



Changing Hearts and Minds: Improving Outcomes in Cancer Treatment-Related Cardiotoxicity

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Abstract

Purpose of Review Cardiovascular effects from cancer treatment remains a leading cause of treatment-associated morbidity and mortality among cancer survivors. The National Cancer Institute and National Heart, Lung, and Blood Institute convened a Workshop in June 2018 entitled “Changing Hearts and Minds: Improving Outcomes in Cancer Treatment-Related Cardiotoxicity” to highlight progress, ongoing work, and update scientific priorities since the 2013 Workshop. Here we will describe these advances and provide an overview of the research priorities identified.

Recent Findings Since 2013, the National Institutes of Health has increased its support of cancer treatment-related cardiotoxicity research through the funding of grants and coordination of internal and external working groups. Workshop participants identified knowledge gaps and recommended over 20 new promising opportunities in basic and clinical cardiotoxicity research.

Summary Significant progress on mechanisms, detection, management, and prevention of cardiotoxicity has been made over the past 5 years, yet some critical gaps remain.

Keywords Cardiotoxicity · Cancer treatment · Cardiovascular disease · Cardio-oncology

Introduction to Cardiotoxicity From Cancer Treatment

The over 15 million pediatric and adult cancer survivors living in the USA demonstrates the impact of continued improvements in anti-cancer treatment efficacy; however, this success

has been tempered by a parallel increased incidence of cancer treatment-related cardiovascular toxicity [1]. Cardiovascular effects from cancer treatment remain a leading cause of treatment-associated morbidity and mortality across cancer survivors [2–4]. Treatment-induced cardiac and vascular damage occurs during cancer treatment and throughout the duration of cancer survivorship, up to 30 years posttherapy [5].

Cancer treatment-related cardiovascular adverse events significantly impact quality of life during treatment and throughout the cancer survivorship continuum [5, 6]. Cardiac and vascular damage may be transient yet influence treatment type, dosing, and timing that could impact cancer outcomes. The damage may also be permanent and influence physical functioning during and after recovery from treatment. The incidence of cardiotoxicity has continued to increase as new treatment modalities with unknown cardiovascular safety profiles are quickly implemented [7]. The cardio-oncology clinician and research community have begun to recognize the information gaps between preclinical studies and clinical investigations including a growing need for preclinical models, toxicology testing, and risk identification to prevent, detect, and manage cardiovascular toxicity in patients with cancer.

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In 2013, the National Cancer Institute (NCI) and National Heart, Lung, and Blood Institute (NHLBI) conducted a cardiotoxicity portfolio analysis, held a scientific meeting and published 41 research priorities to address the range and depth of the scientific questions across cardio-oncology [8]. Funding Opportunity Announcements (FOA) (PA-18-003, PA-18-013) were released in 2015 to encourage collaborative applications that contribute to the identification, characterization, and management of patients at risk of developing cancer treatment-related cardiotoxicity [9, 10].

To capture the ongoing work across cardio-oncology and inform the current state of knowledge, the NCI and NHLBI convened a Workshop in June 2018 entitled “Changing Hearts and Minds: Improving Outcomes in Cancer Treatment-Related Cardiotoxicity” in Bethesda, MD [11]. The Workshop brought together over 100 participants with expertise in oncology, cardiology, epidemiology, patient advocacy, research, and clinical care, to reassess the landscape of research in cardiovascular complications from cancer therapy, to highlight emerging areas of research, and to identify where research gaps exist in the development of clinical guidelines. This report provides an overview of the Workshop research recommendations (Table 1) that build upon the 2013 recommendations [8].

Progress and Advances in Cancer Treatment-Related Cardiotoxicity

Since the 2013 Workshop identified research opportunities and future directions in cancer treatment-related cardiotoxicity, advances have been made on multiple fronts. Advances include, but are not limited to, an expanded cardiotoxicity portfolio at the National Institutes of Health (NIH) resulting from new funding opportunities, the establishment of interdisciplinary working groups within cardiology and oncology, and the development of cardio-oncology specific clinical guidelines. Tangible research-related progress has also been made on the recommendations forwarded by the Workshop attendees in 2013, some of which are highlighted below.

The robust response to the NIH FOAs has led to increased funding in cardio-oncology risk prediction, prevention, and survivorship care. Additional funding through parallel efforts within NCI and NHLBI contributed to mechanism studies and treatment modalities. NCI and NHLBI have also established coordinated efforts supporting studies designed to address research gaps identified in the 2013 Workshop, such as prospectively monitoring cardiovascular function and evaluating interventions to reduce risk of cardiovascular events. Under the NCI Community Oncology Research Program, there are currently five prevention and management cardiotoxicity studies underway: (1) PREVENT statin for prevention, (2) UPBEAT

cardiovascular events after treatment, (3) carvedilol to prevent heart failure, (4) dexrazoxane effects on biomarkers of heart failure, and (5) low-dose carvedilol to prevent left ventricular (LV) ejection fraction decrease (Table 2). NHLBI’s clinical research initiative, the Heart Failure Clinical Research Network, also supports cardio-oncology protocols that are in progress; they include prevention for anthracycline-induced cardiotoxicity (ACT) and blood pressure control in anti-angiogenic tyrosine kinase inhibitor sensitive tumors.

Another outcome of the 2013 Workshop meeting was the formation of the NCI Community Oncology Cardiotoxicity Task Force in January 2014. Members of the Task Force include cardiologists, oncologists, nurses, and clinical trialists from academia, industry, and government; the group meets regularly to discuss the latest research findings, identify priorities for new investigations in cardiotoxicity, vet cardio-oncology study methodology, and standardize clinical trial assessment and endpoints across multiple research studies to characterize cancer and cardiovascular phenotypes and prevent and manage treatment-related cardiotoxicity. The Task Force also focuses on patient management issues, such as survivorship, late effects, and genetic risk.

Moreover, in recognition of the increasing need for clinical guidance for cancer treatment-related cardiotoxicity, consensus recommendations and guidelines by professional societies and think tanks have been developed [12•, 13•] for survivors of pediatric and adult cancers. However, the evidence base on which these recommendations have been made is still limited and many of the recommendations are based on expert opinion and on older data. Further, the focus of these guidelines is specific to certain cardiovascular outcomes—such as asymptomatic cardiomyopathy in childhood cancer survivors and prevention of systolic cardiac dysfunction in survivors of adult-onset cancer—as well as to specific cancer treatments, limiting its utility.

Workshop Findings and Recommendations

Even with recent progress in mitigating cardiovascular complications of cancer treatment, Workshop participants noted that the continued increase in the prevalence of cancer survivors and the proliferation of new cancer therapies will likely exacerbate the problem in the foreseeable future, implying continued progress is urgent. Tools to evaluate cardiotoxicity need to be established, and the inclusion of imaging, histopathology, biomarkers, telemetry, and cardiovascular measures and markers could facilitate for earlier detection. Prevention and intervention strategies to manage cardiovascular adverse events that occur during or after completion of cancer treatment are also needed, especially for newer anti-cancer regimens. Research gaps and opportunities in cancer treatment-

Table 1 2018 Workshop recommendations: research opportunities in cancer treatment-related cardiotoxicity**Mechanisms**

1. Integrate advances in -omics approaches to identify and assess markers of cardiotoxicity (e.g., mitochondrial activity, skeletal muscle health) to enhance the mechanistic understanding of damage.
2. Investigate the role of human induced pluripotent stem cells (e.g., cardiomyocyte, endothelial) in cardiotoxicity disease modeling, cancer drug discovery, patient risk stratification, and intervention studies.

Preclinical and animal studies

3. Devise preclinical *in vitro* and *in vivo* methods and models based upon phenotypic and molecular data in human studies that reflect susceptibility of human cardiovascular tissues to cancer therapies and cardiovascular protective measures.
4. Translate mechanistic evidence to develop preclinical models and validation criteria that identify potential adverse cardiovascular outcomes; investigate mechanisms of cardiovascular toxicity of compounds/regimens based upon profile of known cardiotoxic cancer therapies.
5. Develop and calibrate preclinical cancer agent toxicology methodologies to test repeat and chronic dosing of cancer treatments considered likely to induce cardiac and/or vascular disease states (e.g., hemodynamic abnormalities, coronary artery thrombosis; subclinical cardiac dysfunction, acute, early, and late-onset cardiotoxicity; and heart failure).
6. Develop a broad preclinical strategy by which to evaluate efficacy of potential cardioprotective therapies (e.g., dexrazoxane, beta-blockers, and angiotensin-converting enzyme inhibitors) across the life span of preclinical animal models and tissues (e.g., *in vitro* and *in vivo* assays to evaluate functional liabilities of vascular damage, and heart contractility).

Markers of risk and injury

7. Implement core lab processes for bioimaging studies within known cardiotoxic oncology drug trials for robust data collection and interpretation.
8. Develop, test, and adopt clinically viable and sustainable cardiovascular risk assessments and stratification tools that inform actionable outcomes before, during, and after cancer treatment. Focus on variables that are common across cardiovascular outcomes (e.g., troponins, BNP).
9. Validate promising and actionable cardiotoxicity screening and detection modalities in retrospective cancer cohorts and test effectiveness in prospective cancer cohorts, including cancer survivors greater than 1 year posttreatment to understand utility and feasibility.
10. Conduct cost-effective analyses of promising bioimaging techniques to detect actionable, asymptomatic cardiotoxicity during and postcancer treatment.

Prevention

11. Develop and implement strategies for the prevention and management of cardio-oncology risk factors (e.g., systolic blood pressure, metabolic impairment, physical activity) supported by existing evidence-based cardiovascular clinical recommendations and guidelines during and after cancer treatment.
12. Focus cardiotoxicity prevention strategies on modifiable and actionable risk factors during and after cancer treatment.

Management

13. Conduct lifestyle intervention studies that address the complex etiology of cardiotoxicity, to include but not limited to, weight loss, physical activity, skeletal muscle loss, sleep, energy balance, and cardiorespiratory fitness, and include standardized cardiovascular measures and outcomes.
14. Develop and test individualized treatment plans that address pharmacologic management and modifiable lifestyle and behavioral strategies aimed at improving cardiovascular outcomes.

Cancer survivorship

15. Engage the community-based oncology, cardiology, and primary care groups in cardio-oncology study design to enhance the translation of study finding.
16. Develop and implement risk stratification tools that inform cardio-oncology and primary care health system resource requirements.

Developing standards

17. Employ standard definitions and measures of cancer treatment-related cardiotoxicity in clinical trials and clinical practice to enable comparison of data elements over time.
18. Conduct population-based studies to inform incidence, severity, risk stratification, and disease progression of various cardiotoxicities.
19. Utilize technologies (e.g., natural language processing) to enhance capture and use of meaningful and actionable registry and electronic health record data relevant to cardio-oncology studies.
20. Promote more standardized oncology clinical trial entry eligibility for preexisting cardiovascular disease and comorbidities.
21. Develop standard cardiotoxicity data collection elements for oncology clinical trials Case Report Forms. Promote consistent assessment parameters for trial adverse events reporting (both clinician and patient-reported) through continued input into the NCI Common Terminology Criteria for Adverse Events refinement and health record documentation in clinical practice.
22. Identify, assess, and integrate evolving evidence into existing cancer treatment-related cardiotoxicity practice guidelines with a focus on expanding the cancers and cardiovascular dysfunctions represented and available clinical recommendations.

related cardiotoxicity in the preclinical and clinical settings are described below.

Research Opportunities: Basic Science

Mechanisms of Cancer Treatment-Related Cardiotoxicity

Cell Lines

Understanding the fundamental mechanisms underlying cancer treatment-related cardiotoxicity is essential to the development of new ways to monitor, treat, and prevent these adverse events. Further, given the urgency to identify cardiotoxicity risk earlier, preclinical methods for toxicity screening that can identify problematic antineoplastic therapies are important. Although human ether-a-go-go gene (hERG) assays are used routinely to evaluate investigational agents for the risk of prolonging the QT interval as a predictor of cardiac arrhythmia [14], current preclinical screening assays to detect cardiotoxicity remain suboptimal, with an urgent need to provide platforms for cardiovascular assessment in repeat and chronic dosing regimens and patient-derived cardiac myocytes. Recent studies show skeletal muscle may provide information regarding cardiac mitochondrial and metabolic health and is under investigation in breast cancer participants undergoing anthracycline therapy to elucidate a metabolic profile.

Another approach for which there is large interest is the use of human induced pluripotent stem cells (iPSC) as a potential

“clinical trial in a dish.” Human cardiomyocytes developed through iPSC technology can be used to study mechanisms of cardiac injury, and a recent study demonstrated that human iPSC-derived cardiomyocytes can be used as a screening tool to identify breast cancer patients treated with doxorubicin [15] at risk to develop cardiotoxicity. An accompanying editorial [16] highlighted that the use of iPSC could open new avenues for the prevention of cardiotoxicity. Other ways in which these cells can be used [17, 18•] include disease modeling, transplantation for therapeutic purposes, drug discovery, and as a means to confirm the findings from genome-wide association studies related to cancer treatment-related cardiotoxicity.

Animal Studies

Animal models are currently used to advance our mechanistic understanding of cardiotoxicities and evaluate efficacy of potential cardioprotective approaches. One non-pharmacologic intervention of interest is exercise, as it is a modifiable lifestyle strategy that could potentially be translated into a clinical intervention to improve cardiovascular outcomes. To assess strategies that could limit acute cardiac damage without compromising tumor response, the effect of exercise in mouse models was used to determine whether the introduction of exercise could improve acute and late cardiotoxicity outcomes following treatment with doxorubicin. Preclinical findings from these studies suggested that exercise initiated either during or after treatment with doxorubicin decreased both acute and late cardiotoxicity without compromising therapeutic efficacy in mice [19]. Although doxorubicin is one of the most effective drugs for treating sarcoma, it is accompanied by an

Table 2 NIH-sponsored active cardiotoxicity clinical trials

Study title	Clinicaltrials.gov ID number	Primary outcome measure	Intervention
Effects of Dexrazoxane Hydrochloride on Biomarkers Associated with Cardiomyopathy and Heart Failure after Cancer Treatment (HEART)	NCT01790152	Left ventricular thickness-to-dimension ratio	Physical exam, cardiac imaging, serum biomarkers, behavioral and psychosocial questionnaires (> 15 years posttreatment with anthracycline ± dexrazoxane)
Carvedilol in Preventing Heart Failure in Childhood Cancer Survivors	NCT02717507	Left ventricular thickness-dimension ratio	Arm 1: low dose, oral carvedilol Arm 2: placebo 24-month intervention**
Prospective Evaluation of Carvedilol in Prevention of Cardiac Toxicity in Patients with Metastatic HER-2+ Breast Cancer, Phase III	NCT03418961	Time to cardiac dysfunction (decreased left ventricular ejection fraction)	Arm 1: carvedilol Arm 2: placebo Arm 3: observation 108-day intervention**
Understanding and Predicting Breast Cancer Events After Treatment (UPBEAT)	NCT02791581	Change in fatigue, exercise capacity, and cardiac imaging measures	Cardiac imaging, exercise capacity, serum biomarkers, behavioral and psychosocial questionnaires at 3 months, 12 months, and 24 months posttreatment initiation
Preventing Anthracycline Cardiovascular Toxicity with Statins (PREVENT)	NCT01988571	Preservation of left ventricular ejection fraction	Arm 1: atorvastatin (lipitor) 40 mg daily Arm 2: placebo

elevated risk for late-onset cardiomyopathies, one of the leading causes of death among childhood cancer survivors [20–22], and there is a need to assess the incorporation of exercise into clinical studies.

Research Opportunities: Clinical Science

Risk Detection

The need for clinical assessment of cardiovascular risk prior to initiation of cancer treatment is evident and would likely improve treatment planning. Similarly, there is a need to monitor for cardiotoxicities during and postcancer treatment. Understanding the response of the cardiovascular system to the acute and chronic exposures of anti-cancer agents and regimens will help to identify the specific assessments that are needed to monitor cancer patients over the entire course of treatment and posttreatment. Those assessments may be standard cardiovascular biomarkers, imaging modalities, and/or newer markers that are more specific to the injury resulting from cancer treatment. However, despite the best use of available resources, current evidence is based on multiple small studies and the reported data are inconsistent. Workshop participants noted the need for standard methods for assessment and monitoring with multi-disciplinary oversight. Highlighted below are several areas to improve prevention and management of cancer treatment-related cardiotoxicities identified by Workshop participants.

Biomarkers

Cardiac markers are used in the diagnosis and risk stratification of patients with chest pain and other cardiac outcomes. For example, lipid markers, such as cholesterol, are accepted screening biomarkers of cardiovascular disease risk. Cardiac troponin levels are also measured to diagnose acute myocardial infarction. Other biomarkers that are used to assess cardiac dysfunction include C-reactive protein, brain natriuretic peptide (BNP), myeloperoxidase, and ischemia modified albumin. However, different mechanisms may underlie the cancer treatment-related cardiotoxicities observed. Thus, identifying clinically practical biomarkers to diagnose and monitor cancer treatment-related cardiotoxicity are needed.

One biomarker that is currently studied as a predictor of cardiac dysfunction in cancer patients is BNP levels, which was associated with rates of LV dysfunction and heart failure in a community cohort of patients at risk of heart failure [23]. BNP levels in retrospective cohort of breast cancer survivors were also associated with LV dysfunction at 10-year follow-up [24], although the association was based on small numbers. Other studies under investigation include more frequent biomarker monitoring with BNP to identify cancer patients

treated with anthracycline who may benefit from earlier intervention (i.e., lower the incidence of cardiac dysfunction, heart failure, and overall major adverse cardiovascular events).

Another promising area is the use of pharmacogenetic testing to improve management of ACT. Accurately identifying cancer patients with a genetic predisposition for cardiotoxicity could provide the opportunity to prevent cardiovascular disease in this population. A recent paper by Aminkeng et al. [25] reviewed the scientific evidence and provided clinical recommendations for genetic testing to reduce ACT. Although a few potential genetic variants have been identified (e.g., *RARG* rs2229774, *SLC28A3* rs7853758, and *UGT1A6**4 rs17863783) to predict ACT risk, the evidence base is limited so that these biomarkers remain investigational. To generate more evidence, investigations to assess pharmacogenetic testing for genetic variance in *TOP2B* promoter and its influence of ACT and examine cardiovascular disease event risk in two matched cohorts with and without breast cancer are ongoing. Similarly, a prospective implementation study of *RARG* variants in pediatric patients is being conducted.

Despite the advances made in the understanding of ACT, biomarker studies are needed to evaluate new and combination cancer therapies—such as vascular endothelial growth factor (VEGF), proteasome inhibitors, and immunotherapies. Different mechanisms of anti-cancer activity have been recognized in these newer agents and are thought to contribute to unexpected cardiovascular complications (e.g., myocarditis in cancer patients treated with immunotherapies) [26, 27••]. In the coming decade, the introduction of new cancer therapies could cause cardiotoxicity through unknown mechanisms and more rigorous preclinical screening assays and biomarkers are needed to detect and mitigate these potential cardiac adverse events.

Imaging

Detection using advanced cardiac imaging—such as echocardiography, positron emission tomography, single-photon emission computed tomography, and cardiac magnetic resonance imaging—is another non-invasive method to detect subclinical cardiotoxicity. However, standard methods for detection requires testing and validation in large cohorts to determine their utility. One study assessing the reproducibility of cardiac safety assessments across two academic echocardiography core laboratories initially found persistent differences in their measurement techniques and calculated LV ejection fraction [28••], yet with closer adherence to guidelines, reproducibility improved. In response to the need to optimize the collection of quality imaging data, guidance on how to improve the process of collecting imaging data used in clinical trials was issued [29]. In addition to implementing core lab processes for bioimaging studies and instituting common image acquisition protocols with secure data storage environments,

Workshop participants noted the need for high-quality imaging prior to patient enrollment and cost-effective analyses of promising bioimaging techniques to detect asymptomatic cardiotoxicity during and postcancer treatment.

Prevention and Management

Pharmacological Intervention

Modification of cancer treatment modalities continues to be investigated as a means of preventing damage to the cardiovascular system. The balance between optimizing treatment efficacy and minimizing toxicity remains an area of considerable research and effort. Proton therapy reduces the amount of radiation to the heart compared to photon therapy, but gaps remain regarding the impact on major cardiovascular events and cancer outcomes between the therapies, and the Radiotherapy Comparative Effectiveness (RadComp) Study [30] is aiming to address these questions.

An approach that is being studied to improve prevention and management of cancer treatment-related cardiotoxicities includes pharmacological interventions at different time points (i.e., primary and secondary prevention) on the cancer treatment continuum. Currently, the only drug proven to be protective in preclinical and clinical settings is dexrazoxane in adult cancer patients [31]; it is the only drug, thus far, approved by the US Food and Drug Administration for use as a cardiac protectant in patients treated with anthracyclines. However, the American Society of Clinical Oncology maintains a cautionary position and recommends using dexrazoxane under limited conditions (e.g., patients who have received >399 mg/m² of doxorubicin for metastatic breast cancer and who may benefit from continued anthracycline treatment) [32], suggesting a need for the development other pharmacological interventions to provide cardioprotection [33]. Some cardioprotective agents that are under investigation and show promise include carvedilol for the prevention of ACT [34]; statins to reduce the risk of heart failure in breast cancer patients [35, 36]; and dual-action ribosomal S6 kinase (RSK) inhibitors that restore mitochondrial function, reducing doxorubicin-induced DNA damage and oxidative stress.

Beta-blockers and ACE inhibitors to prevent trastuzumab-associated cardiotoxicity [37] also are under investigation. More specifically, cardioprotective approaches using carvedilol in curative-intent trastuzumab for HER-2-positive breast cancer will soon be evaluated. The central hypotheses are that a preventive approach of therapy with the beta-blocker carvedilol started before trastuzumab therapy, or a proactive preventive approach with therapy started in response to early subclinical signs of cardiac dysfunction/injury (i.e., cardiac troponin elevation or abnormal global longitudinal strain) will reduce cardiotoxicity compared with the “wait-and-see”

approach (carvedilol prescribed once cardiotoxicity has occurred).

At present, there is no standard of cardioprotective strategies in childhood cancer survivors in whom premature heart disease is one of the leading causes of mortality [21, 22, 38]. Studies examining cardioprotection of dexrazoxane in childhood cancer patients found the agent to be protective without compromising doxorubicin efficacy [38, 39]; however, the long-term efficacy of dexrazoxane is unknown. To address this question, the HEART (Health Effects after Anthracycline and Radiation Therapy) Follow-up Study ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier NCT0179012) is examining the long-term efficacy of dexrazoxane in childhood cancer survivors treated in randomized clinical trials exposed to 100 to 360 mg/m² of anthracycline.

Intervention in survivors (i.e., secondary prevention) of childhood and adult cancers with subclinical cardiac dysfunction is also a research area of interest. Carvedilol is a beta-blocker that is being studied to assess whether it can prevent mild heart failure in cancer survivors who had been treated with anthracycline. The Carvedilol Effect in Preventing Chemotherapy Induced Cardiotoxicity trial (CECCY) evaluated carvedilol compared with placebo among patients with HER2-negative breast cancer treated with anthracycline-based chemotherapy ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier NCT01724450). The study failed to show that carvedilol was superior to placebo at preventing a reduction in LV ejection fraction; however, there was a significant reduction in troponin values and diastolic dysfunction, suggesting a potential benefit with carvedilol treatment [40]. The Lisinopril or Coreg CR in Reducing Side Effects in Women with Breast Cancer Receiving Trastuzumab trial compared carvedilol, lisinopril, and placebo among patients with HER2-positive breast cancer receiving trastuzumab ± anthracyclines ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier NCT01009918). The study failed to show a benefit of either drug in the trastuzumab only group; however, there was a benefit to receive either carvedilol or lisinopril in those treated with trastuzumab and anthracyclines [41]. It should be noted that both of these study populations were low risk in regards to preexisting cardiovascular risk factors and studies representative of the general population are needed. An ongoing study ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier NCT02717507) is assessing the effect of carvedilol on preventing chronic cardiac remodeling in a population of childhood cancer survivors who received higher doses of anthracyclines.

With the growing number of cancer survivors at risk of cardiac dysfunction, the need for long-term follow-up studies is clear. However, some challenges noted at the Workshop have included locating and recruiting survivors, limited participation of cancer patients and survivors in clinical research at the large cancer centers, and limited engagement of both oncology and cardiology groups at these sites. Existing clinical trials networks could provide the infrastructure to study

much needed interventions to halt or reverse cancer treatment-related cardiotoxicity, and, again, an understanding of the mechanisms of acute, chronic, and reversible cardiovascular injury is needed to best identify the optimal intervention for specific anti-cancer regimens.

Non-Pharmacologic Interventions

Strategies to prevent and manage cardiovascular dysfunction during and after cancer treatment are built on primary cardiovascular disease prevention efforts in the general population, which include lifestyle modifications such as diet and exercise to control cholesterol, blood pressure, blood sugar, and body mass index levels. Questions remain about the targeted mechanisms, timing, dosing, and overall impact of strategies to prevent cardiovascular dysfunction caused by anticancer therapy. Despite these questions, experts agree that strategies that focus on modifiable cardio-oncology risk factors, including systolic blood pressure and metabolic impairment, are promising and the interaction between risk factors and other comorbid conditions should be considered when developing interventions. For example, skeletal muscle is essential for cardiac muscle and metabolic health, and investigations of fatty acid intake to support cardioprotein remodeling and cardiac mitochondrial function and mitigate cardiac and skeletal muscle decline after cancer therapy are needed.

One prevention and management strategy that merits further study is the incorporation of physical activity to improve cardiovascular outcomes in cancer patients. Exercise interventions have the potential to prevent or decrease cardiac morbidity and improve cardiac health resulting in a better quality of life and longer survival times for cancer patients. However, exercise rehabilitation is not currently considered a standard part of cancer management [42], and the current evidence base is limited in cancer treatment-related cardiotoxicity as an outcome [43]. Evidence-based modifiable lifestyle interventions, such as physical activity, need to be further studied both during and after treatment due to the demonstrated benefit of exercise in other clinical populations (e.g., primary cardiovascular disease) suggesting a role for exercise in cancer patients.

However, there are challenges to incorporating exercise in the oncology setting. First, it is not feasible for all cancer patients and survivors to exercise due to other limitations (e.g., other comorbidities, physical limitations), and the current approach to applying exercise is one size fits all, further limiting its application. Other challenges have been the heterogeneity in physical activity metrics and the need for validated cardiovascular disease study endpoints to measure improvements in outcomes. Some strategies and opportunities that were identified at the Workshop included using software solutions to integrate data into electronic health records and the use of mHealth technology, such as mobile and wearable devices, in exercise interventions to support care delivery.

Another approach discussed was whether precision medicine can be applied to exercise whereby stratifying by dose, amount, or type of exercise could improve cardiovascular outcomes.

Developing Standards for Cancer Treatment-Related Cardiotoxicity

A major finding from the 2013 Workshop was the need for standard definition development of cardiac toxicities. The lexicon for reporting adverse events is the NCI's Common Terminology Criteria for Adverse Event Reporting (CTCAE). Recently updated and released November 2017, version 5.0 has 838 adverse event items, of which 41 are cardiac or vascular event items. Thus, the term cardiotoxicity includes multiple, different types of cardiac and vascular adverse events, and investigators need to specify the type of cardiovascular events under evaluation and outcomes of measure. One of the NCI's Clinical Trials Network Groups, Eastern Cooperative Oncology Group–American College of Radiology Imaging Network (ECOG-ACRIN), has initiated an effort to harmonize data collection in oncology trials, creating a cardiotoxicity working group that has worked to provide feedback to CTCAE regarding grading and cardiovascular classification systems since 2015. Even with the advances made in standardizing collection of adverse outcomes data, the process is still hampered by underestimation, inconsistent, and unreliable reporting of adverse events [44, 45], and this issue has also been highlighted by the American College of Cardiology Roundtable. Clearly, there is still a need to define appropriate data elements, eliminate redundancies, and standardize biomarker and imaging across studies to achieve consensus definitions of cardiotoxicity. Workshop participants stated that potential strategies to improve data collection of cardiac events in oncology clinical trials include using standardized case report forms, patient-reported outcomes [46], intensive training of staff, and leveraging electronic medical record systems.

Conclusion

This report highlights both the progress made in the field of cancer-related cardiotoxicity since the 2013 NCI and NHLBI Cardiotoxicity Workshop and the 20-plus recommendations (Table 1) for additional research opportunities identified through the 2018 Workshop. Some of the research priorities identified include improving animal models and use of human iPSCs to further elucidate cardiotoxicity, developing novel risk prediction tools to identify susceptible patients, supporting large cohort studies and long-term surveillance of adult cancer survivors, and standardizing data collection.

These research priorities, coupled with those from the 2013 Workshop [8], have the potential to contribute to progress in understanding the mechanisms of cancer treatment-related cardiotoxicity and translating findings to improve risk stratification, screening, prevention, and treatment.

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Compliance with Ethical Standards

Conflict of Interest Nonniekaye Shelburne, Naoko I. Simonds, Bishow Adhikari, Michael Alley, Patrice Desvigne-Nickens, Eileen Dimond, Kelly Filipowski, Lisa Gallicchio, and Lori Minasian declare that they have no conflict of interest.

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References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Siegel R, DeSantis C, Virgo K, et al. Current treatment and survivorship statistics. *CA Cancer J Clin*. 2012;62(4):220–41. <https://doi.org/10.1158/1055-9965>.
2. Mertens AC, Yasui Y, Neglia JP, Potter JD, Nesbit ME Jr, Ruccione K, et al. Late mortality experience in five-year survivors of childhood and adolescent cancer: the childhood Cancer survivor study. *J Clin Oncol*. 2001;19(13):3163–72. <https://doi.org/10.1200/JCO.2001.19.13.3163>.
3. Armstrong GT, Chen Y, Yasui Y, Leisenring W, Gibson TM, Mertens AC, et al. Reduction in late mortality among 5-year survivors of childhood cancer. *N Engl J Med*. 2016;374:833–42. <https://doi.org/10.1056/NEJMoa1510795>.
4. Abdel-Qadir H, Austin PC, Lee DS, Amir E, Tu JV, Thavendiranathan P, et al. A population-based study of cardiovascular mortality following early-stage breast cancer. *JAMA Cardiol*. 2017;2:88–93. <https://doi.org/10.1001/jamacardio.2016.3841>.
5. Meacham LR, Chow EJ, Ness KK, Kamdar KY, Chen Y, Yasui Y, et al. Cardiovascular risk factors in adult survivors of pediatric cancer—a report from the childhood cancer survivor study. *Cancer Epidemiol Biomark Prev*. 2010;19(1):170–81. <https://doi.org/10.1158/1055-9965>.
6. Armenian SH, Armstrong GT, Aune G, et al. Cardiovascular Disease in Survivors of Childhood Cancer: Insights into Epidemiology, Pathophysiology, and Prevention. *JCO*. 2018;36(21):2135–44. <https://doi.org/10.1200/JCO.2017.76.3920>.
7. Moslehi JJ. Cardiovascular toxic effects of targeted cancer therapies. *N Engl J Med*. 375(15):1457–67. <https://doi.org/10.1056/NEJMra1100265>.
8. Shelburne N, Adhikari B, Brell J, Davis M, Desvigne-Nickens P, Freedman A, et al. Cancer treatment-related cardiotoxicity: Current state of knowledge and future research priorities. *JNCI*. 2014;106(9). <https://doi.org/10.1093/jnci/dju232>.
9. NIH, 2015a. <https://grants.nih.gov/grants/guide/pa-files/PA-18-003.html>. Accessed 03 Dec 2018.
10. NIH, 2015b. <https://grants.nih.gov/grants/guide/pa-files/PA-18-013.html>. Accessed 03 Dec 2018.
11. NCI, 2018a. <https://epi.grants.cancer.gov/events/cardiotoxicity/improving-outcomes.html>. Accessed 03 Dec 2018.
12. Armenian SH, Lacchetti C, Barac A, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2017;35(8):893–911. <https://doi.org/10.1200/JCO.2016.70.5400>. **This review provides evidence based clinical practice guidelines for cardiotoxicity prevention and management in adult patients with cancer. Guidelines were developed by an expert panel and highlights existing evidence and knowledge gaps.**
13. 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(3):e123–36. [https://doi.org/10.1016/S1470-2045\(14\)70409-7](https://doi.org/10.1016/S1470-2045(14)70409-7). **This review provides evidence based clinical practice guidelines for identifying pediatric cancer survivors at risk for treatment related cardiomyopathy, including surveillance and management modalities. Guidelines were developed by an international expert panel and highlights existing evidence and knowledge gaps.**
14. DuBois VFS, Casarotto E, Danhof M, Della PO. Pharmacokinetic-pharmacodynamic modelling of drug-induced QTc interval prolongation in man: prediction from in vitro human ether-à-go-go-related gene binding and functional inhibition assays and conscious dog studies. *Br J Pharmacol*. 2016;173:2819–32.
15. Burridge PW, Li YF, Matsa E, Wu H, et al. Human induced pluripotent stem cell-derived cardiomyocytes recapitulate the predilection of breast cancer patients to doxorubicin-induced cardiotoxicity. *Nat Med*. 2016;22(5):547–56. <https://doi.org/10.1038/nm.4087>.
16. Biermann M, Kamp TJ. Cardiotoxicity in a dish: new insights for personalized therapy. *Nat Med*. 2016;22:459–60. <https://doi.org/10.1038/nm.4095>.
17. Sun N, Yazawa M, Liu J, Han L, et al. Patient-specific induced pluripotent stem cells as a model for familial dilated cardiomyopathy. *Sci Transl Med*. 2012;4(130):130ra47. <https://doi.org/10.1126/scitranslmed.3003552>.
18. Sharma A, Burridge PW, WL MK, et al. *Sci Transl Med*. 2017;9(377). <https://doi.org/10.1126/scitranslmed.aaf2584>. **This study utilized induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) from patients treated with tyrosine kinase inhibitors (TKI) to generate a cardiac safety index based on cardiomyocyte viability, contractility, electrophysiology, calcium handling and signaling. The cardiac safety index and hiPSC-CMs can play an important role in assessing novel TKI cardiotoxicity during toxicology testing.**
19. Wang F, Iskra B, Kleinerman E, et al. Aerobic exercise during early murine doxorubicin exposure mitigates cardiac toxicity. *J Pediatr Hematol Oncol*. 2018;40:208–15. <https://doi.org/10.1097/MPH.0000000000001112>.
20. Lipshultz SE, Adams MJ, Colan SD, Constine LS, Herman EH, Hsu DT, et al. Long-term cardiovascular toxicity in children, adolescents, and young adults who receive cancer therapy: pathophysiology, course, monitoring, management, prevention, and research directions—a scientific statement from the American Heart

- Association. *Circulation*. 2013;128:1927–95. <https://doi.org/10.1161/CIR.0b013e3182a88099>.
21. Mertens AC, Liu Q, Neglia JP, Wasilewski K, Leisenring W, Armstrong GT, et al. Cause-specific late mortality among 5-year survivors of childhood cancer: the childhood Cancer survivor study. *J Natl Cancer Inst*. 2008;100:1368–79. <https://doi.org/10.1093/jci/djn310>.
 22. Reulen RC, Winter DL, Frobisher C, et al. Long-term cause-specific mortality among survivors of childhood cancer. *JAMA*. 2010;304:172–9. <https://doi.org/10.1001/jama.2010.923>.
 23. Ledwidge M, Gallagher J, Conlon C, Tallon E, O'Connell E, Dawkins I, et al. Natriuretic peptide-based screening and collaborative Care for Heart Failure: the STOP-HF randomized trial. *JAMA*. 2013;310:66–74. <https://doi.org/10.1001/jama.2013.7588>.
 24. Murtagh G, Lyons T, O'Connell E, Ballot J, Geraghty L, Fennelly D, et al. Late cardiac effects of chemotherapy in breast cancer survivors treated with adjuvant doxorubicin: 10-year follow-up. *Breast Cancer Res Treat*. 2016;156:501–6. <https://doi.org/10.1007/s10549-016-3781-4>.
 25. Amingkegeng F, Ross CJD, Rassekh SR, Hwang S, et al. Recommendations for genetic testing to reduce the incidence of anthracycline-induced cardiotoxicity. *Br J Clin Pharmacol*. 2016;82(3):683–95. <https://doi.org/10.1111/bcp.13008>.
 26. Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, et al. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med*. 2016;375:1749–55. <https://doi.org/10.1056/NEJMoa1609214>.
 27. Moslehi JJ, Salem J, Sosman JA, et al. Increased reporting of fatal immune checkpoint inhibitor-associated myocarditis. *Lancet*. 2018;391:933. [https://doi.org/10.1016/S0140-6736\(18\)30533-6](https://doi.org/10.1016/S0140-6736(18)30533-6). **This is the first analysis to describe the clinical features of myocarditis in patients with cancer receiving immune checkpoint inhibitors. The analysis of the World Health Organization's database of individual case safety reports identified early onset and increasing incidence of myocarditis, immune related adverse events and fatalities.**
 28. Khouri MG, Ky B, Dunn G, et al. Echocardiography Core Laboratory Reproducibility of Cardiac Safety Assessments in Cardio-Oncology. *J Am Soc Echocardiogr*. 2017;31(3):361–71. <https://doi.org/10.1016/j.echo.2017.11.018>. **This is the first study to evaluate reproducibility between echocardiography core labs when conducting multi-site cardio-oncology studies. While high reproducibility within core labs was demonstrated, notable differences between labs existed. Improved echocardiogram reproducibility was seen with the institution of standard operating procedures and the application of measurement conventions across core labs, similar to processes when comparing blood assays between laboratories.**
 29. FDA, 2018. <https://www.fda.gov/downloads/drugs/guidances/ucm268555.pdf>. Accessed 27 Dec 2018.
 30. University of Pennsylvania, 2018. https://rt19.pmacs.upenn.edu/crcu_html/radcomp/website/index.html. Accessed 27 Dec 2018.
 31. van Dalen EC, Caron HN, Dickenson HO, Kremer LCM. Cardioprotective interventions for cancer patients receiving anthracyclines. *Cochrane Syst Rev*. 2011. <https://doi.org/10.1002/14651858.CD003917.pub4>.
 32. Schuchter LM, Hensley ML, Meropol NJ, Winer EP. Update of recommendations for the use of chemotherapy and radiotherapy protectants: clinical practice guidelines of the American Society for Clinical Oncology. *J Clin Oncol*. 2002;20:2895–903. <https://doi.org/10.1200/JCO.2002.04.178>.
 33. Menna P, Salvatorelli E. Primary prevention strategies for anthracycline cardiotoxicity: a brief overview. *Chemotherapy*. 2017;62:159–68. <https://doi.org/10.1159/000464276>.
 34. Kheieri B, Abdalla A, Osman M, et al. Meta-analysis of carvedilol for the prevention of anthracycline-induced cardiotoxicity. *Am J Cardiol*. 2018;S0002-9149(18):31738–7. <https://doi.org/10.1016/j.amjcard.2018.08.039>.
 35. Seicean S, Seicean A, Plana JC, Budd GT, Marwick TH. Effect of statin therapy on the risk for incident heart failure in patients with breast cancer receiving anthracycline chemotherapy: an observational clinical cohort study. *J Am Coll Cardiol*. 2012;60:2384–90. <https://doi.org/10.1016/j.jacc.2012.07.067>.
 36. [ClinicalTrials.gov](https://clinicaltrials.gov) [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT01988571. Preventing Anthracycline Cardiovascular Toxicity With Statins 2018 Aug 31 (PREVENT); [cited 2018 Nov 12]; Available from <https://clinicaltrials.gov/ct2/show/NCT01988571>. Accessed 03 Dec 2018.
 37. Pituskin E, Mackey JR, Koshman S, Jassal D, Pitz M, Haykowsky MJ, et al. Multidisciplinary approach to novel therapies in cardio-oncology research (MANTICORE 101-breast): a randomized trial for the prevention of trastuzumab-associated cardiotoxicity. *J Clin Oncol*. 2017;35(8):870–7. <https://doi.org/10.1200/JCO.2016.68.7830>.
 38. Lipshultz SE, Scully RE, Lipsitz SR, et al. Assessment of dexrazoxane as a cardioprotectant in doxorubicin-treated children with high-risk acute lymphoblastic leukemia: long-term follow-up of a prospective, randomized, multicentre trial. *Lancet Oncol*. 2010;11(10):950–61. [https://doi.org/10.1016/S1470-2045\(10\)70204-7](https://doi.org/10.1016/S1470-2045(10)70204-7).
 39. Asselin BL, Devidas M, Chen L, Franco VI, Pullen J, Borowitz MJ, et al. Cardioprotection and safety of dexrazoxane in patients treated for newly diagnosed T-cell acute lymphoblastic leukemia or advanced-stage lymphoblastic non-Hodgkin lymphoma: a report of the Children's oncology group randomized trial pediatric oncology group 9404. *J Clin Oncol*. 2016;34(8):854–62. <https://doi.org/10.1200/JCO.2015.60.8851>.
 40. Avila MS, Ayub-Ferreira SM, de Barros Wanderley MR Jr, et al. Carvedilol for prevention of chemotherapy-related cardiotoxicity: the CECCY trial. *J Am Coll Cardiol*. 2018;71(20):2281–90. <https://doi.org/10.1016/j.jacc.2018.02.049>.
 41. Guglin ME. Lisinopril or carvedilol for prevention of trastuzumab induced cardiotoxicity- lisinopril or carvedilol for cardiotoxicity. 2018. Presented at the American College of Cardiology Annual Scientific Session, Orlando, FL, March 11, 2018.
 42. Lakoski SG, Eves ND, Douglas PS, Jones LW. Exercise rehabilitation in patients with cancer. *Nat Rev Clin Oncol*. 2012;9:288–96. <https://doi.org/10.1038/nrclinonc.2012.27>.
 43. Scott JM, Nilesen TS, Gupta D, Jones LW. Exercise therapy and cardiovascular toxicity in cancer. *Circulation*. 2018;137:1176–91. <https://doi.org/10.1161/CIRCULATIONAHA.117.024671>.
 44. Miller TP, Li Y, Kavcic M, et al. Accuracy of adverse event ascertainment in clinical trials for pediatric acute myeloid leukemia. Alexandria: ASCO; 2015.
 45. Sivendran S, Latif A, McBride RS, et al. Adverse events reporting in cancer clinical trial publication. *J Clin Oncol*. 2014;32(2):83–39. <https://doi.org/10.1200/JCO.2013.52.2219>.
 46. NCI, 2018b. <https://healthcaredelivery.cancer.gov/pro-ctcae>.