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STATE-OF-THE-ART REVIEW

The Evolving Design of NIH-Funded Cardio-Oncology Studies to Address Cancer Treatment-Related Cardiovascular Toxicity

Lori M. Minasian, MD,[a] Eileen Dimond, RN, MS,[a] Myrtle Davis, DVM, PHD, ATS,[b] Bishow Adhikari, PHD,[c] Richard Fagerstrom, PHD,[a] Carol Fabian, MD,[d] Justin Floyd, DO,[e] Joseph M. Unger, PHD, MS,[f] Pamela S. Douglas, MD,[g] Karen M. Mustian, PHD, MPH,[h] Eric J. Chow, MD, MPH,[i] Steven Lipshultz, MD,[j] W. Gregory Hundley, MD,[k] Saro H. Armenian, DO, MPH,[l] Bonnie Ky, MD, MSCE[m]

ABSTRACT

Cardiovascular (CV) toxicity from cancer therapy is a significant and growing concern. Conventional oncology clinical trial designs focused solely on cancer treatment efficacy have not provided sufficient information on both CV risk factors and outcomes. Similarly, traditional CV trials evaluating standard interventions typically exclude cancer patients, particularly those actively receiving cancer therapy. Neither trial type simultaneously evaluates the balance between CV toxicity and cancer outcomes; however, there is increasing collaboration among oncologists and cardiologists to design new cardio-oncology trials that address this important need. In this review, we detail 5 ongoing, oncology-based trials with integrated CV endpoints. Key design features include: 1) a careful assessment of CV risk factors and disease before, during, and after cancer therapy with standardized collection of clinical imaging, functional, and biomarker data; 2) an introduction of cardioprotective interventions at various timepoints in cancer therapy; 3) a balance of the risk of subclinical CV injury with the need for ongoing cancer treatment; and 4) an understanding of the time profile for development of clinically apparent CV toxicity. Additional critical priorities in cardio-oncology clinical research include harmonization of data collection and definitions for all physician- and patient-reported exposures and outcomes. (J Am Coll Cardiol CardioOnc 2019;1:105–13) Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Division of Cancer Prevention, National Cancer Institute, Bethesda, Maryland, USA; [b]Bristol-Myers Squibb Pharmaceutical Candidate Optimization, Princeton, New Jersey, USA; [c]National Heart, Lung, and Blood Institute (NHLBI), Division of Cardiovascular Sciences, Bethesda, Maryland, USA; [d]University of Kansas Medical Center Cancer Center Westwood, Kansas, USA; [e]Cancer Care Specialists of Illinois, Heartland NCORP, Swansea, Illinois, USA; [f]Fred Hutchinson Cancer Research Center, Public Health Sciences Division, SWOG Statistics and Data Management Center, Seattle, Washington, USA; [g]Duke University School of Medicine, Duke Clinical Research Institute, Durham, North Carolina, USA; [h]University of Rochester Medical Center, Wilmot Cancer Institute, Rochester, New York, USA; [i]Fred Hutchinson Cancer Research Center, Public Health Sciences and Clinical Research Divisions, Department of Pediatrics, University of Washington, Seattle, Washington, USA; [j]University at Buffalo Jacobs School of Medicine and Biomedical Sciences, Kaleida Health, John R. Oishei Children's Hospital, UBMD Pediatrics, Buffalo, New York, USA; [k]Virginia Commonwealth University, VCU Pauley Heart Center, Richmond, Virginia, USA; [l]City of Hope Comprehensive Cancer Center, Department of Population Sciences, Duarte, California, USA; and the [m]University of Pennsylvania, Perelman School of Medicine, Philadelphia, Pennsylvania, USA. This project has been funded in whole or in part with federal funds from the National Cancer Institute, National Institutes of Health, Bethesda, Maryland, under grants UG1CA189955, UG1CA189974, UG1CA189824, UG1CA189961, R34 HL146927-01, R01CA211996, R01HL118740, R01CA199167, R01CA181064, and R01CA196854. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Anju Nohria, MD, served as Guest Editor-in-Chief, and Lynne W. Stevenson, MD, served as Guest Editor for this paper.

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ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

CV = cardiovascular

HER2 = human epidermal growth factor receptor 2

LVEF = left ventricular ejection fraction

NCI = National Cancer Institute

NCTN = NCI National Clinical Trials Network

NIH = National Institutes of Health

Cardiovascular (CV) toxicity from cancer therapy is of substantial concern among a growing cancer population (1–6). Several position papers and clinical guidelines have addressed CV toxicity (7–10), but they are often based upon limited available clinical data. This lack of data highlights the need for clinical studies designed to characterize and manage the adverse CV effects of cancer therapy. Conventional cancer clinical trials focused on efficacy have generally provided insufficient information on CV effects, especially those that may not be associated with overt clinical events (11). CV clinical trials evaluating standard CV interventions in cancer patients often do not account for the current or past use of cancer therapies (12).

The field of cardio-oncology seeks to balance CV and cancer outcomes from past and present cancer therapies considering the biology and risk factors for both diseases (**Central Illustration**). Because patients are living longer after cancer treatment, the potential for subacute CV effects to develop into acute or late adverse clinical events needs to be studied. Specifically, subclinical CV injury may result in long-term risk after initial treatment that diminishes the overall survival of otherwise successfully treated cancer patients. Standard CV interventions to reduce the risk of CV disease may not have the same level of effectiveness in cancer treatment-induced CV events. To better understand the effects of subclinical injury on both the delivery of cancer therapy and the long-term CV effects, clinical trials need to capture laboratory and imaging measures, as well as clinical events for both cancer and CV outcomes in well-defined cancer populations.

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The U.S. National Institutes of Health (NIH) has funded initiatives to study cardio-oncology and provides resources to investigators to capture CV endpoints in cancer trials (**Table 1**). This article focuses on 5 large NIH-funded clinical trials (**Table 2**) to illustrate innovative study designs that are shaping the evolving field of cardio-oncology research. Because oncologists and cardiologists historically approach trial design from different perspectives, the purpose of this review is to promote collaboration between the cancer and cardiovascular communities in the design of cardio-oncology studies. We do so by highlighting examples of currently funded clinical trials that were designed to be feasible, rigorous, and informative.

HIGHLIGHTS

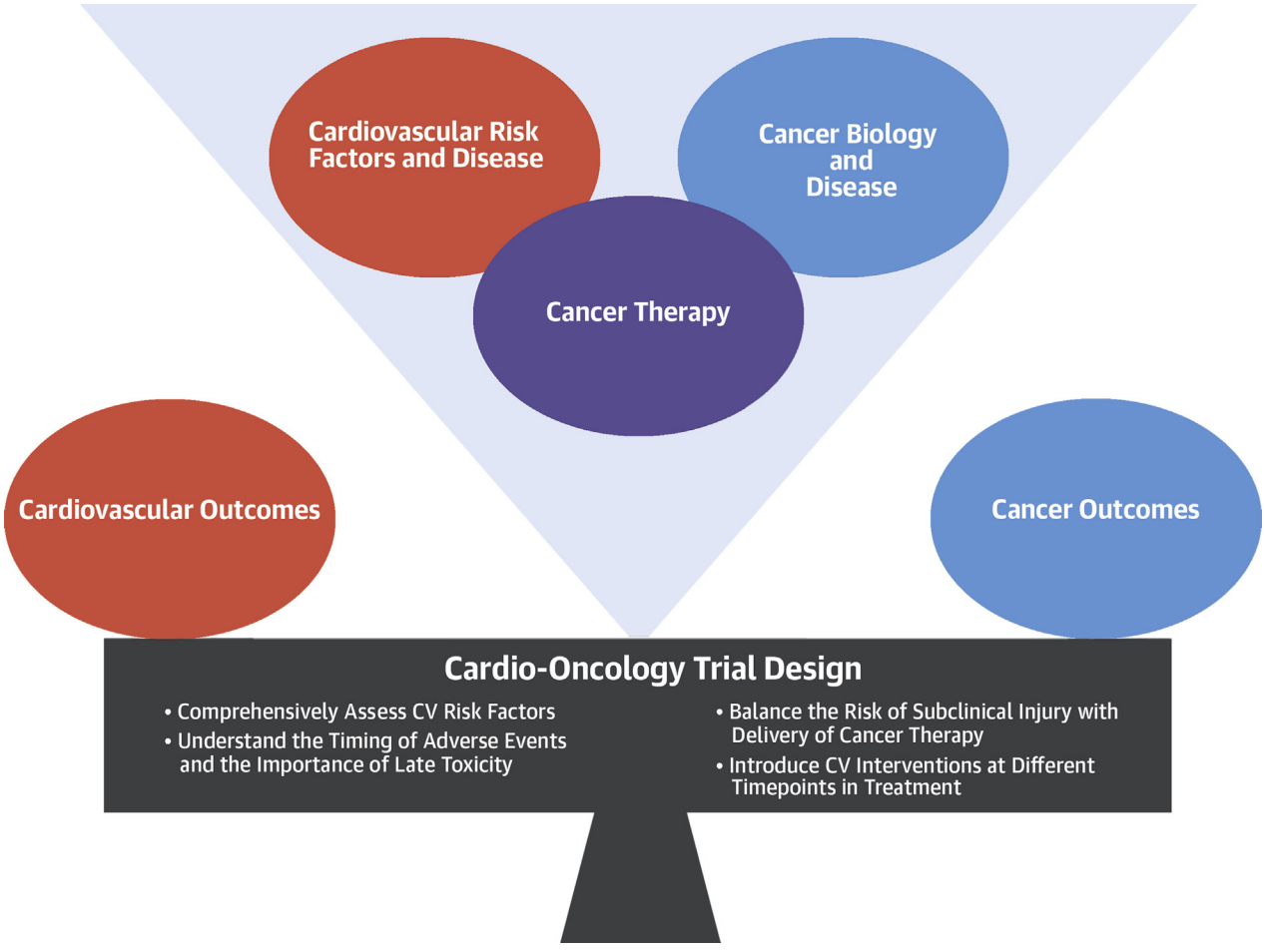
- Prospective assessment of CV risk factors before, during, and after cancer treatment.
- Longitudinal monitoring of CV function with standardized review of CV imaging and functional and biomarker endpoints for evidence of subclinical cardiotoxicity.
- Consideration for the timing of the introduction of the cardioprotective strategy.
- Need to balance the delivery of cancer treatment with the risk of CV injury.
- Long-term follow-up beyond cancer treatment intervention to determine clinical cardiotoxicity outcomes.
- Rigorous collection of cancer and CV endpoints to answer questions about the impact of CV events on the delivery of cancer treatment and the long-term patient outcomes.

We present 5 studies that are being conducted through the National Cancer Institute (NCI)-sponsored clinical trials programs, the NCI National Clinical Trials Network (NCTN) (13), and the NCI Community Oncology Research Program (14). Each of these cancer-based trials integrates CV endpoints in partnership with cardiology investigators. The key design aspects highlighted are the: 1) assessment of CV risk factors and disease before, during, and after cancer therapy with standardized collection of clinical, imaging, functional, and biomarker data; 2) introduction of cardioprotective interventions at various timepoints relative to cancer treatment; 3) balancing the risk of subclinical CV injury with the ongoing need for cancer treatment; and 4) development of a comprehensive understanding of the timing of adverse events and the importance of late toxicity. The trials described here are reflective of the current portfolio of funded studies, and focus largely on traditional cancer therapies; however, these design elements are generalizable to trials evaluating CV toxicity for newer agents, for which there is clearly a need.

COMPREHENSIVELY ASSESS CV RISK FACTORS AND DISEASE

CV adverse events have been reported in cancer trials for decades, traditionally through the use of the Common Terminology Criteria for Adverse Events;

CENTRAL ILLUSTRATION CardioOncology Trial Design



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CV = cardiovascular.

however, prospective cardiovascular risk factor identification, standardized cardiac image monitoring, and adequately assessed CV endpoints have often been suboptimal. This lack of information hinders both the ability to attribute adverse CV events to treatment and the successful delivery of cancer treatment regimens to patients with clinical or subclinical CV disease. Indeed, efforts to retrospectively examine late CV effects for cancer clinical trial patients have limited applicability because of the complexities of recruitment and retention of a secondary long-term study (15). Understanding the subacute CV effects that develop during cancer treatment and which of those effects result in overt clinical adverse events will help to identify approaches to manage those effects and potentially reduce the long-term CV morbidity from cancer therapy (11).

UPBEAT (Understanding and Predicting Breast Cancer Events After Treatment) (NCT02791581) (16) is designed to determine the incidence and time course of changes in left ventricular function, aortic function, exercise capacity, and fatigue in patients who are receiving any type of chemotherapy for early-stage breast cancer. This study collects exposure and outcomes data, including risk factors, blood-based cardiac biomarkers, centrally adjudicated imaging data by cardiac magnetic resonance imaging, exercise capacity by measuring maximal oxygen consumption, and 6-min walk test. In addition, patient-reported outcomes assessing fatigue,

TABLE 1 National Institutes of Health Funding Opportunity Announcements Supporting Cardio-Oncology

Funding Opportunity Announcement	Website Address	Summary
National Cancer Institute and National Heart Lung and Blood Institute: "Improving Outcomes in Cancer Treatment-Related Cardiotoxicity"	https://grants.nih.gov/grants/guide/pa-files/PA-19-112.html (R01 Clinical Trial Optional) https://grants.nih.gov/grants/guide/pa-files/PA-19-111.html (R21 Clinical Trial Optional)	Seeks collaborative applications that will contribute to the identification and characterization of patients at risk of developing cancer treatment-related cardiotoxicity. Focus: mitigation/management of cardiovascular adverse events associated with anti-cancer treatments while optimizing cancer outcomes. Expires January 8, 2022.
National Cancer Institute: "Improving Outcomes for Pediatric, Adolescent and Young Adult Cancer Survivors	https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-19-033.html (U01 Clinical Trial Required)	The purpose of this funding opportunity announcement is to stimulate the development, testing, and/or scaling of innovative, feasible, and effective interventions to prevent, mitigate or manage adverse physical, psychosocial, and behavioral effects in survivors of pediatric and/or adolescent/young adult cancer survivors or to improve health care delivery. Interventions may be targeted to the patient or to the patient-caregiver dyad, and may include multilevel interventions delivered by providers, teams, communities, and/or care delivery systems. Expires January 4, 2020.
Multiple NIH Institutes are participating, including the National Cancer Institute: "Serious Adverse Drug Reaction Research"	https://grants.nih.gov/grants/guide/pa-files/PAR-16-275.html (R01) https://grants.nih.gov/grants/guide/pa-files/PAR-16-274.html (R21)	Advance the knowledge of serious ADRs resulting from anti-cancer therapies (e.g., organ toxicities, immune-related ADRs); biomarkers for prediction, early detection, or monitoring of ADRs; development and validation of clinical assays or tools for measuring ADR markers; alleviation of severe and/or chronic ADRs; development, testing, interpretation, and the use of patient-reported outcome measures to capture symptomatic toxicities, such as fatigue, nausea, and neuropathy; epidemiologic surveillance over time of serious ADRs. Expires September 8, 2019.
National Cancer Institute: "Mechanisms of Cancer and Treatment-Related Symptoms and Toxicities"	http://grants.nih.gov/grants/guide/pa-files/PA-16-258.html (R21)	Seeks innovative pilot projects/feasibility studies to identify, describe, and quantify the complex interaction of biological, cognitive, behavioral, and sociocultural factors that contribute to cancer and treatment-related symptoms and toxicities throughout the cancer care trajectory. Data from the preliminary studies would be used to validate and extend the findings via the R01 funding mechanism. There is a particular interest in minority, underserved, the elderly, and pediatric and young adult populations. Expires September 8, 2019.
National Cancer Institute: "Clinical Characterization of Cancer Therapy-induced Adverse Sequelae and Mechanism-based Interventional Strategies (R01 Clinical Trial Optional)"	https://grants.nih.gov/grants/guide/pa-files/PAR-19-325.html (R01 Clinical Trial Optional)	Supports collaborative basic, translational, and/or clinical research projects designed to address adverse sequelae of cancer therapies that persist and become chronic comorbidities or develop as delayed post-treatment effects. Focus: 1) mechanistic studies with translational endpoints; and/or 2) longitudinal clinical phenotyping to identify and validate clinical endpoints. Expires February 12, 2022.

ADR = adverse drug reaction.

depression, cognition, and mobility are obtained before and during treatment and over a 10-year follow-up period.

Uniquely, this trial also will help to advance our understanding of the relationship among exercise capacity, symptomatic fatigue, and subclinical and clinical changes in CV function. Fatigue can result from cancer, cancer treatment, and CV disease, making it challenging to attribute fatigue to 1 cause (17,18). Therefore, a separate, parallel cohort of age-matched participants who do not have cancer are recruited and followed with the same assessments and patient-reported outcomes to assess noncancer components of fatigue, exercise capacity, and left ventricular function.

To understand the epidemiology and pathophysiology of cardiotoxicity, the variables, measurements, and data collection efforts need to be standardized, as do imaging and biomarker assessments of phenotypes (19–21). UPBEAT and the other studies in this review standardize imaging endpoints through the use of core laboratories (22). Second, the Cardiotoxicity Working Group of the Eastern Cooperative Oncology Group and the American College of Radiology Imaging Network has developed a list of common measures of exposure to be collected in cardio-oncology studies of adults (23). In addition, the Common Terminology Criteria for Adverse Events needs to be augmented with more specific measures of CV status to ensure CV complications of cancer treatment are fully understood (11).

INTRODUCE CARDIOPROTECTIVE INTERVENTIONS AT DIFFERENT TIMEPOINTS IN CANCER TREATMENT

Several interventions used to reduce the risk of CV outcomes in patients with CV disease are now being explored in cancer patients. Given that the mechanisms of cardiac injury with cancer treatment likely differ from traditional CV disease, it is unclear if standard protective or preventive interventions, such as statins and antihypertensive agents, will reduce the incidence and severity of cancer-treatment induced CV adverse events. Additionally, it is not clear when these interventions need to be delivered (before, during, or after cancer therapy) and for what duration.

PREVENT (Preventing Anthracycline Cardiovascular Toxicity with Statins) (NCT01988571) (24) is

TABLE 2 National Institutes of Health Sponsored Active CV Toxicity Studies

Title, NCT#	Research Base Conducting	Target Population	Target Enrollment	Intervention	Primary and Secondary Outcome Measures	Estimated Completion Date (Based on Data in clinicaltrials.gov)	Key Design Elements
Observational							
Understanding and Predicting Breast Cancer Events After Treatment (UPBEAT) NCT02791581	Wake Forest University Health Sciences	Women newly diagnosed with stage I-III breast cancer receiving: 1) adjuvant anthracycline chemotherapy 2) nonanthracycline treatment and; 3) noncancer controls	1,000	Observational: cardiac imaging, exercise capacity, serum biomarkers, behavioral and psychosocial questionnaires at 3, 12, and 24 months posttreatment initiation	1) Change in fatigue, exercise, capacity, and cardiac imaging measures 2) Change in left ventricular ejection fraction exercise capacity and fatigue	November 2021	Prospective monitoring; standardized endpoints; long-term monitoring
Randomized controlled trials							
Preventing Anthracycline CV Toxicity with Statins (PREVENT) NCT01988571	Wake Forest University Health Sciences	Women diagnosed with stage I-III breast cancer receiving adjuvant anthracycline chemotherapy	279 (active, not recruiting)	Arm 1: Atorvastatin by mouth daily for 24 months Arm 2: Placebo table by mouth daily for 24 months	1) Left ventricular ejection fraction at 24 months 2) Difference in left ventricular baseline and 6 months	May 2020	Prospective monitoring; standardization of imaging and biomarker data; timing of intervention (during chemotherapy)
Carvedilol in Preventing Heart Failure in Childhood Cancer Survivors NCT02717507	Children's Oncology Group	Diagnosed with cancer <22 yrs of age, lifetime cumulative anthracycline dose of ≥250 mg/m^2, and completed cancer treatment ≥2 yrs before enrollment	250	Low dose, oral carvedilol versus placebo give once or twice daily for 24 months	Left ventricular posterior wall thickness to dimension ratio	April 2022	Prospective monitoring; standardization of endpoints; timing of intervention (completion of chemotherapy)
S1501 Carvedilol in Preventing Cardiac Toxicity in Patients with Metastatic HER2-Positive Breast Cancer NCT03418961	Southwest Oncology Group	Metastatic breast cancer initiating or continuing trastuzumab based HER-2 targeted therapy without concurrent anthracyclines	817	Arm 1: Carvedilol by mouth twice a day Arm 2: Usual care Arm 3: Observation	1) Time to cardiac dysfunction (decreased left ventricular ejection fraction) 2) Time to treatment interruption (secondary outcome)	February 2023	Prospective monitoring; standardization of endpoints; timing of intervention (during chemotherapy)
Late effects							
Effects of Dexrazoxane Hydrochloride on Biomarkers Associated with Cardiomyopathy and Heart Failure After Cancer Treatment NCT01790152	Children's Oncology Group	Previously enrolled on P9404, P9425, P9426, or DFI 95-01 and randomized to ± dexrazoxane	420	Observational: Physical examination, cardiac imaging, serum biomarkers, behavioral and psychosocial questionnaires	Left ventricular thickness-to-dimension ratio and systolic function	March 2022	Standardization of endpoints; long-term follow-up

HER2 = human epidermal growth factor receptor 2.

testing whether the 3-hydroxy-3-methylglutaryl-coenzyme reductase inhibitor atorvastatin reduces cardiac dysfunction in patients with either early-stage breast cancer or lymphoma who receive conventional anthracycline-containing chemotherapy regimens. Detailed data on cancer history and baseline CV risk factors are being collected. The atorvastatin intervention begins before chemotherapy and continues for a total of 2 years. This study will determine if atorvastatin given during treatment with anthracyclines will preserve left ventricular ejection fraction (LVEF) derived from centrally adjudicated cardiac magnetic resonance imaging, and the extent to which early subclinical changes result in clinical heart failure and other adverse events. Biomarkers of cardiac injury and patient-reported outcomes assessing fatigue and quality of life are incorporated as well.

Carvedilol in Preventing Heart Failure in Childhood Cancer Survivors (NCT02717507) (25) is testing the effect of low-dose carvedilol, a guideline-directed heart failure medication, on cardiac remodeling in children and adolescent and young adult survivors who have completed their childhood cancer treatment with high-dose anthracyclines at least 2 years before enrollment. A normal LVEF is required before enrollment. The main outcome measure at 2 years is the ratio of the left ventricular posterior wall thickness to the internal cavity dimension as measured by echocardiography. Serum biomarkers of cardiac remodeling, including natriuretic peptides, troponins, and galectin-3, are collected at the beginning of the study and over the 2-year course of low-dose carvedilol. Safety and tolerability of low-dose carvedilol as well as patient adherence to carvedilol will be assessed as well.

Although the PREVENT study evaluates a statin during chemotherapy to preserve LV function, the second study evaluates low-dose carvedilol after completion of chemotherapy to potentially reverse the subclinical cardiac injury resulting from chemotherapy.

BALANCE THE RISK OF SUBCLINICAL INJURY WITH CONTINUED DELIVERY OF CANCER THERAPY

Balancing the recognition and the management of subclinical CV injury with the need for ongoing cancer therapy may improve survival. The impact of both subclinical and overt clinical CV toxicity on all-cause and cancer-specific mortality remains to be determined. Patients with metastatic disease are living longer and some are receiving years of continuous cancer treatment. For example, patients with metastatic breast cancer expressing the human epidermal growth factor receptor 2 (HER2+) are treated with long-term HER2-targeted treatment, often in combination with a second HER2-targeting agent (26,27). Chronic administration of HER2-targeted treatment frequently results in subclinical CV injury, including reduction in LVEF and worsening of cardiac strain (28-30). In the general population, similar abnormalities in sensitive measures of cardiac dysfunction, such as longitudinal strain assessed by echocardiography, may be associated with overall poor prognosis (31). Thus, continuing the HER2-directed therapy without addressing subclinical cardiac injury may potentially increase the risk of poor CV outcomes. However, interrupting HER2 blockade in response to asymptomatic echocardiographic findings may increase the risk of poor cancer outcomes (31,32).

The innovative design of S1501 Carvedilol in Preventing Cardiac Toxicity in Patients with Metastatic HER2 Positive Breast Cancer trial (NCT03418961) (33) addresses this critical issue by testing whether prophylactic low-dose carvedilol will reduce the incidence of cardiac dysfunction, as defined by blinded, real-time, centrally adjudicated echocardiography-derived LVEF. Patients with metastatic HER2+ breast cancer who are not receiving angiotensin-converting enzyme (ACE) inhibitors or β-blockers are randomly assigned to low-dose carvedilol or usual care. Prospective CV assessment with echocardiography is performed every 3 months. LVEF and longitudinal strain, the latter if available, are centrally interpreted and reported to the clinician in real-time. Cardiac dysfunction is defined as a decrease in the LVEF of ≥10% from baseline to a value of <50% or decrease of LVEF by ≥5% from baseline to LVEF <50% in those patients having a baseline LVEF of 50% to 54%. Dose modification or interruption of HER2-targeted therapy is determined at the local site where the clinical CV events are identified and reported. White blood cell DNA at baseline is being collected for SNP analysis and blood is collected every 3 months for biomarkers predictive of early cardiac dysfunction. This trial also will evaluate the incidence of clinical CV events (arrhythmia, unstable angina, myocardial infarction, or heart failure) and the interruption of HER2-targeted therapy.

As part of S1501, a separate, observational cohort of patients who are receiving ACE inhibitors or β-blockers for other clinical indications is being followed prospectively using the same CV assessment. Because many patients with breast cancer also have hypertension or other comorbidities for which they are taking ACE inhibitors or β-blockers, this pragmatic, observational cohort will provide estimates of the incidence of cardiac dysfunction and interruption of HER2-targeted therapy in clinical practice.

UNDERSTAND THE TIME PROFILE OF ADVERSE EVENTS AND THE IMPORTANCE OF LATE TOXICITY

More than 15 million cancer survivors in the United States attest to the fact that patients are living long enough to experience late CV effects, which may ultimately contribute to worse overall survival and quality of life (1,34). Late toxicities are being studied in pediatric cancer survivors. Almost 30 years ago, dexrazoxane was evaluated as a cardioprotective agent during anthracycline chemotherapy (35). Although short-term outcomes have shown a CV

benefit, the long-term CV outcomes are not known, particularly in survivors of childhood cancers (36-38).

The Effects of Dexrazoxane Hydrochloride on Biomarkers Associated with Cardiomyopathy and Heart Failure after Cancer Treatment trial (NCT01790152) (39) addresses this issue by collecting a detailed CV evaluation of adult survivors of pediatric leukemia and lymphoma who were previously treated on 4 randomized clinical trial protocols and received anthracycline chemotherapy with dexrazoxane or a placebo. Archived echocardiograms of patients from the 4 clinical trials (40-43) conducted in the late 1990s are being collated and re-reviewed. Those patients alive without subsequent cancer are also being contacted to participate in prospective CV evaluations. In addition, the study is linking the patients treated on the aforementioned clinical trials with administrative datasets, such as the U.S. Organ Procurement and Transplantation Network (44) and the National Death Index (45) to ascertain whether patients randomized to dexrazoxane have a differential risk of heart or heart/lung transplants and to determine the overall mortality rates compared with those who were not assigned to receive dexrazoxane. This clinical study highlights the importance of long-term follow-up to fully assess late toxicity in cancer survivors, particularly survivors of pediatric cancer.

LOOKING TO THE FUTURE

Both cancer and CV disease substantially affect a growing population. Patients, however, continue to receive care for heart disease and cancer in separate cardiology and oncology clinical settings. Abnormalities in CV function from cancer treatment may offset the substantial gains made in cancer-specific mortality. Collaboration between cardiologists and oncologists is needed to design trials that answer questions about the optimal delivery of cancer treatment with cardiovascular toxicity.

Cancer therapy is rapidly evolving with many new molecular entities approved for specific cancer indications (46). CV toxicity has been identified with newer anticancer agents, such as vascular endothelial growth factor inhibitors, proteasome inhibitors, tyrosine kinase inhibitors, and immunotherapy agents (47-50). There are many questions in the clinical care of patients who receive these agents. For example, what are the factors that best predict risk for CV toxicity? To what extent can patients continue to receive cancer therapies after experiencing a CV event? What are the optimal approaches to mitigate or prevent CV toxicity? Does aggressive treatment of CV risk factors translate to differences in oncologic outcomes? More specifically, does aggressive blood pressure control allow for more prolonged exposure of vascular endothelial growth factor inhibitors and does that translate into improved progression-free survival? This question is being asked in an upcoming NCTN study EAQ191, CARISMA (Cancer Therapy Risk-reduction with Intensive Systolic BP Management). A question relevant to patients with a history of atrial arrhythmias who are receiving Bruton tyrosine kinase inhibitors includes defining the most effective strategies to manage rhythm control and anticoagulation.

These and other similar questions can be answered through studies designed collaboratively by cardiologists and oncologists using the key design factors presented in this review. Additionally, translational endpoints in these clinical studies can potentially inform the mechanisms for CV adverse effects and improve the identification of cardioprotective strategies (51).

Four of the studies presented were designed to evaluate treatment-emergent CV adverse events in well-defined populations of patients. These studies captured pretreatment CV risk factors and incorporated standardized, prospective monitoring of CV function. These studies include several of the key design elements (Highlights Box, **Table 2**, **Central Illustration**) depending upon the study's primary question and patient population. In particular, the evaluation of cardioprotective interventions to reduce CV damage needs to be understood in the context of the patient population receiving specific cancer treatment regimens and should include endpoints relevant to cancer treatment, such as treatment interruption or progression of disease. Cancer treatment increasingly is targeted to cancer subtypes and thus selecting the most appropriate population of patients for a cardioprotective intervention will be critical. Efforts are under way to broaden the eligibility criteria for cancer clinical trials to improve the generalizability of trial results (48), which may increase the number of participants with CV risk factors at trial entry. Ultimately, the goal of the CV intervention is to provide sufficient support to enable the full cancer treatment course and maintain efficacy while maintaining quality of life.

Although 4 of the 5 studies discussed have evaluated a drug intervention to prevent cardiac dysfunction, behavioral and lifestyle interventions, particularly exercise, may also play a key role in protecting against CV complications of cancer treatment and need to be evaluated in randomized clinical trials (52-56). There remains a critical need to understand the extent to which exercise can improve CV

reserve and reduce acute and chronic CV toxicity. The extent of vascular and metabolic changes from cancer treatment and their subsequent impact on CV function also need to be defined.

As more cardio-oncology clinical trials are conducted, there is a growing need to compare results across trials. Efforts are ongoing to harmonize CV and cancer data collection of both exposures (baseline clinical variables) and outcomes, including patient-reported outcomes, and promote the use of common case report forms. One of the NCI Clinical Trials Network Groups, the Eastern Cooperative Oncology Group and the American College of Radiology Imaging Network, through the Cardiotoxicity Subcommittee, has developed a comprehensive list of common data elements, consolidated as case report forms (23). In the absence of long-term assessments of CV events and outcomes, which may be very costly to capture for clinical trials, opportunities to link trial records to external data sources, such as Medicare claims and the National Death Index, may provide an alternative and more feasible approach (4).

The intersection of CV and oncologic disease has been a focus of multiple, dedicated funding initiatives within the NIH (**Table 1**) and is incorporated into the National Institute of Heart, Lung, and Blood's strategic vision (57) and NCI Symptom Management and Quality of Life Steering Committee priorities (58) denoting that research on CV toxicity within the NCI NCTN and NCI Community Oncology Research Program clinical trials networks is among its highest priorities.

Collaborations between oncologists and cardiologists will serve to improve the design of cardio-oncology studies by integrating both cardiovascular and cancer endpoints. These new studies will generate the evidence needed to optimize the delivery of cancer treatment, thereby, improving both quality of life and survival for cancer patients.

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ADDRESS FOR CORRESPONDENCE: Dr. Lori Minasian, Division of Cancer Prevention, National Cancer Institute, 9609 Medical Center Drive, 5E-342, MSC-9784, Bethesda, Maryland 20892, USA. E-mail: minasilo@mail.nih.gov.

REFERENCES

1. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 2016;66:271–89.

2. Armstrong GT, Chen Y, Yasui Y, et al. Reduction in late mortality among 5-year survivors of childhood cancer. N Engl J Med 2016;374:833–42.

3. Henson KE, Reulen RC, Winter DL, et al. Cardiac mortality among 200,000 five-year survivors of cancer diagnosed at 15 to 39 years of age: the teenage and young adult cancer survivor study. Circulation 2016;134:1519–31.

4. Hershman DL, Till C, Shen S, et al. Association of cardiovascular risk factors with cardiac events and survival outcomes among patients with breast cancer enrolled in SWOG clinical trials. J Clin Oncol 2018;36:2710–7.

5. Patnaik JL, Byers T, DiGuiseppi C, Dabelea D, Denberg TD. 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.

6. Abdel-Qadir H, Austin PC, Lee DS, et al. A population-based study of cardiovascular mortality following early-stage breast cancer. JAMA Cardiol 2017;2:88–93.

7. 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.

8. Zamorano JL, Lancellotti P, Rodriguez Munoz D, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur J Heart Fail 2016;37:2768–801.

9. Maitland ML, Bakris GL, Black HR, et al. Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors. J Natl Cancer Inst 2010;102:596–604.

10. 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;35:893–911.

11. Witteles RM, Telli M. Underestimating cardiac toxicity in cancer trials: lessons learned? J Clin Oncol 2012;30:1916–8.

12. 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;71:2281–90.

13. National Cancer Institute. NCTN: NCI's National Clinical Trials Network. Available at: https://www.cancer.gov/research/areas/clinical-trials/nctn. Accessed April 10, 2019.

14. National Cancer Institute. NCI Community Oncology Research Network (NCORP). Available at: https://ncorp.cancer.gov/. Accessed April 10, 2019.

15. Ganz PA, Hussey MA, Moinpour CM, et al. Late cardiac effects of adjuvant chemotherapy in breast cancer survivors treated on Southwest Oncology Group protocol S8897. J Clin Oncol 2008;26:1223–30.

16. U.S. National Institutes of Health, National Library of Medicine, ClinicalTrials.gov. Understanding and predicting breast cancer events after treatment (UPBEAT). Available at: https://clinicaltrials.gov/ct2/show/NCT02791581. Accessed April 10, 2019.

17. Barsevick AM, Irwin MR, Hinds P, et al. Recommendations for high-priority research on cancer-related fatigue in children and adults. J Natl Cancer Inst 2013;105:1432–40.

18. Fisch MJ, Zhao F, O'Mara AM, Wang XS, Cella D, Cleeland CS. Predictors of significant worsening of patient-reported fatigue over a 1-month timeframe in ambulatory patients with common solid tumors. Cancer 2014;120:442–50.

19. Narayan HK, Finkelman B, French B, et al. Detailed echocardiographic phenotyping in breast cancer patients: associations with ejection fraction decline, recovery, and heart failure symptoms over 3 years of follow-up. Circulation 2017;135:1397–412.

20. Finkelman BS, Putt M, Wang T, et al. Arginine-nitric oxide metabolites and cardiac dysfunction in patients with breast cancer. J Am Coll Cardiol 2017;70:152–62.

21. Zardavas D, Suter TM, Van Veldhuisen DJ, et al. Role of troponins I and T and N-terminal prohormone of brain natriuretic peptide in monitoring cardiac safety of patients with early-stage human epidermal growth factor receptor 2-positive breast cancer receiving trastuzumab: a herceptin adjuvant study cardiac marker substudy. J Clin Oncol 2017;35:878–84.

22. Khouri MG, Ky B, Dunn G, et al. Echocardiography core laboratory reproducibility of cardiac safety assessments in cardio-oncology. J Am Soc Echocardiogr 2018;31:361–71.e363.

23. National Cancer Institute. Division of Cancer Prevention. Available at: https://prevention.cancer.gov/major-programs/supportive-and-palliative-care/topic-areas/cardiotoxicity. Accessed August 28, 2019.

24. U.S. National Institutes of Health, National Library of Medicine, ClinicalTrials.gov. Preventing anthracycline cardiovascular toxicity with statins (PREVENT). Available at: https://clinicaltrials.gov/ct2/show/NCT01988571. Accessed April 10, 2019.

25. U.S. National Institutes of Health, National Library of Medicine, Clinicaltrials.gov. Carvedilol in preventing heart failure in childhood cancer survivors. Available at: https://clinicaltrials.gov/ct2/show/NCT02717507. Accessed April 10, 2019.

26. Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med 2015;372:724–34.

27. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. N Engl J Med 2017;377:122–31.

28. Jacquinot Q, Paget-Bailly S, Fumoleau P, et al. Fluctuation of the left ventricular ejection fraction in patients with HER2-positive early breast cancer treated by 12 months of adjuvant trastuzumab. Breast 2018;41:1–7.

29. Seidman A, Hudis C, Pierri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol 2002;20:1215–21.

30. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344:783–92.

31. Park JJ, Park JB, Park JH, Cho GY. Global longitudinal strain to predict mortality in patients with acute heart failure. J Am Coll Cardiol 2018;71:1947–57.

32. Dang CT, Yu AF, Jones LW, et al. Cardiac surveillance guidelines for trastuzumab-containing therapy in early-stage breast cancer: getting to the heart of the matter. J Clin Oncol 2016;34:1030–3.

33. U.S. National Institutes of Health, National Library of Medicine, Clinicaltrials.gov. S1501 Carvedilol in preventing cardiac toxicity in patients with metastatic HER-2+ breast cancer. Available at: https://clinicaltrials.gov/ct2/show/NCT03418961. Accessed April 10, 2019.

34. Benetou DR, Stergianos E, Geropeppa M, et al. Late-onset cardiomyopathy among survivors of childhood lymphoma treated with anthracyclines: a systematic review. Hellenic J Cardiol 2018 Sep 29 [E-pub ahead of print].

35. Hasinoff BB, Hellmann K, Herman EH, Ferrans VJ. Chemical, biological and clinical aspects of dexrazoxane and other bisdioxopiperazines. Curr Med Chem 1998;5:1–28.

36. van Dalen EC, Caron HN, Dickinson HO, Kremer LC. Cardioprotective interventions for cancer patients receiving anthracyclines. Cochrane Database Syst Rev 2011;6:Cd003917.

37. Lipshultz SE, Scully RE, Lipsitz SR, et al. Assessment of dexrazoxane as a cardioprotectant in doxorubicin-treated children with high-risk acute lymphoblastic leukaemia: long-term follow-up of a prospective, randomised, multicentre trial. Lancet Oncol 2010;11:950–61.

38. Asselin BL, Devidas M, Chen L, 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;34:854–62.

39. U.S. National Institutes of Health, National Library of Medicine, Clinicaltrials.gov. Effects of dexrazoxane hydrochloride on biomarkers associated with cardiomyopathy and heart failure after cancer treatment. Available at: https://clinicaltrials.gov/ct2/show/NCT01790152. Accessed April 10, 2019.

40. Tebbi CK, Mendenhall NP, London WB, et al. Response-dependent and reduced treatment in lower risk Hodgkin lymphoma in children and adolescents, results of P9426: a report from the Children's Oncology Group. Pediatr Blood Cancer 2012;59:1259–65.

41. Schwartz CL, Constine LS, Villaluna D, et al. A risk-adapted, response-based approach using ABVE-PC for children and adolescents with intermediate- and high-risk Hodgkin lymphoma: the results of P9425. Blood 2009;114:2051–9.

42. Moghrabi A, Levy DE, Asselin B, et al. Results of the Dana-Farber Cancer Institute ALL consortium protocol 95-01 for children with acute lymphoblastic leukemia. Blood 2007;109:896–904.

43. Asselin BL, Devidas M, Wang C, et al. Effectiveness of high-dose methotrexate in T-cell lymphoblastic leukemia and advanced-stage lymphoblastic lymphoma: a randomized study by the Children's Oncology Group (POG 9404). Blood 2011;118:874–83.

44. U.S. Department of Health and Human Services. Organ Procurement and Transplantation Network (OPTN). Available at: https://optn.transplant.hrsa.gov. Accessed April 10, 2019.

45. Centers for Disease Control and Prevention, National Center for Health Statistics. National Death Index. Available at: https://www.cdc.gov/nchs/ndi/index.htm. Accessed April 10, 2019.

46. Beaver JA, Howie LJ, Pelosof L, et al. A 25-year experience of U.S. Food and Drug Administration accelerated approval of malignant hematology and oncology drugs and biologics: a review. JAMA Oncol 2018;4:849–56.

47. Iannaccone A, Bruno G, Ravera A, et al. Evaluation of cardiovascular toxicity associated with treatments containing proteasome inhibitors in multiple myeloma therapy. High Blood Press Cardiovasc Prev 2018;25:209–18.

48. Touyz RM, Herrmann J. Cardiotoxicity with vascular endothelial growth factor inhibitor therapy. NPJ Precis Oncol 2018;2:13.

49. Asnani A. Cardiotoxicity of immunotherapy: incidence, diagnosis, and management. Curr Oncol Rep 2018;20:44.

50. Caldeira D, Alves D, Costa J, Ferreira JJ, Pinto FJ. Ibrutinib increases the risk of hypertension and atrial fibrillation: systematic review and meta-analysis. PloS One 2019;14:e0211228.

51. Moslehi J, Amgalan D, Kitsis RN. Grounding cardio-oncology in basic and clinical science. Circulation 2017;136:3–5.

52. Scott JM, Nilsen TS, Gupta D, Jones LW. Exercise therapy and cardiovascular toxicity in cancer. Circulation 2018;137:1176–91.

53. Duncan M, Moschopoulou E, Herrington E, et al. Review of systematic reviews of non-pharmacological interventions to improve quality of life in cancer survivors. BMJ Open 2017;7:e015860.

54. Yu AF, Jones LW. Breast cancer treatment-associated cardiovascular toxicity and effects of exercise countermeasures. Cardiooncology 2016;2.

55. Mustian KM, Sprod LK, Janelsins M, et al. Multicenter, randomized controlled trial of yoga for sleep quality among cancer survivors. J Clin Oncol 2013;31:3233–41.

56. Lin PJ, Peppone LJ, Janelsins MC, et al. Yoga for the management of cancer treatment-related toxicities. Curr Oncol Rep 2018;20:5.

57. U.S. National Institutes of Health, National Heart Lung, and Blood Institute. Strategic vision. Available at: https://www.nhlbi.nih.gov/about/strategic-vision. Accessed April 10, 2019.

58. National Cancer Institute. 2015 Strategic Priorities Symptom Management & Quality of Life Steering Committee (SxQoL SC). Available at: https://www.cancer.gov/about-nci/organization/ccct/steering-committees/2015-SxQoLSC-StrategicPriorities. Accessed April 10, 2019.

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