarkers of cardiotoxicity that can detect cardiac injury at earlier stages of disease and could be used as an adjunctive prognostic measure to routine LVEF assessment. Thus, imaging and circulating biomarkers are currently under active investigation for use throughout the continuum of cancer care—for risk stratification of cardiotoxicity prior to treatment, detection of early cardiotoxicity during treatment and diagnosis of late cardiotoxicity in survivorship. Myocardial strain, cardiac troponin and brain natriuretic peptide are the most prominent biomarkers currently being studied, although data on novel circulating biomarkers are emerging.

INTRODUCTION

Cardiotoxicity is a well-recognised adverse effect of many commonly used cancer therapies. The clinical manifestations of cardiotoxicity are broad and can include heart failure, cardiomyopathy, arrhythmia, ischaemia, valvular heart disease, pericardial disease,

Correspondence to: Dr Bonnie Ky, Division of Cardiovascular Medicine, Perelman School of Medicine at the University of Pennsylvania, Division of Cardiovascular Medicine, Smilow Center for Translational Research, 3400 Civic Center Boulevard, 11-105, Philadelphia, PA 19104, USA; Bonnie.ky@uphs.upenn.edu.

Contributors BK responded to the call for the manuscript. AFY and BK participated in drafting and revision of the manuscript. All the authors read and approved the final version of the manuscript.

Disclaimer BK has an investigator-initiated research award from Pfizer and has served as a consultant for Roche Diagnostics and Bristol Myers Squibb. AFY has served as a consultant for Bristol Myers Squibb.

Competing interests None declared.

Provenance and peer review Commissioned; externally peer reviewed.

hypertension or thrombosis. While the adverse cardiovascular effects of traditional therapies such as anthracyclines and radiation therapy have been described since the 1970s,[1] the use of newer therapies that exert 'off-target' effects has resulted in increased incidence of unanticipated cardiotoxicity. [2] As cancer outcomes continue to improve, cardiovascular disease is emerging as a major cause of morbidity and mortality among survivors.[3]

The inability to predict or prevent cardiotoxicity during and after cancer therapy represents a major challenge within the field of cardio-oncology.[4] As such, there is a need to develop methods for personalised risk assessment. These strategies would help to inform clinical decisions that balance the therapeutic benefit of cancer therapy with cardiotoxicity risk, and identify high-risk patients who warrant close cardiac surveillance or institution of cardioprotective strategies (figure 1).

As cardiomyopathy and heart failure are some of the most common and most devastating clinical manifestations of cardiotoxicity, they are the focus of this review. Heart failure and cardiomyopathy can occur at variable time intervals, classified by some investigators as follows: acute (during therapy), early progressive (within 1 year of therapy) and late progressive (greater than 1 year of therapy).[5] For both early and late cardiomyopathy and heart failure, assessment of left ventricular ejection fraction (LVEF) has been the most common method used to monitor and diagnose these adverse sequelae. However, there is significant heterogeneity in the diagnostic criteria for cardiotoxicity according to LVEF as reported in the literature, resulting in difficulty comparing and harmonising findings across studies. Furthermore, LVEF as a prognostic and diagnostic tool has several limitations, including interobserver and intraobserver variability and a lack of sensitivity to detect early subclinical changes.[6]

There is considerable enthusiasm in the potential role that alternative biomarkers can have in identifying vulnerable patients in the preclinical stage of cardiotoxicity, improving diagnostic accuracy and in providing insight into prognosis once cardiotoxicity occurs. In this review, we will briefly summarise the current data on imaging and circulating biomarkers prior to, during and after cancer therapy for early detection and prognosis of cardiotoxicity. We also propose future directions in the field with the ultimate goal of improving cardiovascular outcomes in cancer survivors.

BIOMARKERS FOR RISK STRATIFICATION OF CARDIOTOXICITY PRIOR TO THERAPY

Current data on the utility of baseline biomarker assessment for risk stratification of cardiotoxicity are limited. Echocardiography is the most common cardiac assessment performed at baseline in patients prior to the administration of cardiotoxic therapy.[7] Some of the advantages of this imaging modality include its widespread availability, absence of radiation exposure and ease of use.

Two studies in breast cancer have shown that baseline LVEF, as an 'imaging biomarker', holds some predictive value in defining the risk of subsequent heart failure. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31, a randomised phase III

adjuvant trial of trastuzumab in 1830 patients with HER2-positive breast cancer, borderline low LVEF (50%–54%) at baseline was strongly associated with heart failure (HR 6.72, 95% CI 2.67 to 16.92, p<0.001).[8] In a regression analysis, baseline LVEF and age were used to develop a cardiac risk score: [(7+(0.4×age in years)−(0.1×baseline LVEF)]×100/4.76, which was proposed as a means to predict the probability of a cardiac event (ie, cardiac death or heart failure). Similarly, in the Herceptin Adjuvant (HERA) trial, a lower baseline LVEF was reported to be a risk factor for a cardiac end point including cardiac death, severe heart failure, or significant LVEF decline (≥10% to less than 50%).[9]

A major limitation of baseline echocardiography for risk prediction of cardiotoxicity is in its limited negative predictive value. It has been recognised that patients with a normal baseline LVEF will go on to develop subsequent cardiomyopathy and heart failure, and suffer from adverse cardiovascular events.[6] For example, although a borderline low LVEF was strongly associated with heart failure in NSABP B-31, heart failure was also reported in 2.1% and 4.2% of patients with a baseline LVEF of ≥65% and 55%–64%, respectively.[8] Another disadvantage of echocardiography is the variability of LVEF, in part attributed to interobserver and intraobserver variability and limitations in image quality. While baseline LVEF assessment will remain an important screening tool to exclude patients with pre-existing cardiovascular disease from receiving cardiotoxic therapy, more sensitive metrics will be needed to accurately detect subclinical dysfunction and predict the risk of subsequent disease (table 1).

BIOMARKERS FOR THE DETECTION OF EARLY CARDIOTOXICITY DURING CANCER THERAPY

Imaging biomarkers

During cardiotoxic therapy, echocardiography remains the most commonly used modality.[7] Newer techniques using contrast echocardiography and three-dimensional (3D) echocardiography have resulted in significant improvement in the accuracy of LVEF assessment. This was demonstrated in a small study of 50 patients with breast cancer undergoing serial LVEF assessments, in which 3D-echocardiography was feasible and reproducible for assessing changes in LV volumes and LVEF compared with the gold standard cardiac MRI.[10] Similarly, in a study by Thavendiranathan *et al*,[7] non-contrast 3D-echocardiography was the most reproducible technique for LVEF assessment capable of detecting smaller changes in LVEF (~5%). However, a decrease in LVEF is still considered to be a late manifestation of cancer therapy-associated cardiotoxicity and may reflect the presence of irreversible myocardial damage. Thus, efforts have focused on identifying more sensitive measures of LV systolic function.

Newer techniques of assessing myocardial deformation (eg, strain, strain rate, twist and torsion) have been proposed as more sensitive tools for the detection of subclinical LV systolic dysfunction. Strain was initially measured with tissue Doppler imaging (TDI), but this technique is limited by the angle dependence inherent to TDI as well as the inability to differentiate translational motion or tethering effects from adjacent segments. Speckle tracking echocardiography (STE), which uses an image-processing algorithm to track

patterns of ‘speckles’ or natural echocardiographic signals, has replaced TDI as the preferred method for multidirectional strain measurement (ie, longitudinal, radial and circumferential).

Global longitudinal strain (GLS) has thus far been identified as the most robust strain parameter for cardiotoxicity monitoring during therapy. Several studies have shown that GLS determined by STE can detect myocardial injury before the development of an overt decline in LVEF. In a prospective study by Sawaya *et al*,[11] STE was performed at baseline (before anthracycline chemotherapy), after the completion of anthracyclines and every 3 months over 15 months in 81 patients treated with adjuvant anthracycline-based chemotherapy plus trastuzumab. A GLS of <19% (derived as an average of the apical 4-chamber and 2-chamber views, excluding the apex) after the completion of anthracycline treatment was predictive of later development of cardiotoxicity (positive predictive value 53%, negative predictive value 87%), defined as a symptomatic reduction of LVEF ≥5% to <55% or an asymptomatic reduction of LVEF ≤10% to <55%. Although reductions were also observed in radial and circumferential strain, these parameters were not associated with subsequent heart failure. A similar study by Negishi *et al*[12] of 81 women receiving adjuvant trastuzumab also demonstrated that GLS was an independent early predictor of later declines in LVEF. STE was performed at baseline and at 6 and 12 months, and an 11% reduction in GLS was the strongest predictor of cardiotoxicity, defined by a reduction of LVEF ≥10%. Findings from this study also suggest that the change in GLS from baseline is predictive of cardiotoxicity. These two studies have informed the development of the expert consensus for multimodality imaging in patients with cancer by the American Society of Echocardiography (ASE), which recommends the use of GLS in the assessment of cardiac function in patients with cancer, and suggests that a change in GLS can be used to detect early subclinical changes in LV systolic function.[13]

Cardiac MRI, which is the gold standard for the measurement of ventricular volumes and function, has the unique ability to characterise myocardial tissue and potentially identify early signs of cardiac injury.[14] Two techniques have been investigated for the detection of cardiotoxicity. Late gadolinium enhancement (LGE) is an established imaging method for the detection of focal myocardial fibrosis and scar, but has shown poor diagnostic and prognostic value in cancer survivors.[15] Alternatively, estimation of extracellular volume fraction using T1 mapping is able to identify diffuse patterns of myocardial injury likely to be associated with cancer therapy, but requires further investigation.[16]

Practice guidelines have been published by professional organisations including the National Comprehensive Cancer Network (NCCN),[17] European Society of Medical Oncology (ESMO),[18] and ASE[13] that provide recommendations for cardiac imaging during cardiotoxic cancer therapy. However, evidence supporting the effectiveness of cardiac imaging to reduce cardiotoxicity remains limited and current recommendations are largely based upon expert opinion and cardiac monitoring algorithms used in the context of large clinical trials. Future studies are needed to determine the most appropriate modality of cardiac imaging, the optimal frequency and threshold of testing, and how interventions based on cardiac imaging impact cancer or cardiac-related outcomes (table 1).

Circulating biomarkers

Circulating blood-based biomarkers are actively under investigation as possible alternatives to cardiac imaging for the diagnosis and prediction of cardiotoxicity (table 1). Widely established biomarkers have the advantage of being reproducible measures that are often readily attainable. In addition, circulating biomarkers provide biologic insight and may inform the underlying mechanism of cardiotoxicity.

Troponin

Cardiac troponins are markers of myocardial injury and play an important role in the diagnosis of acute coronary syndromes.[19] In cardio-oncology, troponin has been the most widely studied biomarker. In a study by Cardinale *et al* of 204 patients receiving high-dose chemotherapy, troponin I (TnI) elevation was observed in 32% of patients and was predictive of subsequent LVEF decline.[20] A follow-up study was performed by the same group in 703 patients treated with high-dose chemotherapy. These patients underwent serial TnI monitoring at multiple time-points with each cycle of treatment (immediately after, 12, 24, 36 and 72 h after each cycle) and 1 month after chemotherapy. [21] The pattern of TnI elevation identified patients at various levels of risk for cardiotoxicity. Specifically, the highest cardiotoxicity event rate was observed among patients with early (within 72 h) TnI elevation (≥0.08 ng/mL) that persisted at 1 month after treatment. A similar study performed in patients treated with trastuzumab demonstrated that an elevated TnI was associated with a lack of LVEF recovery despite heart failure therapy.[22]

New high-sensitivity troponin assays are currently available that provide superior diagnostic accuracy for acute coronary syndromes,[19] and have been under investigation for the early detection of cardiotoxicity. A study by Sawaya *et al*[11] demonstrated a significant increase in ultrasensitive TnI among patients with HER2-positive breast cancer treated with anthracyclines and trastuzumab. The mean ultrasensitive TnI concentration after completion of anthracycline chemotherapy was higher among women who developed cardiotoxicity (32 vs 17 pg/mL), and an elevated ultrasensitive TnI >30 pg/mL was predictive of subsequent cardiotoxicity (p=0.04).

There have been multiple reports on the association between TnI elevation and cardiotoxicity with other treatment exposures (eg, sunitinib, sorafenib, lapatinib, etc), but with mixed results.[23–25] The 2012 ESMO Clinical Practice Guidelines for cardiovascular toxicity recommend troponin testing at baseline, during and after cancer therapy (Level of evidence III, Grade B).[18]

Brain-type natriuretic peptides

Natriuretic peptides have been studied extensively for their diagnostic and prognostic role in heart failure. Brain-type natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) are standard biomarkers used in clinical practice for the diagnosis and management of heart failure. However, conclusions regarding the role of natriuretic peptides for the prediction and diagnosis of cardiotoxicity remain conflicting. In the largest study of BNP in the cancer setting, Skovgaard *et al*[26] showed that BNP >100 pg/mL was predictive

of heart failure (HR 5.5, 95% CI 1.8 to 17.2, p=0.003) in a heterogeneous cohort of 333 patients with cancer with different tumour types and cardiotoxic treatment exposures.

There is a clear need for additional studies to clarify the role of TnI and BNP assessment during and after cancer therapy. The effectiveness of using biomarkers to detect and identify cardiotoxicity and inform treatment is currently underway (NCT01032278) to assess the role and timing of TnI and BNP testing in patients undergoing anthracycline-based chemotherapy.

Novel biomarkers

Many novel biomarkers have been proposed in the monitoring of cardiotoxicity (eg, high sensitivity C-reactive protein, myeloperoxidase, galectin 3, interleukin family molecules including ST2, matrix metalloproteinase and human heart-type fatty acid-binding protein). In a study by Ky *et al*[27] of multiple novel biomarkers in a cohort of 78 patients with breast cancer undergoing doxorubicin and trastuzumab therapy, early increases in TnI and myeloperoxidase (MPO) a neutrophil-derived enzyme of oxidative stress, were associated with an increased risk of first cardiotoxic event.

Despite many of the above studies demonstrating the promise of biomarkers for their predictive value of cardiotoxicity, many questions remain. These include the timing of biomarker testing, the threshold for each individual biomarker, optimal assay, the incremental clinical value of new biomarkers and the validation of these results in larger independent cohorts. Furthermore, the role and type of biomarkers used for the detection of cancer therapy-associated cardiotoxicity must continue to evolve and adapt as new targeted cancer therapeutics with differing mechanisms of cardiac injury are introduced into clinical practice.

Multimodality approach

An approach that integrates multiple circulating biomarkers and/ or non-invasive cardiac imaging measures may provide additive value. In a study by Sawaya *et al*,[11] an elevation of ultrasensitive TnI or a decrease in GLS <19% was associated with a sensitivity of 87% for the prediction of trastuzumab cardiotoxicity compared with either parameter alone (74% and 48%, respectively). Similarly, the combination of elevated TnI and MPO levels was shown to identify a group of patients with breast cancer at increased risk for cardiotoxicity than each individual biomarker alone.[27] Thus, a combined multimodality approach in selected individuals may provide incremental value in predicting cardiotoxicity and ultimately prove to be the most useful in clinical practice.

BIOMARKERS FOR DETECTION OF LATE CARDIOTOXICITY IN CANCER SURVIVORS

In cancer survivors, the rationale to perform routine surveillance in the absence of symptoms is that this practice will allow for early identification of LV systolic dysfunction and delay the progression to or onset of clinical heart failure. This issue has been extensively studied among childhood cancer survivors treated with anthracyclines and cardiac radiation, a

patient population known to be at increased risk for late-onset cardiotoxicity. The International Late Effects of Childhood Cancer Guideline Harmonization Group was established to resolve differences in guidelines across groups in North America and Europe and proposed an algorithm for cardiomyopathy surveillance that is risk-specific and dependent on treatment exposures.[28]

There has been growing interest in the use of STE for the evaluation of subclinical LV dysfunction among childhood cancer survivors. In the St. Jude Lifetime Cohort Study, Armstrong *et al* performed echocardiography assessment with measurement of 3D LVEF and GLS in 1820 survivors of childhood cancer. Although only 5.8% of survivors had an LVEF <50%, 31.8% had evidence of cardiac dysfunction as defined by a GLS >2 SDs below the mean.[29] While certainly quite intriguing, studies are needed to determine the natural history of asymptomatic GLS declines, to examine whether abnormal GLS is predictive of subsequent LVEF declines or clinical heart failure and to study the efficacy of early intervention strategies to improve clinical outcomes.

There have been few studies on the use of circulating biomarkers for the assessment of late cardiotoxicity in cancer survivors. In a study of 200 childhood cancer survivors previously treated with varying doses of anthracycline chemotherapy, NT-proBNP levels were higher in survivors treated with ≥300 mg/m^2 anthracyclines compared with survivors treated with <300 mg/m^2 (median 71 vs 37 pg/dL, p=0.01).[30] No differences in other biomarkers including BNP, troponin-T, galectin 3 or ST2 were observed. Similar findings of elevated NT-proBNP were reported in two cross-sectional studies of childhood cancer survivors previously treated with anthracyclines.[31] Long-term follow-up studies are needed to determine whether NT-pro-BNP levels can identify survivors at increased risk for late cardiotoxicity.

FUNDAMENTAL GAPS IN KNOWLEDGE AND FUTURE DIRECTIONS

Despite the important body of research published to date in cardio-oncology biomarkers, many questions remain unanswered. Which biomarkers provide the greatest prognostic and predictive value, what is the optimal threshold for each biomarker, and what is the optimal timing and frequency of biomarker testing? What is the reproducibility of these measures, and can they be implemented in both academic and community settings? Long-term studies are needed to determine the relationship between biomarker abnormalities and well-defined clinical outcomes, and determine how these markers can better inform the use of cardioprotective strategies. In order to accomplish these goals, a first step could be to leverage the use of imaging and biospecimen repositories from existent studies, and build collaborations among cooperative oncology and cardiology groups. Ultimately, prospective studies and randomised trials are necessary to inform whether the application of biomarkers can improve patient outcomes.

CONCLUSIONS

Cardiotoxicity remains an important adverse sequela of cancer treatment. The variability in a patient's response to the beneficial and toxic effects of cancer therapy is an increasingly

recognised problem within cardio-oncology and has stimulated a close collaborative effort between medical oncologists and cardiologists. Further investigation is needed to identify the best practices for cardiac monitoring prior to, during and after exposure to cardiotoxic therapy. The incorporation of both imaging and circulating biomarkers will likely be a critical component in the development of an evidence-based and risk-specific strategy for cardiac surveillance in order to mitigate the individual patient's risk of cardiotoxicity.

Acknowledgments

Funding BK is supported by NIH NHLBI R01 HL 118018 for this work. This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748.

References

1. Von Hoff DD, Layard MW, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med. 1979; 91:710–17. [PubMed: 496103]
2. Cheng H, Force T. Molecular mechanisms of cardiovascular toxicity of targeted cancer therapeutics. Circ Res. 2010; 106:21–34. [PubMed: 20056943]
3. Patnaik JL, Byers T, DiGuiseppi C, et al. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. Breast Cancer Res. 2011; 13:R64. [PubMed: 21689398]
4. Shelburne N, Adhikari B, Brell J, et al. Cancer treatment-related cardiotoxicity: current state of knowledge and future research priorities. J Natl Cancer Inst. 2014; 106 pii:dju232.
5. Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. J Am Coll Cardiol. 2009; 53:2231–47. [PubMed: 19520246]
6. Shah AM, Solomon SD. Myocardial deformation imaging: current status and future directions. Circulation. 2012; 125:e244–8. [PubMed: 22249531]
7. Thavendiranathan P, Grant AD, Negishi T, et al. Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes: application to patients undergoing cancer chemotherapy. J Am Coll Cardiol. 2013; 61:77–84. [PubMed: 23199515]
8. Romond EH, Jeong JH, Rastogi P, et al. Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol. 2012; 30:3792–9. [PubMed: 22987084]
9. de Azambuja E, Procter MJ, van Veldhuisen DJ, et al. Trastuzumab-associated cardiac events at 8 years of median follow-up in the Herceptin adjuvant trial (BIG 1-01). J Clin Oncol. 2014; 32:2159–65. [PubMed: 24912899]
10. Walker J, Bhullar N, Fallah-Rad N, et al. Role of three-dimensional echocardiography in breast cancer: comparison with two-dimensional echocardiography, multiple-gated acquisition scans, and cardiac magnetic resonance imaging. J Clin Oncol. 2010; 28:3429–36. [PubMed: 20530277]
11. Sawaya H, Sebag IA, Plana JC, 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; 5:596–603. [PubMed: 22744937]
12. Negishi K, Negishi T, Hare JL, et al. Independent and incremental value of deformation indices for prediction of trastuzumab-induced cardiotoxicity. J Am Soc Echocardiogr. 2013; 26:493–8. [PubMed: 23562088]
13. Plana JC, Galderisi M, Barac A, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of echocardiography and the European Association of cardiovascular imaging. J Am Soc Echocardiogr. 2014; 27:911–39. [PubMed: 25172399]
14. Jordan JH, D'Agostino RB Jr, Hamilton CA, et al. Longitudinal assessment of concurrent changes in left ventricular ejection fraction and left ventricular myocardial tissue characteristics after

administration of cardiotoxic chemotherapies using T1-weighted and T2-weighted cardiovascular magnetic resonance. Circ Cardiovasc Imaging. 2014; 7:872–9. [PubMed: 25273568]

15. Thavendiranathan P, Wintersperger BJ, Flamm SD, et al. Cardiac MRI in the assessment of cardiac injury and toxicity from cancer chemotherapy: a systematic review. Circ Cardiovasc Imaging. 2013; 6:1080–91. [PubMed: 24254478]
16. Neilan TG, Coelho-Filho OR, Shah RV, et al. Myocardial extracellular volume by cardiac magnetic resonance imaging in patients treated with anthracycline-based chemotherapy. Am J Cardiol. 2013; 111:717–22. [PubMed: 23228924]
17. National Comprehensive Cancer Network. [accessed 30 Jun 2015] NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. Version 1. 2012. http://www.nccn.org
18. Curigliano G, Cardinale D, Suter T, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO clinical practice guidelines. Ann Oncol. 2012; 23(Suppl 7):vii155–66. [PubMed: 22997448]
19. Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med. 2009; 361:858–67. [PubMed: 19710484]
20. Cardinale D, Sandri MT, Martinoni A, et al. Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. J Am Coll Cardiol. 2000; 36:517–22. [PubMed: 10933366]
21. Cardinale D, Sandri MT, Colombo A, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. Circulation. 2004; 109:2749–54. [PubMed: 15148277]
22. Cardinale D, Colombo A, Torrisi R, et al. Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. J Clin Oncol. 2010; 28:3910–16. [PubMed: 20679614]
23. Schmidinger M, Zielinski CC, Vogl UM, et al. Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. J Clin Oncol. 2008; 26:5204–12. [PubMed: 18838713]
24. Morris PG, Chen C, Steingart R, 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; 17:3490–9. [PubMed: 21372222]
25. Chu TF, Rupnick MA, Kerkela R, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. Lancet. 2007; 370:2011–p9. [PubMed: 18083403]
26. Skovgaard D, Hasbak P, Kjaer A. BNP predicts chemotherapy-related cardiotoxicity and death: comparison with gated equilibrium radionuclide ventriculography. PLoS ONE. 2014; 9:e96736. [PubMed: 24800827]
27. Ky B, Putt M, Sawaya H, 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; 63:809–16. [PubMed: 24291281]
28. Armenian SH, Hudson MM, Mulder RL, et al. Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol. 2015; 16:e123–36. [PubMed: 25752563]
29. Armstrong GT, Joshi VM, Ness KK, et al. Comprehensive echocardiographic detection of treatment-related cardiac dysfunction in adult survivors of childhood cancer: results from the St. Jude Lifetime Cohort Study. J Am Coll Cardiol. 2015; 65:2511–22. [PubMed: 26065990]
30. Armenian SH, Gelehrter SK, Vase T, et al. Screening for cardiac dysfunction in anthracycline-exposed childhood cancer survivors. Clin Cancer Res. 2014; 20:6314–23. [PubMed: 24947931]
31. Mavinkurve-Groothuis AM, Groot-Loonen J, Bellersen L, et al. Abnormal NT-pro-BNP levels in asymptomatic long-term survivors of childhood cancer treated with anthracyclines. Pediatr Blood Cancer. 2009; 52:631–6. [PubMed: 19127569]
32. Erven K, Florian A, Slagmolen P, et al. Subclinical cardiotoxicity detected by strain rate imaging up to 14 months after breast radiation therapy. Int J Radiat Oncol Biol Phys. 2013; 85:1172–8. [PubMed: 23149005]
33. Fallah-Rad N, Walker JR, Wassef A, et al. The utility of cardiac biomarkers, tissue velocity and strain imaging, and cardiac magnetic resonance imaging in predicting early left ventricular

dysfunction in patients with human epidermal growth factor receptor II-positive breast cancer treated with adjuvant trastuzumab therapy. J Am Coll Cardiol. 2011; 57:2263–70. [PubMed: 21616287]

34. Sandri MT, Cardinale D, Zorzino L, et al. Minor increases in plasma troponin I predict decreased left ventricular ejection fraction after high-dose chemotherapy. Clin Chem. 2003; 49:248–52. [PubMed: 12560347]
35. Romano S, Fratini S, Ricevuto E, et al. Serial measurements of NT-proBNP are predictive of not-high-dose anthracycline cardiotoxicity in breast cancer patients. Br J Cancer. 2011; 105:1663–8. [PubMed: 22068815]
36. Lipshultz SE, Miller TL, Scully RE, 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; 30:1042–9. [PubMed: 22370326]
37. Daugaard G, Lassen U, Bie P, et al. Natriuretic peptides in the monitoring of anthracycline induced reduction in left ventricular ejection fraction. Eur J Heart Fail. 2005; 7:87–93. [PubMed: 15642537]
38. Dodos F, Halbsguth T, Erdmann E, et al. Usefulness of myocardial performance index and biochemical markers for early detection of anthracycline-induced cardiotoxicity in adults. Clin Res Cardiol. 2008; 97:318–26. [PubMed: 18193371]
39. Putt M, Hahn VS, Januzzi JL, et al. Longitudinal Changes in Multiple Biomarkers Are Associated with Cardiotoxicity in Breast Cancer Patients Treated with Doxorubicin, Taxanes, and Trastuzumab. Clin Chem. 2015; 61:1164–72. [PubMed: 26220066]

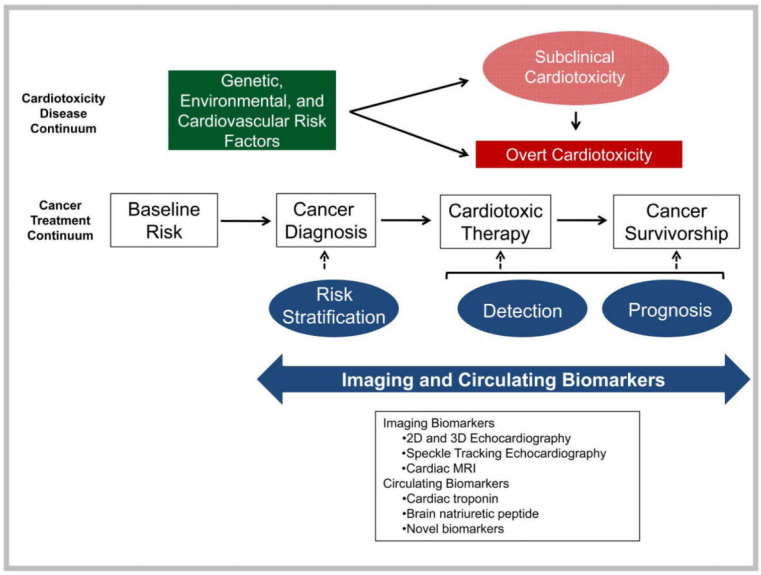

Figure 1.

Biomarkers for risk stratification, surveillance and management of cardiotoxicity. During cancer treatment, progression from the presence of baseline risk factors to the development of overt cardiotoxicity can occur throughout the continuum of cancer treatment, from the time of cancer diagnosis to cancer survivorship. Use of imaging and circulating biomarkers may help to determine baseline risk of cardiotoxicity and identify patients that could benefit from intensive cardiac monitoring or cardioprotective strategies. Early detection of subclinical cardiotoxicity may provide an opportunity to intervene earlier in the course of disease. After the development of cardiotoxicity, biomarkers may provide important prognostic information and guide cardiotoxicity treatment. Further investigation is needed to determine the optimal timing and follow-up of biomarker testing. 2D, two dimensional; 3D, three dimensional.

Table 1

Advantages and disadvantages of imaging and circulating biomarkers

	Advantages	Disadvantages	References
Imaging biomarkers			
LVEF—TTE	• Widely accessible • Ease of use • Established prognostic value of abnormal LVEF in heart failure	• Interobserver and intraobserver variability • Limited negative predictive value • LVEF may remain normal despite subclinical damage • Limited by image quality • Load dependent	7
Global longitudinal strain—STE	• Emerging data suggest strain can detect early cardiotoxicity prior to overt LVEF decline • Established prognostic value in other cardiovascular disease states (eg, heart failure and myocardial infarction)	• Limited availability and expertise • Variability between different vendors • Similar to LVEF assessment, limited by image quality and also load dependent • Need for additional research prior to widespread clinical implementation	11–13
Late gadolinium enhancement—cMRI	Allows for detection of focal myocardial fibrosis or scar	• Limited availability and potential cost of cMRI • Poor diagnostic and prognostic value for cardiotoxicity	15
Extracellular volume—cMRI	Allows for detection of diffuse myocardial fibrosis	• Limited availability and high cost of cMRI • Limited data	16
Circulating Biomarkers			
Troponin	• Widely available • Commonly studied cardiac biomarker for multiple cancers and treatment exposures • Elevated levels during cancer treatment may predict subsequent LVEF decline • Elevated levels may predict response to heart failure therapy • Established diagnostic reference ranges	• Optimal threshold value for risk prediction uncertain • Unknown optimal timing (ie, before, during, or after treatment) or frequency of troponin testing • Limited availability of high-sensitivity assays • Inconsistent associations with cardiotoxicity risk	1120–22242732–36
Brain-type natriuretic peptide	• Widely available • Gold-standard biomarker for clinical heart failure with established prognostic significance	• Optimal threshold value for risk prediction uncertain • Unknown optimal timing (ie, before, during or after	11263133353738

	Advantages	Disadvantages	References
	• Established diagnostic reference ranges	treatment) or frequency of testing • Inconsistent associations with cardiotoxicity risk	
Myeloperoxidase	May be mechanistically relevant and associated with risk of anthracycline and trastuzumab cardiotoxicity	• Limited data and need for external validation • Sensitive to processing conditions	2739

cMRI, cardiac MRI; LVEF, left ventricular ejection fraction; STE, speckle tracking echocardiogram; TTE, transthoracic echocardiogram.