REVIEW ARTICLE

Cardiovascular Disease in Survivors of Childhood Cancer: Insights Into Epidemiology, Pathophysiology, and Prevention

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ABSTRACT

Cardiovascular disease (CVD), which includes cardiomyopathy/heart failure, coronary artery disease, stroke, pericardial disease, arrhythmias, and valvular and vascular dysfunction, is a major concern for long-term survivors of childhood cancer. There is clear evidence of increased risk of CVD largely attributable to treatment exposures at a young age, most notably anthracycline chemotherapy and chest-directed radiation therapy, and compounded by traditional cardiovascular risk factors accrued during decades after treatment exposure. Preclinical studies are limited; thus, it is a high priority to understand the pathophysiology of CVD as a result of anticancer treatments, taking into consideration the growing and developing heart. Recently developed personalized risk prediction models can provide decision support before initiation of anticancer therapy or facilitate implementation of screening strategies in at-risk survivors of cancer. Although consensus-based screening guidelines exist for the application of blood and imaging biomarkers of CVD, the most appropriate timing and frequency of these measures in survivors of childhood cancer are not yet fully elucidated. Longitudinal studies are needed to characterize the prognostic importance of subclinical markers of cardiovascular injury on long-term CVD risk. A number of prevention trials across the survivorship spectrum are under way, which include primary prevention (before or during cancer treatment), secondary prevention (after completion of treatment), and integrated approaches to manage modifiable cardiovascular risk factors. Ongoing multidisciplinary collaborations between the oncology, cardiology, primary care, and other subspecialty communities are essential to reduce therapeutic exposures and improve surveillance, prevention, and treatment of CVD in this high-risk population.

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INTRODUCTION

Cardiovascular disease (CVD), which includes cardiomyopathy/heart failure, coronary artery disease, stroke, pericardial disease, arrhythmias, and valvular and vascular dysfunction, is a major concern for long-term survivors of childhood cancer.[1-5] These survivors are seven times more likely than the general population to die as a result of CVD, making CVD the leading cause of noncancer mortality in this population.[6] This increased risk for development of CVD is largely attributed to cancer treatment exposures at a young age, most notably anthracycline (eg, doxorubicin, daunorubicin, epirubicin, idarubicin), mitoxantrone chemotherapy, and chest-directed radiation therapy (RT). It is estimated that as many as one in eight survivors of childhood cancer treated with anthracyclines and chest RT will experience a life-threatening cardiovascular event 30 years after treatment of childhood cancer.[5] However, the cumulative burden of CVD, including both the quantity and severity of events, is inherently different when comparing survivors of individual cancers (eg, Hodgkin lymphoma) to both the general population[7] and other disease groups.[8] These differences are largely due to well-characterized clinical and treatment-related modifiers of risk related to cumulative dose exposure of cardiotoxic agents and modalities (Table 1).[1-5] The large body of literature on CVD-related outcomes in survivors of childhood cancer has informed risk-based guidelines for early detection and treatment of CVD. The purpose of this review article is to highlight emerging paradigms in childhood cancer survivorship and CVD, with a focus on preclinical and clinical models of anthracycline-induced cardiotoxicity, the epidemiology of heart failure and coronary artery disease,

Table 1. Cardiovascular Disease, Treatment-Related Risk Factors, and Modifiers of Risk in Survivors of Childhood Cancer

Disease	Treatment-Related Risk Factor	Dose Exposure Associated With Highest Risk	Modifier of Risk
Cardiac structure/function			
Cardiomyopathy/heart failure	Anthracyclines Chest RT†	Anthracycline ≥ 250 mg/m²* Chest RT ≥ 35 Gy Anthracycline ≥ 100 mg/m²* and ≥ 15 Gy RT	Younger age (< 5 years) at diagnosis Hypertension Diabetes
Valvular disease	Chest RT	≥ 15 Gy	Younger age (< 5 years) at diagnosis Hypertension Dyslipidemia
Pericardial disease	Chest RT	≥ 15 Gy	
Arrhythmia	Chest RT	≥ 30 Gy	Hypertension Diabetes
Vascular disease			
Coronary artery disease	Chest RT	≥ 15 Gy	Hypertension Dyslipidemia Diabetes Obesity
Cerebrovascular disease	Cranial RT Neck RT	≥ 30 Gy	Hypertension

Abbreviation: RT, radiotherapy.
*Cumulative, doxorubicin equivalent dose.
†Any radiation in which the heart is in the field of treatment (mediastinal, thoracic, spinal, left or whole upper abdominal or total-body irradiation).

cardiovascular sequelae associated with newer cancer therapies, and strategies for screening and prevention, taking into consideration lessons learned from oncology and cardiology populations.

PATHOPHYSIOLOGY OF TREATMENT-RELATED HEART FAILURE

Anthracyclines such as doxorubicin are frequently used to treat childhood cancer, and there is a well-characterized dose-dependent risk of cardioxicity and heart failure with these agents. However, the exact mechanism of anthracycline-induced cardiotoxicity has not been fully elucidated. Early studies pointed to cardiotoxicity through reduction–oxidation reaction cycling and the generation of reactive oxygen species.[9] More recently, topoisomerase IIB (Top2) has been proposed to be a mediator of doxorubicin-mediated cardiac injury.[10] Experimental evidence for this model is supported by cardioprotection from doxorubicin in mice with cardiomyocyte-specific deletion of *Top2b*, the gene encoding Top2.[10] Other models suggest roles for impairment of mitochondrial biogenesis,[11] mitochondrial iron accumulation,[12] and transcription factors such as aryl hydrocarbon receptor[13] and hypoxia-inducible factor[14] in the pathogenesis of anthracycline-induced cardiotoxicity. These models are not necessarily mutually exclusive. For example, Top2 may mediate doxorubicin-induced myocardial injury by defective mitochondrial biogenesis and reactive oxygen species formation.[10] Caution must be applied to generalize in vitro and mice studies to the toxicity observed in humans. For example, many of the early mice studies used high doses of doxorubicin leading to acute cardiotoxicity, which do not truly recapitulate the chronic development of cardiomyopathy in humans.[9]

There is a paucity of preclinical studies that have evaluated chronic cardiotoxicity in the context of the growing and developing heart—an especially important consideration when extrapolating laboratory findings to survivors of childhood cancer. A recent study[15] used mouse models to show how mitochondria from the hearts of young mice and humans are primed for apoptosis, predisposing them to undergo cell death in response to genotoxic damage as a result of chemotherapy or radiation exposure. Conversely, mitochondria from adult hearts were more resistant to pro-apoptotic signaling, leading to cellular resistance to doxorubicin-induced cardiomyopathy.[15] These findings may explain, in part, the higher incidence of cardiotoxicity seen in children compared with adults[16] and argue for the use of pediatric-specific preclinical models to help elucidate the pathophysiology of cardiotoxicity in children. This can be done using a variety of platforms, taking into consideration the advantages and limitations of each model (Fig 1).

CHARACTERIZATION OF CVD RISK

In the general population, calculators such as the Framingham Risk Score[17] are routinely used to estimate CVD risk to guide therapeutic interventions (eg, aggressive management of cardiovascular risk factors [hypertension, dyslipidemia]) to lower the likelihood of developing cardiac events such as myocardial infarction or heart failure. However, risk estimates derived from the Framingham Risk Score do not account for key drivers of risk in survivors of cancer, such as anthracycline chemotherapy or chest RT. The need to understand survivor-specific risks has prompted the development of heart failure prediction models that take into account both clinical (age at diagnosis, sex) and treatment-related (anthracycline dose, chest RT) risk factors to reliably classify individuals into low, moderate, and high risk, (ie, the incidence of heart failure at 40 years is 0.5%, 2.4%, and 11.7%, respectively).[18] This can then provide a framework on which to determine future screening strategies and interventions.

However, there is marked individual variability in the prevalence and severity of heart failure in survivors of childhood cancer that is not explained exclusively by risk factors such as
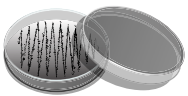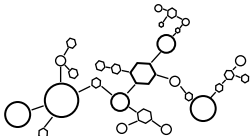
Model system	Examples	Strengths	Limitations
Cell culture systems	**Cardiomyocytes** (*contractile cells of heart tissue*) **IPS cells** (*induced pluripotent stem cells - differentiated into cardiomyocytes*) **H92 cardiomyocytes** (*immortalized cardiomyocyte cell line*)	**Cardiomyocytes** Cell morphology and functional integrity intact Mature ion channels **IPS cells** Renewable source Human sarcomere proteins and ion channels Genetically identical to patient from whom they were isolated **H92** Homogenous Replicate in culture **All cell lines** Low cost High throughput	**Cardiomyocytes** Diffcult to isolate and maintain in culture Limited mostly to rodent sources **IPS cells** Highly variable phenotype Altered expression of ion channels Varied sarcomere organization **H92** Immortalized (in contrast to terminally differentiated state in vivo) Similar to embryonic cardiomyocytes **All cell lines** Do not account for complex cell-to-cell interactions that are likely important in vivo
Animal models	**Zebrafish** **Rodents** (*mouse and rat*) **Dog** **Primate**	**Zebrafish** High-throughput phenotyping Ion channels similar to vertebrates **Rodents** Allows for tumor xenograft models Efficient genetic manipulation Functional measurements possible **Dog** Large numbers treated similar to human conditions—veterinary oncology **Primate** Closest similarity to humans	**Zebrafish** Anatomic differences: two-chambered heart Adult cardiac regeneration potential **Rodents** Lack of comorbidities such has hyperlipidemia and hypertension Different physiology: faster heart rate (10x) **Dog** Clinical trial infrastructure needs to be developed **Primate** Expensive Dwindling numbers of colonies in United States
Computer modeling	**O'Hara-Rudy** (*mathematical model derived from experimental data of 140 human hearts*)	High throughput Accounts for physiologic and genetic contributions Assessment of multiple ion channels	Limited understanding of utility in toxicity screening Lack of established standards for data deposited into database

Fig 1. Preclinical models of cardiotoxicity. Robust and diverse preclinical models that include cell culture systems, animal models, and computer simulations have provided a better understanding of the molecular and cellular mechanisms that mediate cancer treatment–related cardiotoxicity. The strengths and limitations of these preclinical models are highlighted. Studies are under way to combine information obtained from clinical observational studies with preclinical models, facilitating the development of novel cardioprotective strategies.

cumulative anthracycline dose.[19] Studies have used genome-wide association[20-22] or candidate gene[23-26] approaches to describe how key host genetic polymorphisms could result in differential risk for cardiotoxicity among survivors with otherwise similar clinical and treatment-related risk factors. Variations in genes involved in anthracycline transport and metabolism (eg, SLC28A3,[23] UGT1A6,[23,27] ABCC1,[26] HFE,[28,29] CBR3[25]), cardiomyocyte injury and antioxidant defense (eg, RARG,[20] CELF4[22,27], HAS3[21,27]), and cardiac remodeling (eg, RARG,[20] HAS3[21,27]) have been independently associated with increased risk of anthracycline-induced cardiotoxicity. Validation studies are under way to confirm many of the unique (and at times discrepant) findings from these studies. Ultimately, the ability to accurately identify individuals with a genetic predisposition for cardiotoxicity would provide the opportunity to tailor cancer therapy at the time of diagnosis, keeping in mind health outcomes that extend beyond the immediate treatment period.

EMERGING THERAPIES AND THE POTENTIAL FOR FUTURE CVD RISK

The introduction of targeted cancer therapies into adult oncology practice, while dramatically altering prognosis for certain cancers,

has brought to light new cardiovascular sequelae (Table 2).[30] Specifically, the recognition that abnormal activation of kinases plays a critical role in tumorigenesis led to introduction of small molecular tyrosine kinase inhibitors as a strategy for cancer treatment.[30] However, each tyrosine kinase inhibitor can target more than one kinase, resulting in adverse effects. For example, although both dasatinib and imatinib inhibit the Abelson tyrosine kinase in Philadelphia chromosome (Ph)–positive chronic myelogenous leukemia (CML) and acute lymphoblastic leukemia (ALL), each kinase inhibitor targets a diverse array of additional kinase receptors, leading to a different toxicity profile for each drug.[30] Dasatinib can lead to pulmonary hypertension and possibly arterial ischemic events, whereas imatinib is relatively well tolerated in adults with Ph-positive CML and ALL.[31] Sorafenib, an FLT3 kinase inhibitor typically used in AML, attenuates vascular endothelial growth factor receptors, leading to hypertension, cardiomyopathy, ischemia, and vascular complications in up to approximately 25% of patients.[32] Crizotinib, an anaplastic lymphoma kinase inhibitor used to treat a number of solid cancers, including neuroblastoma, can result in bradycardia.[33] Finally, immune checkpoint inhibitors (eg, inhibitors of programmed cell death-1) have been shown to have unprecedented activity in hematologic malignancies such as Hodgkin lymphoma but in rare instances can cause fulminant myocarditis.[34]

Table 2. Targeted Cancer Therapies and Reported Cardiovascular Toxicities

Class	Drug*	Cellular Target	Cardiovascular Toxicity
VEGF signaling pathway inhibitors	Bevacizumab, afibercept	VEGF signaling pathway	Hypertension, venous or arterial thromboembolic events, proteinuria, cardiomyopathy
TKI with anti-VEGF activity	Sunitinib, sorafenib, pazopanib, axitinib, cabozantinib, vandetanib	VEGF receptors and other kinases	
Multitargeted TKIs	Dasatinib	ABL, ABL mutants (except T3151), and other kinases	Pulmonary hypertension, arterial events, QT interval prolongation
	Nilotinib	ABL, ABL mutants (except T3151), and other kinases	Coronary, cerebral, peripheral arterial events, QT interval prolongation
	Ponatinib	ABL, ABL mutants (including T3151), and other kinases	Coronary, cerebral, peripheral arterial events
Anaplastic lymphoma kinase inhibitors	Crizotinib, ceritinib	Anaplastic lymphoma kinase	Bradycardia, QT interval prolongation
PI3K-AKT-mTOR inhibitors	Everolimus, temsirolimus	PI3K-AKT-mTOR signaling pathway	Cardiometabolic impairments: dyslipidemia, hyperglycemia
Bruton's kinase inhibitors	Ibrutinib	Bruton's tyrosine kinase	Atrial fibrillation, other cardiac arrhythmias
Immunomodulatory drugs	Thalidomide, lenalidomide	Lymphoid transcription factors IKZF1 and IKZF3	Venous or arterial thromboembolic events
Proteasome inhibitors	Carfilzomib	Ubiquitin-proteasome system	Cardiomyopathy, hypertension, venous or arterial thromboembolic events, cardiac arrhythmia
Immune checkpoint inhibitors	Pembrolizumab, nivolumab	Programmed cell death 1	Myocarditis

NOTE. Adapted with permission from Moslehi.[30]
Abbreviations: ABL, Abelson tyrosine kinase; AKT, protein kinase B; IKZF, IKAROS family zinc finger; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.
*Examples of agents that have shown preclinical or clinical efficacy in childhood cancer.

EARLY SCREENING AND CVD DETECTION

In the general population, biologic markers are widely used to detect subclinical or overt CVD, identify risk for future disease, and guide treatment strategies.[35] As an example, lipid markers (total cholesterol, LDL, or HDL) are accepted screening markers of CVD risk and measures of response to lipid-lowering therapy. In heart failure, N-terminal pro brain natriuretic peptide is a guideline-recommended measure of diagnosis and prognosis.[36] Two-dimensional echocardiography is widely used to detect abnormalities in cardiac left ventricular ejection fraction (LVEF), diastolic function, and valvular disease. More recently, advanced imaging modalities, such as tissue characterization by cardiac magnetic resonance imaging (MRI)[37,38] and echocardiography-derived myocardial deformation imaging (strain), have been used to detect subclinical cardiac dysfunction in populations at risk for heart failure (eg, after myocardial infarction).[39]

Although guidelines exist for the application of blood biomarkers, echocardiography, and cardiac MRI in the general population,[36] the timing and frequency of these measures in at-risk survivors of childhood cancer has not been established. Research has suggested that elevated troponin and N-terminal pro brain natriuretic peptide levels during anthracycline exposure can be associated with subclinical cardiac dysfunction,[40,41] but the association between these early findings and subsequent clinically significant disease (eg, symptomatic heart failure) is less clear. Studies evaluating myocardial strain imaging have demonstrated a high prevalence of abnormal longitudinal strain in childhood survivors exposed to anthracyclines and/or chest radiotherapy, despite the presence of preserved systolic function (LVEF).[42] Longitudinal studies are needed to examine the prognostic value of abnormal strain in these survivors. Cardiac MRI has been used to improve functional characterization[43] and to detect adverse LV remodeling, including fibrosis, in survivors of childhood cancer, but as with strain, the long-term prognostic utility of these abnormalities has yet to be determined in this population.[38]

Despite these limitations, for certain diseases, such as anthracycline-related cardiomyopathy, routine screening for asymptomatic cardiac systolic dysfunction (abnormal LVEF) may be cost effective, allowing for pharmacologic and lifestyle interventions to slow the progression to symptomatic disease.[44,45] With this in mind, the International Late Effects of Childhood Cancer Guideline Harmonization Group provided a uniform guideline for cardiomyopathy screening (Fig 2).[1] Routine surveillance is recommended for survivors at high risk for cardiomyopathy, defined as those with anthracycline exposure ≥ 250 mg/m², or ≥ 35 Gy chest RT, or a combination of ≥ 100 mg/m² of anthracyclines and ≥ 15 Gy chest RT. Although screening may be reasonable for survivors with lower-dose exposures, evidence directly comparing specific screening modalities or schedules is lacking. On the basis of expert consensus, echocardiography remains the recommended primary surveillance modality, is to begin no later than 2 years after exposure, and should be repeated a minimum of every 5 years thereafter. Cardiology consultation is strongly recommended for those with asymptomatic cardiomyopathy.[1] Simulation models to estimate the efficacy of surveillance guidelines[44,45] suggest that although routine surveillance reduces risks for heart failure and extends life expectancy, less-frequent assessments may be more cost effective for certain subsets of survivors who are at lower risk.

Characterization of vascular disease in survivors of childhood cancer is also important, because accelerated atherosclerosis is a contributing factor to coronary and carotid artery disease after cancer therapy.[3] Studies among survivors of Hodgkin lymphoma were the first to recognize the association between chest RT and

General recommendation
Survivors treated with anthracyclines and/or chest radiation and their providers should be aware of the risk of cardiomyopathy.

Who needs cardiomyopathy surveillance? *Anthracyclines*
Cardiomyopathy surveillance *is recommended* for survivors treated with high dose (≥ 250 mg/m^2) anthracyclines.
Cardiomyopathy surveillance *is reasonable* for survivors treated with moderate dose (≥ 100 to < 250 mg/m^2) anthracyclines.
Cardiomyopathy surveillance *may be reasonable* for survivors treated with low dose (< 100 mg/m^2) anthracyclines.

Who needs cardiomyopathy surveillance? *Chest radiation*
Cardiomyopathy surveillance *is recommended* for survivors treated with high dose (≥ 35 Gy) chest radiation.
Cardiomyopathy surveillance *may be reasonable* for survivors treated with moderate dose (≥ 15 to < 35 Gy) chest radiation.
No recommendation can be formulated for cardiomyopathy surveillance for survivors treated with low dose (< 15 Gy) chest radiation with conventional fractionation.

Who needs cardiomyopathy surveillance? *Anthracyclines + chest radiation*
Cardiomyopathy surveillance *is recommended* for survivors treated with moderate-high dose anthracyclines (≥ 100 mg/m^2) and moderate-high dose chest radiation (≥ 15 Gy).

What surveillance modality should be used?
Echocardiography *is recommended* as the primary cardiomyopathy surveillance modality for assessment of left ventricular systolic function in survivors treated with anthracyclines and/or chest radiation.
Radionuclide angiography or cardiac magnetic resonance imaging *may be reasonable* for cardiomyopathy surveillance in at risk survivors for whom echocardiography is not technically feasible/optimal.
Assessment of cardiac blood biomarkers (eg, natriuretic peptides and troponins) *is not recommended* as the primary cardiomyopathy surveillance in at-risk survivors.

At what frequency should surveillance be performed for *high-risk* survivors?
Cardiomyopathy surveillance *is recommended* for *high-risk* survivors to begin no later than 2 years after completion of cardiotoxic therapy, repeated at 5 years after diagnosis, and continued every 5 years thereafter.
More frequent cardiomyopathy surveillance *is reasonable* for *high-risk* survivors.
Lifelong cardiomyopathy surveillance *may be reasonable* for *high-risk* survivors.

At what frequency should surveillance be performed for *moderate/low-risk* survivors?
Cardiomyopathy surveillance *is reasonable* for *moderate/low-risk* survivors to begin no later than 2 years after completion of cardiotoxic therapy, repeated at 5 years after diagnosis, and continue every 5 years thereafter.
More frequent cardiomyopathy surveillance *may be reasonable* for *moderate/low-risk* survivors.
Lifelong cardiomyopathy surveillance *may be reasonable* for *moderate/low-risk* survivors.

Fig 2. Harmonized recommendations for cardiomyopathy surveillance for survivors of childhood cancer. Green represents a strong recommendation with a low degree of uncertainty (high quality evidence). Yellow (moderate-quality evidence) and orange (weak-quality evidence) represent moderate-level recommendations. Red represents a recommendation against a particular intervention, with harms outweighing benefits. ACE, angiotensin-converting enzyme; AHA, American Heart Association; ESC, European Society of Cardiology; LV, left ventricular. Reprinted with permission.[1]

> **At what frequency should surveillance be performed for survivors who are pregnant or planning to become pregnant?**
>
> Cardiomyopathy surveillance *may be reasonable* prior to pregnancy or in the first trimester for all female survivors treated with anthracyclines and/or chest radiation
>
> No recommendations can be formulated for the frequency of ongoing surveillance in pregnant survivors who have normal LV systolic function immediately prior to or during the first trimester of pregnancy.
>
> **What should be done when abnormalities are identified?**
>
> Cardiology consultation *is recommended* for survivors with asymptomatic cardiomyopathy following treatment with anthracyclines and/or chest radiation.
>
> Based on data from other groups of patients with asymptomatic cardiomyopathy, treatment with ACE inhibitors *may be reasonable* for survivors with asymptomatic cardiomyopathy following treatment with anthracyclines and/or chest radiation.
>
> **What advice should be given regarding physical activity?**
>
> Regular exercise, as recommended by the AHA and ESC, offers potential benefits to survivors treated with anthracyclines and/or chest radiation.
>
> Regular exercise *is recommended* for survivors treated with anthracyclines and/or chest radiation who have normal LV systolic function.
>
> Cardiology consultation *is recommended* for survivors with asymptomatic cardiomyopathy to define limits and precautions for exercise.
>
> Cardiology consultation *may be reasonable* for *high-risk* survivors who plan to participate in high-intensity exercise to define limits and precautions for physical activity.

Fig 2. (Continued).

future coronary artery disease.[46] To date, investigations of vascular biomarkers and functional testing in survivors of cancer have been limited by heterogeneous populations and small numbers of survivors studied. Brouwer et al[47] quantified a panel of blood biomarkers of arterial injury (plasminogen activator inhibitor, plasminogen activator inhibitor type-1), and imaging (intima-media thickness) among 277 survivors of childhood cancer (median age, 18 years; range, 5 to 31 years after treatment).[47] Survivors of childhood cancer who received RT had increased intima-media thickness outside the radiation field and had higher blood biomarkers of arterial injury compared with sibling controls, suggesting subclinical vascular injury may be present decades after completion of cancer-directed therapy.[47]

Challenges impede the widespread implementation of these vascular screening modalities. Serum biomarkers have been variably applied, and the ideal biomarker(s) to detect or diagnose subclinical disease, or even determine prognosis, remains elusive. Lack of reproducibility, interlab and intrapatient variability, and challenges in the interpretation of these biomarkers in asymptomatic individuals have limited their use in routine clinical practice. Additional studies are needed to define the relationship between one-time measures of subclinical vascular disease and subsequent progression to clinically overt disease. Continued follow-up of survivors across their lifespan is necessary to test and develop evidence-based recommendations for screening and intervention.

STRATEGIES FOR CVD PREVENTION

The existing large body of observational studies has facilitated the development of CVD prevention trials across the survivorship spectrum. Trials covering primary prevention (before or during cancer treatment), secondary prevention (after completion of treatment), as well as integrated approaches to improve CVD screening and the management of modifiable cardiovascular risk factors (Table 3).

Primary Prevention

In the oncology community, it is generally understood that anthracyclines and/or chest RT should only be used if they provide established antitumor efficacy over less cardiotoxic regimens.[48] If anthracyclines cannot be avoided, several strategies to minimize cardiotoxicity have been proposed.

Less cardiotoxic analogs. In adults, liposomal-encapsulated doxorubicin is favored over conventional doxorubicin, but pediatric randomized controlled trial (RCT) data are lacking.[49] An RCT comparing the doxorubicin analog pirarubicin with daunorubicin in the treatment of childhood leukemia demonstrated equivalent survival and seemingly less subclinical cardiotoxicity.[50] Anthracycline-loaded nanoparticles also seem promising,[51] but studies have been limited to animal and in vitro models.

Longer anthracycline infusion durations. Although an infusion duration of $\geq$ 6 hours has been shown to be cardioprotective in adults, RCTs in childhood leukemia have not identified a protective effect.[52]

Cardioprotective agents. RCTs in children with different malignancies show some relatively short-term (< 10 years from treatment) cardioprotection with dexrazoxane, whereas concerns about interference of dexrazoxane with antitumor efficacy of anthracyclines and increased risk of secondary malignancies have not been substantiated.[53-56] An ongoing Children's Oncology Group (COG) study (ALTE11C2; ClinicalTrials.gov identifier: NCT0179012) is examining the long-term (> 10 years) efficacy of

Table 3. Cardiovascular Disease Prevention Studies in Survivors of Childhood Cancer				
Study Objective	Population (Setting)	Study Design	Primary Outcome	Current Status
Primary prevention				
Determine the long-term efficacy of dexrazoxane cardioprotection	Individuals treated in pediatric clinical trials that featured up-front random assignment to ± dexrazoxane (COG)	Prospective cross-sectional study	Echocardiographic measures of ventricular function and remodeling	Enrolling participants NCT0179012 PMID 26014292
Develop a cardiomyopathy risk prediction tool using imaging, blood biomarker, and genomic information for primary as well as secondary prevention	A cohort of children with newly diagnosed cancer and a second cohort of anthracycline-treated survivors (six North American sites)	Prospective cohort study	Echocardiographic measures of ventricular function, remodeling, and strain	Analyzing data NCT01805778 PMID 28774277
Secondary prevention				
Determine if a survivorship care plan counseling intervention can increase rates of cardiomyopathy screening	Adult-age survivors at high risk of cardiomyopathy (CCSS)	RCT	Rates of cardiac imaging after 12 months	Primary analysis completed NCT01003574 PMID 25366684
Determine the safety and efficacy of carvedilol for heart failure risk reduction in long-term survivors treated with high-dose anthracyclines	Long-term (≥ 2 years from end of cancer treatment) survivors; treated with cumulative anthracycline dose ≥ 250 mg/m^2 (COG)	RCT	Echocardiographic measures of ventricular function and remodeling	Enrolling participants NCT02717507 PMID 27716152
Targeting conventional cardiovascular risk factors				
Determine if a web-based diet and activity intervention can achieve meaningful weight loss	Adult-age, obese survivors of acute lymphoblastic leukemia (CCSS)	RCT	Weight loss after 24 months	In follow-up NCT02244411
Determine if a web-based physical activity intervention can improve fitness	Childhood patients with ALL within 3 months of completing therapy (COG)	RCT	Difference in the physiologic cost index 24 weeks after intervention	Enrolling participants NCT03223753
Determine if a survivorship care plan counseling intervention can improve control of cardiovascular risk conditions	Adult-age survivors at high risk of premature cardiovascular disease (CCSS)	RCT	Blood pressure, blood cholesterol, sugar, and lipid measurements after 12 months	Enrolling participants NCT03104543

Abbreviations: ALL, acute lymphoblastic leukemia; CVD, cardiovascular disease; CCSS, Childhood Cancer Survivor Study; COG, Children's Oncology Group; NCT, ClinicalTrials.gov identifier; PMID, PubMed identification number; RCT, randomized controlled trial.

dexrazoxane in survivors treated in RCTs across a range of anthracycline exposures (100 to 360 mg/m^2). Other agents, such as coenzyme Q10[57] and amifostine,[58] have not been shown to be effective in small pediatric RCTs; however, carvedilol may have potential efficacy.[59] Strategies to minimize the risk of cardiotoxicity resulting from chest RT include limiting the radiation dose and volume, tailoring radiation fields to exclude as much of the heart as possible, deep-inspiration breath holding, or use of intensity-modulated RT or proton RT.[16] Unfortunately, despite these efforts, cardiotoxicity can still occur, and secondary prevention is thus necessary.

Secondary Prevention

Strategies for intervening in survivors who have been exposed to cardiotoxic therapies have mostly been adapted from studies in adults with asymptomatic cardiac dysfunction resulting from causes other than anthracyclines. These include early screening and initiation of angiotensin-converting enzyme (ACE) inhibitors and β-blockers to prevent the progression of subclinical cardiac dysfunction to symptomatic heart failure.[36] Several animal studies have shown that statins protect against anthracycline-induced cardiotoxicity,[60,61] and there have been some retrospective[62] and prospective[63] human studies to suggest that these agents protect against deterioration of cardiac function in adults with cancer. The aldosterone antagonist spironolactone has also been shown to prevent cardiac deterioration in patients with breast cancer.[64]

In survivors of childhood cancer, timely dissemination of a survivorship care plan and counseling can result in a two-fold increase in cardiomyopathy screening rates.[65] However, there are few studies to guide which pharmacologic agents, if any, should be used once cardiac dysfunction has been identified. A retrospective study of 18 survivors treated with anthracycline showed that although the ACE inhibitor enalapril improved LV structure and function in individuals with cardiac dysfunction,[66] this was short lived. The only RCT in survivors of childhood cancer treated with anthracycline assessed the effectiveness of enalapril versus placebo in survivors with normal LVEF but at high risk for heart failure because of a history of cardiac dysfunction.[67] The study failed to show an effect on its primary outcome (myocardial contractility index), but there was improvement in other cardiac measures (LV wall stress). Because β-blockers may be more likely to reverse the chronic cardiac remodeling than ACE inhibitors, an ongoing COG study (ALTE1621) is assessing the effect of carvedilol (ν placebo) on prognostic markers of LV remodeling in approximately 250 survivors treated with high-dose (≥ 250 mg/m^2) anthracyclines (ClinicalTrials.gov identifier: NCT0271750).

Targeting Conventional Cardiovascular Risk Factors

Multiple studies in survivors of childhood and adult cancer show that conventional cardiovascular conditions like hypertension, diabetes, and dyslipidemia are more prevalent[68,69] and tend to occur at younger ages compared with sibling controls or the

general population,[70-72] increasing the likelihood of under-diagnosis and under-treatment. Survivors exposed to anthracycline who have hypertension or diabetes are at an especially high risk of developing CVD later in life.[69] Lifestyle factors are also important. In survivors of Hodgkin lymphoma, vigorous exercise has been associated with a lower risk of CVD in a dose-dependent manner, independent of clinical and treatment-related risk factors,[73] and should be encouraged in all survivors of cancer per established guidelines.[1,16] Greater adherence to healthier lifestyle patterns (eg, healthier [Mediterranean] diet) has also been associated with reduced CVD risk in adult survivors of cancer.[68] At present, there are several clinical trials that have leveraged the information obtained from these observational studies to reduce under-diagnosis and under-treatment of modifiable cardiovascular risk factors (eg, ClinicalTrials.gov identifier: NCT03104543) and to improve adherence to recommended lifestyle practices (eg, ClinicalTrials.gov identifiers: NCT02244411 and NCT03223753).

SUMMARY AND FUTURE DIRECTIONS

The evolution of childhood cancer treatment during the past four decades (eg, reduction in cumulative anthracycline dose, elimination of or reduction in dose and/or volume of radiation to the heart) has brought with it a need to understand how temporal changes in both cancer treatment and screening for late effects have altered health outcomes in long-term survivors. Armstrong et al[74] from the Childhood Cancer Survivor Study (CCSS) recently reported a 50% reduction in the cumulative incidence of CVD-related late mortality (death > 5 years from diagnosis) between survivors of childhood cancer treated in the 1970s and those treated in the 1990s. Studies are under way to examine whether there has been a comparable decrease in the incidence of other CVD-related outcomes (eg, nonmortality). This information is necessary for the development of comprehensive (clinical, treatment, genetic) risk prediction models relevant to survivors treated with contemporary approaches.

The introduction of newer targeted agents has, in some instances, facilitated the decrease in treatment intensity for childhood cancer (eg, Ph-positive [like] ALL or CML). As such, there is a need for long-term follow-up studies in children exposed to these agents, keeping in mind the relatively small number of patients treated to date and the long latency of CVD in survivors of childhood cancer. Clinical trials networks such as the COG or large cohort studies such as the CCSS could provide the necessary infrastructure to examine short-term (COG) and long-term cardiovascular (COG, CCSS) sequelae in children treated with newer targeted therapies.

The growing number of survivors of childhood cancer at risk for CVD makes it imperative to continue our efforts to investigate the pathophysiology of cardiac and vascular injury resulting from established or newer cancer treatments. Longitudinal studies are needed to better characterize the prognostic effect of subclinical markers of cardiovascular injury, facilitating much-needed interventions to halt or reverse the trajectory of chronic CVD. These efforts will undoubtedly be strengthened by ongoing multidisciplinary collaborations between the oncology, cardiology, primary care, and other subspecialty communities.[1,16,75]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

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■■■

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Cardiovascular Disease in Survivors of Childhood Cancer: Insights Into Epidemiology, Pathophysiology, and Prevention

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