

COMMENTARY |

Cancer Treatment–Related Cardiotoxicity: Current State of Knowledge and Future Research Priorities

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Cardiotoxicity resulting from direct myocyte damage has been a known complication of cancer treatment for decades. More recently, the emergence of hypertension as a clinically significant side effect of several new agents has been recognized as adversely affecting cancer treatment outcomes. With cancer patients living longer, in part because of treatment advances, these adverse events have become increasingly important to address. However, little is known about the cardiovascular pathogenic mechanisms associated with cancer treatment and even less about how to optimally prevent and manage short- and long-term cardiovascular complications, leading to improved patient safety and clinical outcomes. To identify research priorities, allocate resources, and establish infrastructure required to address cardiotoxicity associated with cancer treatment, the National Cancer Institute (NCI) and National Heart, Lung and Blood Institute (NHLBI) sponsored a two-day workshop, “Cancer treatment–related cardiotoxicity: Understanding the current state of knowledge and future research priorities,” in March 2013 in Bethesda, MD. Participants included leading oncology and cardiology researchers and health professionals, patient advocates and industry representatives, with expertise ranging from basic to clinical science. Attendees were charged with identifying research opportunities to advance the understanding of cancer treatment–related cardiotoxicity across basic and clinical science. This commentary highlights the key discussion points and overarching recommendations from that workshop.

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The primary goal of cancer treatment is to eradicate and prevent recurrence of cancer, thereby prolonging life. Improvements in the efficacy of treatment are demonstrated by the approximately 13.7 million cancer survivors alive today in the United States (1). However, cancer survival gains have revealed unintended consequences of therapy, such as increased incidence of cardiovascular injury. Studies have shown that cancer treatment–related cardiotoxicity is the third leading cause of treatment-associated mortality in survivors of pediatric and adolescent cancers, with recurrence and second malignancies being the two leading causes (2). The incidence of treatment-induced heart damage in pediatric survivors of cancer increases over time, even after 30 years post-therapy (3). In adult patients, cardiotoxicity is agent-dependent, and incidence can be as high as 50%, depending on the type of cardiac condition (4). Five-to-ten year male survivors of adult cancer self-report heart problems to be the most common post-treatment issue, while in women survivors it is the second most reported problem following arthritis or osteoporosis (5). Although the exact proportion of cancer survivors who develop treatment-related cardiotoxicity is unknown, the emergence of cardio-oncology subspecialty clinics suggests the prevalence and impact are clinically significant. The reasons behind the increase may be due to the increasing number of cancer survivors, use of targeted therapies, multimodality and multidrug regimens, and longer courses of cancer therapy.

Cancer patients who cannot receive optimal therapy because of concern about potential cardiotoxicity may experience compromised treatment outcomes. Thus, the overall management strategies for cardiotoxicity during and following cancer treatment are critical aspects of cancer care, potentially influencing overall prognosis, survival, and quality of life. Research is needed to better understand the acute and long-term effects of all cancer treatment modalities—including cytotoxic chemotherapy, targeted therapy, and radiation—on cardiovascular function and ways to mitigate these effects (6–8). Clinicians need information to screen high-risk patients and prevent cancer treatment–related cardiotoxicity, to balance effective cancer treatment and cardiac risk assessment in treatment decision making, and to manage long-term cardiac risks and effects of treatment in cancer survivors. A fiscal year 2012 National Institutes of Health (NIH) cardiotoxicity portfolio analysis (Supplementary Materials, available online) indicates that while NIH research support is continuing, it may be insufficient to address the range and depth of the scientific questions in this area.

The National Cancer Institute (NCI) and the National Heart, Lung, and Blood Institute (NHLBI) convened a workshop in March 2013 entitled “Cancer treatment–related cardiotoxicity: Understanding the current state of knowledge and developing

future research priorities” in Bethesda, MD (9). The goal of this workshop was to identify research opportunities and determine scientific priorities for issues related to cancer treatment–related cardiotoxicity. Although cardiotoxicity encompasses a wide trajectory of disorders (Box 1), this workshop focused on hypertension and heart failure and included all cancer treatment modalities. Over 60 participants with expertise in oncology, cardiology, epidemiology, patient advocacy, research and clinical care participated in person; in addition, over 200 online participants viewed the real-time and archived meeting videocast (10,11). This report provides an overview of workshop recommendations that highlight gaps in knowledge about cancer treatment–related cardiotoxicity, research questions that will address these gaps, and resources and collaborations required to move this field forward. Box 2 lists recommendations for each of the workshop findings discussed herein.

Workshop Findings

Developing Standards for Cancer Treatment–Related Cardiotoxicity

One finding the workshop participants repeatedly noted is the nonuniform collection of cardiovascular outcomes in oncology research and clinical care. A lack of nomenclature, assessment of baseline status and toxicity grading, and existence of disparities and/or omission of cardiovascular side effects present challenges in the medical literature for evaluating cancer treatment–related cardiotoxicity. The American Heart Association’s

Box 1. Common terminology criteria for adverse events v4.0 (CTCAE) cardiotoxicity events (9).

Cardiac disorders

Acute coronary syndrome
Aortic valve disease
Asystole
Atrial fibrillation / flutter
Atrioventricular block
Cardiac Arrest / sudden cardiac death
Chest pain and palpitations
Conduction disorder
Constrictive pericarditis
Heart failure
Hypertension
Left ventricular dysfunction
Mitral valve disease
Myocardial infarction
Myocarditis
Paroxysmal atrial tachycardia
Pericardial effusion
Pericardial tamponade
Pericarditis
Restrictive cardiomyopathy
Right ventricular dysfunction
Sick sinus syndrome
Sinus bradycardia and tachycardia
Supraventricular tachycardia
Thromboembolic events
Tricuspid valve disease
Ventricular arrhythmia
Ventricular fibrillation
Ventricular tachycardia
Vascular disorders

Box 2. Workshop recommendations.

Developing standards

1. Consider an optimal classification system to characterize and grade cardiovascular safety parameters.
2. Develop standard definitions, common data elements, and valid measures of baseline cardiac status for cancer treatment–related cardiotoxicity in clinical trials and clinical practice to enable comparison of data elements over time.
3. Develop a national database/repository consisting of the common data elements to conduct epidemiologic studies for determination of cardiotoxicity incidence, severity, natural history, and phenotypic characteristics

Mechanisms

4. Utilize cutting-edge technology and biomarker approaches to identify new agents of potential concern and elucidate mechanisms of cardiac toxicity.
5. Utilize metabolomics to assess mitochondrial activity, myocardial energy and efficiency, signaling pathways and response to injury to enhance understanding of cardiotoxicity.
6. Examine the utility of –omics approaches in identifying cardiotoxicity of cancer therapies.
7. Engage systems biology approaches to better understand how anticancer drugs might interact with various biologic pathways and targets and potentially worsen cardiac damage.
8. Identify on- and off-target effects of drugs at the gene, pathway, organelle, cellular, organ, and organismal levels to inform cardiac toxicity screening and prediction approaches.
9. Explore the pathogenesis of cancer treatment–related cardiotoxicity using ex vivo models.
10. Identify the role of cardiac fibroblasts, endothelial cells, and the vascular bed in cancer treatment–related cardiotoxicity.
11. Investigate the role of cardiac progenitor and stem cells in cardiac repair and remodeling during and after cancer treatment.
12. Elucidate the ways that dysregulation of fundamental pathways (eg, inflammation, angiogenesis) in cancer patients interacts with cardiac conditions.

Preclinical and animal studies

13. Enhance preclinical toxicology assessments for new cancer agents with potential cardiac toxicity.
14. Support cellular and molecular studies by enhancing access to human cardiac system tissues.
15. Modify treatment-dosing schedules in animal studies and look at quantitative damage to the cardiovascular and other systems to potentially minimize toxicity clinically.
16. Use human data to validate existing vertebrate models of human age-related disease and obesity, for use in mechanistic studies of anticancer agents.
17. Develop preclinical models and validation criteria that can be used to identify risk of cardiac toxicity, investigate mechanisms of cardiac toxicity of novel compounds, and evaluate potential of cardioprotective therapies.
18. Utilize reverse translation of known treatment-induced cardiotoxic agents and primary cardiac disease pathways in the approach to cancer drug development that avoid or minimize cardiotoxicity.

Early phase therapeutic studies

19. Develop a phase I clinical trial database of in-depth cardiac information early in drug development.
20. Standardize oncology clinical trial entry eligibility for preexisting cardiovascular disease and comorbidities.

Minimally invasive methods for diagnosing and monitoring

21. Develop cardiotoxicity risk stratification tools utilizing promising clinical, genomic, and imaging data.
22. Compare promising cardiotoxicity screening and detection modalities via large retrospective and prospective cancer cohorts that include genomic, biomarker, and imaging data.
23. Identify and confirm genetic markers linked to cardiac myocyte and endothelial cell damage and cardiomyopathy risk during and after cancer treatments through cardiomyopathy gene panels, whole genome or exome sequencing, candidate gene studies, and single nucleotide polymorphism arrays.
24. Conduct biomarker studies with the goal of discovering and validating mechanistic markers that can be utilized as robust screening tools for early identification of cardiotoxicity with greater sensitivity and specificity.
25. Support replication studies to validate cardiac biomarkers in the cancer clinical trial population by enhancing access to biorepositories.
26. Examine the role of kinetic biomarkers, microRNA, and etcin in the prediction and detection of cardiotoxicity.
27. Develop minimally invasive MRI methods (eg, late-gadolinium enhancement, T1 and T2 mapping, and MR spectroscopy) to assess and monitor early in vivo changes in myocardial tissue, including apoptosis, fibrosis, oxidative stress and other metabolic perturbations because of cancer treatments.
28. Identify promising imaging modalities and test their effectiveness to predict or stratify cancer therapeutics-induced cardiac toxicity risk in humans.
29. Conduct comparative effectiveness studies for noninvasive imaging techniques that may detect early onset of cancer treatment-related cardiotoxicity.

Prevention

30. Identify the most effective pharmacologic cardio-protective interventions that do not interfere with anticancer treatment efficacy and that mitigate or reverse cardiac damage, specifically pertaining to dose, type, and duration of medication.
31. Examine and measure the impact of nonpharmacologic cardio-protective interventions, including diet, physical activity, and comorbidity management, in preventing cardiotoxicity and determining effects on cancer recurrence, progression, and survival.
32. Identify the optimal strategy for cardio-protection approaches for hypertension and heart muscle damage during cancer treatment and patient subgroups that receive the greatest benefit from prophylactic cardio-protection.

Treatment

33. Develop treatment guidelines for determining when to utilize pharmacologic interventions for cancer treatment-related cardiotoxicity.
34. Determine the optimal medications most effective for the treatment of cardiotoxicity and treatment targets.
35. Examine and measure the impact of nonpharmacologic protective interventions, including diet and physical activity, in

treating cardiotoxicity and the effect on cancer recurrence, progression, and survival.

36. Develop cancer treatment-related, cardiotoxicity evidence-based practice guidelines for risk prediction, screening, prevention, diagnostics, treatment, and follow-up utilizing a trans-disciplinary working group.

Survivorship

37. Conduct epidemiologic studies to determine incidence, severity, and natural history of various cardiotoxicities and identify the specific clinical and epidemiologic risk profile that is associated with susceptibility to the development of cardiotoxicity.
38. Identify the major determinants of cardiac reserve via large cohort studies with direct assessment and longitudinal follow-up, including pediatric and adult cancer survivors.
39. Identify the impact of early detection and treatment of cardiotoxicity on cardiac and cancer outcomes in the cancer survivor.
40. Investigate the long-term effects of newer cancer therapies and combination therapy in cancer survivors.
41. Develop care coordination and communication methods, implementation standards and evaluation measures among multidisciplinary teams for cardiotoxicity surveillance and potential interventions for prevention and/or treatment in cancer survivors.

(AHA) statements and guidelines (12) on cardiac events may not be entirely pertinent for patients receiving cancer therapies. The current version of Common Terminology Criteria for Adverse Events v4.0 (CTCAE) developed by NCI classifies the undesired effects of the novel agent(s) with criteria for grading the severity of each event (13), but, by design, it does not utilize standards for assessing the event severity. Nonetheless, cardiotoxicity criteria (CTCAE v4.0 or AHA) are not consistently utilized and assessment measures for toxicities are often developed for individual studies. These challenges clearly preclude concise and consistent definitions to optimally reconcile and compare patient outcomes and cardiovascular side effects across studies and in clinical practice. Consensus nomenclature for definitions of cardiac events and utilization of common data elements in cancer clinical trials could ensure that key information is uniformly collected during each study.

To address this barrier, workshop participants recommended the need for standard definition development, including but not limited to: a mechanism-based classification of hypertension and heart failure events, the creation of common data elements and a national database. Having a data repository with defined common elements could enhance the accuracy of the diagnosis of cardiac toxicity. Furthermore, such a population resource could provide researchers a way to investigate the natural history of cardiotoxicity. It could also facilitate association studies of phenotype characteristics, genotype and pharmacogenomic information, and cardiac outcomes that could better predict at-risk patients and provide personalized cardiotoxicity care.

Workshop participants raised the challenges of creating such an infrastructure. Not only are there technical difficulties—standardization of data, incomplete or missing data—but some unique data elements may potentially be required for some anticancer

therapies. These problems are compounded by the fact that not all clinics and hospitals have access to the same equipment or laboratories for identifying cardiac conditions. Despite these scientific and logistical issues, the science of cancer treatment-related cardiotoxicity will be advanced by a consensus classification system.

Research Opportunities: Basic Science

Mechanisms of Cancer Treatment-Related Cardiotoxicity

Understanding fundamental mechanisms underlying cancer treatment-related cardiotoxicity is essential to the development of new methods to monitor, treat, and prevent these toxicities. For example, mechanistic studies contributed to the approval of dexrazoxane by the Food and Drug Administration (FDA) as a pretreatment for prevention of cardiac injury in adults receiving anthracycline therapy (14,15). In addition, recent studies suggest that topoisomerase II β inhibition and engineered neuregulin ligands may offer novel ways to protect the heart from anthracycline injury without reducing its therapeutic efficacy (4,16–18). Additional mechanistic studies may lead to novel cardioprotective strategies, not only for anthracyclines but for other targeted agents as well.

Compared with research that has revealed mechanisms of anthracycline-induced cardiotoxicity, very little is known about the molecular pathways that underlie cardiotoxicities associated with emerging cancer therapeutics. This is particularly true for the small molecule tyrosine kinase inhibitors developed for various forms of cancer treatments, which at present include 19 agents, with many more in development (18). The majority of these agents have off-tumor target cardiovascular effects (19) and there is poor understanding of the role the various kinases and defined drug targets play in the heart and peripheral vasculature.

As our mechanistic understanding of cardiotoxicity progresses, it is becoming increasingly apparent that the key signaling pathways involve less understood and vulnerable cellular signaling pathways that affect the cardiovascular mitochondria, cardiomyocytes, endothelial cells, fibroblasts, vascular pericytes, and cells involved in inflammation, angiogenesis, cardiac repair and regeneration. Future studies are needed to not only characterize how these signaling pathways are affected by the therapeutic agents, but also to develop strategies to minimize their injury and reduce the associated cardiotoxicity. This approach requires defining cardiovascular risk phenotypes so injury can be accurately connected to translational findings.

Preclinical and Animal Studies in Cancer Treatment-Related Cardiotoxicity

The application of more suitable disease models and more effective methods for toxicity screening will serve to advance our understanding of cardiotoxicity. Animal models have been successfully employed to predict potential problems in some cases (18), but more highly predictive models are needed. For instance, in rodent models, adding an additional stressor, such as hypertension or thoracic aortic constriction, may be needed to inform risk for cancer patients with these comorbidities. Large animal models, although believed to be superior in some cases, could also be improved by more advanced monitoring and application of clinical biomarkers.

Given the urgency to identify risk of cardiotoxicity earlier, strategies that can identify problematic agents and elucidate mechanisms of toxicity are needed. In the preclinical drug discovery setting, however, animal models are typically not as amenable to compound screening intended for comparing several compounds. Screening alternatives such as zebrafish, human induced pluripotent (hiPS)-derived cardiomyocytes, and human cardiac microtissue arrays to test for toxicity were suggested as opportunities (20–22). All of these approaches may be adaptable to high-throughput screening. It is also possible to derive information on metabolism using metabolomic approaches in cell culture and zebrafish models, with possibilities of identifying novel biomarkers of injury that could then be tested and validated in patients.

Research Opportunities: Clinical Care

Early Phase Therapeutic Studies in Cancer Treatment-Related Cardiotoxicity

In the absence of adverse preclinical toxicology and pharmacologic observations, novel anticancer agents are first clinically evaluated in cancer patients. Not uncommonly, however, when agents are administered for the first time in humans, unanticipated toxicities emerge. It is important to identify potential cardiotoxicity using validated measures early in drug development without premorbid cardiovascular risks compounding the clinical evaluation for cardiac safety and to assure patient safety. While this is the ideal scenario, this approach is not entirely pragmatic, as the majority of patients ineligible for Phase I trials are often older with multiple pretrial comorbid cardiovascular risks or overt atherosclerotic cardiovascular disease. Workshop participants suggested that it may be possible to include cancer patients with premorbid cardiovascular disease in early phase trials, similar to the approach taken by the NCI Organ Dysfunction Working Group, which evaluates patients with hepatic and renal dysfunction (23).

Once an agent's cardiotoxic risk has been established, other obstacles to early phase testing remain. Only a minority of Phase I agents advance to phase II testing, usually due to intolerable toxicity. While cardiac assessment of subsequently abandoned drugs has scientific merit, resources are not available to sort out the challenging cardiovascular safety profiles for a given agent. Even if the requirements for cardiovascular system-focused preclinical and toxicology testing are satisfied, drug sponsors may not want to engage in further toxicity assessments, especially if the results invite restrictions to the drug label at time of FDA approval. Given the high incidence of baseline cardiovascular disease and the shared risk factors with drug development, cancer treatment-related cardiotoxicity should be well-described and managed for patient safety (24,25).

Minimally-Invasive Methods for Diagnosis and Monitoring

Biopsy-based approaches have been used to diagnose and monitor (anthracycline-induced) cardiotoxicity, but more noninvasive or minimally invasive approaches to diagnosing and monitoring cancer treatment-related cardiotoxicity are needed. The following section outlines areas of research opportunities identified by workshop attendees, categorized into biomarkers and imaging.

Biomarkers. Biomarkers may represent one of the most cost-effective and minimally invasive means for diagnosing and monitoring cardiac injury in an oncology setting. Workshop attendees discussed the similarities of cancer treatment-induced cardiac damage to the traditional process of cardiac damage because of aging and environmental factors, with an exception around timing, as the injury process is accelerated and compressed after cancer treatment. As a result, studies are needed to investigate the potential of known cardiac biomarkers to detect asymptomatic cancer treatment-related cardiac damage and to predict cumulative effects of initial injury or loss of cardiac myocytes. High sensitivity troponin is, at present, considered the biomarker of choice for the detection of cardiac injury (26–28). Although the biochemical characteristics and utility of troponins for the diagnosis of cardiac injury and acute myocardial infarction have been extensively reviewed (29), it is clear that application of troponins in a cardio-oncology setting will require understanding the basic science of these proteins, validation against true clinical phenotypes, and if and how they are influenced by other treatments. There is also considerable debate about whether biomarkers such as troponins or creatinine kinase MB fraction are released with reversible as well as irreversible cardiac injury, warranting further study.

Additional research to investigate whether these biomarkers may fulfill the role as an indicator of acute risk as well as serving as a risk factor in prediction of the long-term adverse effects of myocardial injury and hypertension is warranted. Studies of cardiac remodeling in response to certain agents appear promising. Further investigation of biomarkers (eg, galactin-3, N-terminal brain natriuretic peptide, titin, neuregulin-1, hypoxia-inducible factor-1, Topoisomerase II beta) that measure changes in pathways that drive cardiac and cancer disease processes and therapeutic response is needed (27,30–32). Of paramount importance, investigators will need to consider the meaningfulness of these assay results in cancer treatment-related cardiotoxicity and how clinicians should respond to biomarker changes. The ultimate goal would be to identify patients at an asymptomatic stage and intervene. Investigators may need to identify multiple markers to more accurately measure risk and make decisions about early intervention.

There is a need to improve available biomarker data, including access to biospecimens. Workshop participants suggested using existing cohort studies, where possible, and encouraging collaborations between cooperative oncology groups. For example, the reorganized NCI's Clinical Trials Network could be leveraged where blood and tissue from prospectively studied cancer patients are collected and stored. Although cost, consent for older studies, and patient management issues might be a barrier to developing such a resource, it would allow pretreatment genetic assessment as well as longitudinal follow-up.

Imaging. Minimally invasive imaging methods are indispensable tools to monitor cardiac function and cardiac injury. Unfortunately, current clinical cardiac imaging modalities lack the resolution (or sensitivity) and specificity to assess early, subclinical changes in myocardial tissue (33). Imaging methods that allow tissue analysis in vivo will be important because there is strong experimental evidence supporting cell- and tissue-level changes preceding functional alterations at the organ level (33–35). Early and non-invasive

detection of cancer therapy-induced cardiac tissue injury would clearly not only help optimize cancer treatment but could also provide insights leading to novel cardio-protective interventions.

Current approaches to assess cardiac function primarily utilize ultrasound-based techniques, such as transthoracic echocardiography and 2D echocardiography. Compared with other available methods, these techniques are inexpensive, easy to use, noninvasive and highly portable and therefore preferable. However, most commonly used means to assess cardiac function by echocardiography suffers from poor reproducibility (36). Scintigraphic methods, such as multigated acquisition scan or gated blood pool scan, are much more reproducible at measuring left ventricular ejection fraction but the radiation dose with repeated examinations dampens enthusiasm for using this approach long term (36). Newer ultrasound approaches, such as 3D echocardiography, strain rate imaging, and tissue Doppler imaging, continue to improve, and further innovation is needed to make these methods more reproducible for serial monitoring in the assessment of toxicity progression over time.

Workshop attendees stated that cardiac magnetic resonance imaging (MRI) methods should be further developed and tested for cardiac toxicity assessment. For example, recent advances in late-gadolinium enhancement and T1 and T2 mapping approaches, together with the development of molecularly targeted imaging probes, offer unique opportunities to monitor tissue fibrosis and apoptosis in vivo (37). Continuing advances in multimodal imaging that combine complementary imaging modalities may also offer unique advantages and need to be explored. In summary, while substantial advances have been made in noninvasive imaging, many questions remain as to the utility of these strategies, specifically in cancer patients with possible cardiotoxicity.

Prevention and Treatment of Cancer Treatment-Related Cardiotoxicity

The aging of cancer patients, application of combination therapy, and emerging novel agents offer both challenges and opportunities. Older patients are more likely to have comorbidities including pre-existing cardiovascular disease, which in turn may exacerbate cardiotoxicity, complicating cancer therapy. The workshop attendees noted the need to examine both the prevention and treatment of cardiotoxicity, noting that as cancer therapies continue to improve, the prevalence of cancer treatment-related cardiovascular dysfunction will likely increase.

The need for clinical assessment of cardiovascular risk prior to initiation of cancer treatment is evident and would likely have implications for treatment planning, including weighing cancer and cardiac risk/benefit, which may change in early vs late-stage cancer. Standard surveillance assessments to determine pretreatment risk, as well as serial measures of cardiovascular integrity during and in follow-up of cancer therapy are needed. These assessments will inform patient management and are needed to better understand individual risk (eg, age, comorbidities, genetic susceptibility), inform drug and radiation dose, predict response to cancer therapy, and develop effective prevention of cardiotoxicity. Evidence-based nonpharmacologic cardio-protective interventions, including diet, physical activity, and comorbidity management, need to be studied within various at-risk cancer populations in order to determine efficacy. Existing infrastructure such as the NHLBI funded

Cardiovascular Research Network and NCI funded Clinical Trials Network are potential resources to establish, implement, and evaluate standard measures in clinical trials, identify imaging and biomarkers sensitive to subclinical changes, and identify reversible and long-term adverse cardiovascular outcomes.

Further identification of clinical, genetic, biomarker, and imaging cardiac risk factors might allow for better stratification of patients at low and high risk for cancer treatment-induced cardiotoxicity and lead to improved treatment and monitoring options and increased safety of cancer therapy without compromising survival. Several investigators have attempted to develop risk prediction models that include a number of these risk factors, although they exclude radiation therapy as a risk factor and their use in clinical care has been limited (26–28). Large retrospective and prospective cancer cohorts that include detailed genomic, biomarker, and imaging data linked to cardiovascular outcomes will ultimately be required to allow the discovery of factors that accurately predict the development of cardiotoxicity for specific anticancer agents and also permit the direct comparison of different risk factor algorithms.

Clinical practice guidelines for controlling cardiovascular complications of cancer treatment across disciplines are essential. Systematic surveillance data and standard metrics from clinical trials and patient management studies are lacking and are needed to improve evidence. Further, the current large number of recommendations for managing cardiovascular and oncology diseases are cumbersome, making consistent application a challenge, especially given the limited recommendation on the intersection of the two

diseases. (38). As noted earlier, recognition and reporting of cardiotoxicity suffers from lack of standards and long-term surveillance. The utility of conventional cardiovascular treatments in cancer treatment-induced cardiotoxicity management offers promise and is supported by preclinical, observational, and small trials, but lacks rigorous randomized trial evidence, standard reporting of adverse outcomes, and infrastructure for long term surveillance (4,25,39).

Survivorship and Cancer Treatment-Related Cardiotoxicity

As the number of pediatric and adult cancer survivors continues to increase, surveillance and monitoring for cancer treatment-related cardiotoxicity is an essential care component for at-risk persons. While the extent to which cardiac status is affected in short- and long-term cancer survivors exposed to various cardiotoxic treatment regimens remains unclear, evidence suggests that the risk of toxicity continues to increase many years after treatment (3). The timing and types of cardiosafety surveillance lack universal definition and implementation across cancer survivors. Likewise, existing health screening recommendations, based on patient history and potential cardiovascular effects of predisposing therapy, lack consistent diagnostic definitions and interventions (12,40).

There is a critical need to conduct well-designed epidemiologic studies to determine incidence, severity, and natural history of various cardiotoxicities. Previous studies have varied widely (0% to 57%) in reporting the incidence rate of cancer therapy-induced cardiotoxicity, which can be attributed to differences in study design (41–45). Previous studies have focused

Table 1. Established and recommended resources for cardiotoxicity research*

Category	Established resources	Resource needs
Practice standards	The FDA Global Data Elements Initiative—defining cardiovascular endpoints and imaging International Cardio-oncology Society	A joint NHLBI, NCI, professional society task force to develop common, feasible goals and guideline topics by identifying small pre-, during, and post-therapy topics and addressing effectiveness as well as other domains of quality
Mechanisms	The National Council on Radiation Protection and Measurements, National Library of Medicine, National Center of Biomedical Oncology, and others—linking terminologies for a revised ontology FDA is collaborating with academic institutions to build ontology in the adverse event—reported terms, in a way that maps back to biology	Gene and tissue arrays Cell cultures or ‘organs on chips’ New in vitro and in vivo models Systematic database to organize the network across levels in computable and quantifiable ways Data linked by phenotype Transdisciplinary approach to otology
Markers of risk and injury		Prospective, longitudinal cohorts with common data elements
Prevention, treatment, and survivorship	Models for patient-centered medical home (PCMH) and survivor care plans exist to assist patients and providers coordinate post-treatment care between disciplines	Tools for stratification of samples Prospective, longitudinal studies Centralized databases Common data elements Larger sample size studies with common data elements and repeated measures
General	NCI DCCPS EGRP Knowledge Integration website on cancer treatment-related cardiotoxicity http://epi.grants.cancer.gov/cardiotoxicity/	

* DCCPS = Division of Cancer Control and Population Sciences; EGRP = Epidemiology and Genomics Research Program; FDA = US Food and Drug Administration; NCI = National Cancer Institute; NHLBI = National Heart, Lung and Blood Institute.

Box 3. Infrastructure needed to advance cancer treatment–related cardiotoxicity research.

1. Interprofessional education and cardio-oncology training programs.
2. Requests for applications and proposals from professional societies representing primary care providers, oncologists, and cardiologists to collaboratively develop both research and clinical guidelines.
3. Create mechanisms for investigators to leverage existing infrastructure within the National Cancer Institute and National Heart Lung and Blood Institute, such as the Clinical and Translational Science Awards, oncology and cardiology trial networks, the Childhood Cancer Survivorship Study, existing funded (primarily clinical) studies, genetic databases, existent clinical data and resources, and informatics resources.
4. Studies across institutions with centralized recruitment.
5. Examine the role of implementation science to improve translation.
6. Supplements for cross collaborators to be added to large grants.
7. Create novel mechanisms of funding and resource support for exploratory studies or the creation of a new cross-disciplinary research network.
8. Use special emphasis panels or other multidisciplinary review groups for cross-cutting science.
9. Large, longitudinal cohort studies and epidemiology.
10. Case-control studies will be useful for investigating rare outcomes to examine mortality and provide insight into mechanisms for various cardiotoxic outcomes.
11. Mechanisms are needed to foster broad interdisciplinary science across the study of pharmacology, computational science, biostatistics, epidemiology, and other scientific disciplines.
12. Biobanks of blood and other biospecimens would facilitate the testing of biomarkers, genome analyses, and biology.
13. Develop cancer treatment–related cardiotoxicity research consortium or task force.

on the effects of many different drug and radiation therapies, all with different incidence rates (46). In addition, these studies used different classifications, such as symptomatic, subclinical, acute, early (within one year) or late effects, for varying conditions across the cardiotoxicity spectrum. Other major factors affecting the incidence of cancer therapy–induced cardiotoxicity in the various populations studied include age, cancer types, stage, follow-up length, sample size, health status of the patients, and cardiovascular risk factors.

Workshop participants also stated that large longitudinal studies of cardiotoxicity in cancer survivors need to be conducted. Collecting detailed cancer and concomitant treatment, biomarker, and imaging data in a standardized manner is required to allow direct comparison of screening modalities and novel identification of cardiovascular injury. In addition, data on host factors, comorbid conditions, health behaviors (eg, diet, physical activity), and genetic factors need to be collected. Follow-up over many years is also recommended for determining long-term cardiotoxic outcomes, as well as effectiveness of cardioprotective interventions among new and combination therapies. Longitudinal studies of childhood cancer survivors could provide insights into whether cancer treatment accelerates the aging process in relation to cardiovascular damage.

Workshop participants recommended mining cancer registries and electronic health records for retrospective data, as well as modeling future cohort studies after the Childhood Cancer Survivorship Study and Framingham Study, emphasizing the need for biospecimen collection. Other possible sources to mine include the FDA and industry data.

Strategies are needed to implement patient-centered and collaborative approaches to caring for cancer survivors. This type of approach might help resolve certain barriers to assessing, preventing, and treating cardiotoxicity. The patient-centered medical home, survivorship clinics, and dynamic survivorship care plans are potential resources to identify, monitor, and treat long-term cardiac effects with the involvement of oncology, cardiology, and primary care providers. This team-oriented approach provides coordinated and managed care across specialties and includes care planning and shared decision making (47). More research is needed to determine when to transition survivors from the oncology team to a multidisciplinary survivorship care team and the optimal approach to developing a cancer survivorship plan. As evidence is being developed, consensus recommendations and guidelines by oncology and cardiology professional societies and think tanks are needed.

Summary

This report highlights the broad scope of basic and clinical cardiotoxicity research across all cancer treatment regimens needed to inform the field of cardio-oncology and improve patient outcomes. This is an area of great interest and the conceptualized and developed approaches above 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. The NCI-NHLBI workshop on cancer treatment–related cardiotoxicity was a first step in bringing together a transdisciplinary team to identify the research priorities, resources and infrastructure needed (9). Outcomes of this workshop to date include the archived meeting videocast available online (10,11), over 40 research recommendations across the cardiotoxicity spectrum (Box 2), identification of established and recommended resources (Table 1) and infrastructure (Box 3) needed to move cardiotoxicity research forward, development of the NCI Community Oncology Cardiotoxicity Task Force, and several new collaborations spanning basic and clinical science. The workshop recommendations are being used to develop and shape NCI's and NHLBI's research priorities around cancer treatment–related cardiotoxicity, as well as generate new and expanded research collaborations within the cardio-oncology community.

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