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AHA SCIENTIFIC STATEMENT

Cardiovascular Toxicity in Patients Treated for Childhood Cancer: A Scientific Statement From the American Heart Association

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ABSTRACT: The field of cardio-oncology has expanded over the past 2 decades to address the ever-increasing issues related to cardiovascular disease in patients with cancer and survivors. There is increasing recognition that nearly all cancer treatments pose some short- or long-term risk for development of cardiovascular disease and that pediatric patients with cancer may be especially vulnerable to cardiovascular disease because of young age at treatment and expected long life span afterward. Anthracycline chemotherapy and chest-directed radiotherapy are the most well-studied cardiotoxic therapies, and dose reduction, use of cardioprotection for anthracyclines, and modern radiotherapy approaches have contributed to improved cardiovascular outcomes for survivors. Newer treatments such as small-molecule inhibitors, antibody-based cytotoxic therapy, and immunotherapy have expanded options for previously difficult-to-treat cancers but have also revealed new cardiotoxic profiles. Application of effective surveillance strategies in patients with cancer and survivors has been a focus of practitioners and researchers, whereas the prevention and treatment of extant cardiovascular disease is still developing. Incorporation of new strategies in an equitable manner and appropriate transition from pediatric to adult care will greatly influence long-term health-related outcomes in the growing population of childhood cancer survivors at risk for cardiovascular disease.

Key Words: AHA Scientific Statements ■ cardio-oncology ■ cardiotoxicity ■ child ■ drug therapy ■ heart failure ■ neoplasms ■ radiotherapy

The field of cardio-oncology, also referred to as onco-cardiology, has grown over the past 2 decades to address the ever-increasing cardiovascular issues of patients with cancer and survivors. With >18 million cancer survivors in the United States alone,[1] much of the focus of cardio-oncology has been on adults. Although children represent ≈5% of new cancer diagnoses each year, the high 5-year survival rate (>85%) in this age group equates to nearly 500 000 survivors of pediatric cancer, which, when coupled with decades of life expectancy after cancer treatment, results in a growing and aging population at risk for therapy-related cardiovascular disease (CVD).[2]

Although the first evidence for cancer treatment–related cardiotoxicity (CTRC) emerged shortly after the introduction of chest-directed radiotherapy and anthracycline chemotherapy in the late 1960s and 1970s,[3,4] there has since been an increasing recognition that many chemotherapeutic agents pose some short- or longer-term CVD risk. These include systolic ventricular dysfunction, diastolic ventricular dysfunction, coronary artery disease (CAD), arrhythmias, valvular disease, autonomic dysfunction, endothelial dysfunction, and pericardial disease.[5–7]

This document, focused on current data in pediatric patients and survivors of pediatric cancer, builds on the prior American Heart Association scientific statement[6] and provides updates on emerging concepts related to established cardiotoxic therapies while also expanding to include consideration of novel agents. In addition, we focus on issues related to transition of care after cancer treatment, examine the role for cardiovascular risk factors and exercise, and provide an update on the clinical

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management of cardiovascular complications, particularly cardiac dysfunction.

ANTHRACYCLINE CARDIOTOXICITY

Anthracyclines are highly effective and commonly used pediatric cancer therapies,[8] but they confer a risk of dose-dependent cardiotoxicity (Figure 1 and Table).[40] Molecular mechanisms of anthracycline cardiotoxicity include topoisomerase II–mediated DNA damage and reactive oxygen species formation,[41] which may result in cardiomyocyte vacuolization and myofibrillar loss, atrophy, and cell death.[40,42] The cardiotoxic effects of anthracyclines most commonly manifest clinically as cardiomyopathy/left ventricular (LV) dysfunction, although pericarditis or arrhythmia may also occur.[43] The degree of cardiotoxicity varies by anthracycline analog. Recent international multicohort efforts have shown that, compared with the same dose of doxorubicin, daunorubicin confers half the risk of heart failure, and mitoxantrone confers a 10-fold increased risk.[44]

Early manifestations of anthracycline cardiotoxicity include reduction in LV mass, relative wall thickness, and cardiac function.[45,46] A recent clinical trial in pediatric acute myeloid leukemia documented a >20% incidence of grade II cardiotoxicity (LV ejection fraction [LVEF] <50% or fractional shortening <24%) during and shortly after treatment completion.[47] Although most patients will not develop overt cardiac dysfunction on therapy, a mild decrement in LVEF or LV fractional shortening is observed on average.[45] During survivorship, these changes in cardiac size and function may progress.[48] The reduced relative wall thickness results in increased myocardial wall stress and vulnerability to secondary stressors such as hypertension, which can precipitate the development of heart failure.[48–50] High-dose (≥250 mg/m^2) doxorubicin equivalent exposure is associated with a 7.2% 30-year cumulative incidence of heart failure, which is a 7-fold higher rate than in survivors who did not receive anthracycline therapy.[51] In comparison, siblings of survivors have an estimated heart failure incidence of only 0.3% by 45 years of age.[50] Recent data suggest that some long-term survivors may develop an alternative remodeling phenotype that includes reduced LV cavity size with preserved or increased relative wall thickness, although this phenotype may be driven more by radiotherapy than chemotherapy.[52] However, the clinical implications of these findings, including response to standard "heart failure" therapies, have not been established. In addition, a growing body of literature has sought to elucidate the interindividual variability in heart failure risk and cardiac remodeling patterns that is not explained exclusively by cumulative anthracycline dose exposure.[53] Studies have highlighted how host germline genetic polymorphisms associated with anthracycline metabolism, antioxidant defense, and cardiomyocyte injury could result in differential risk for cardiotoxicity among survivors with otherwise similar treatment-related and other clinical risk factors.[54–60]

Various strategies have been explored to mitigate the cardiotoxic effect of anthracyclines in children. Although

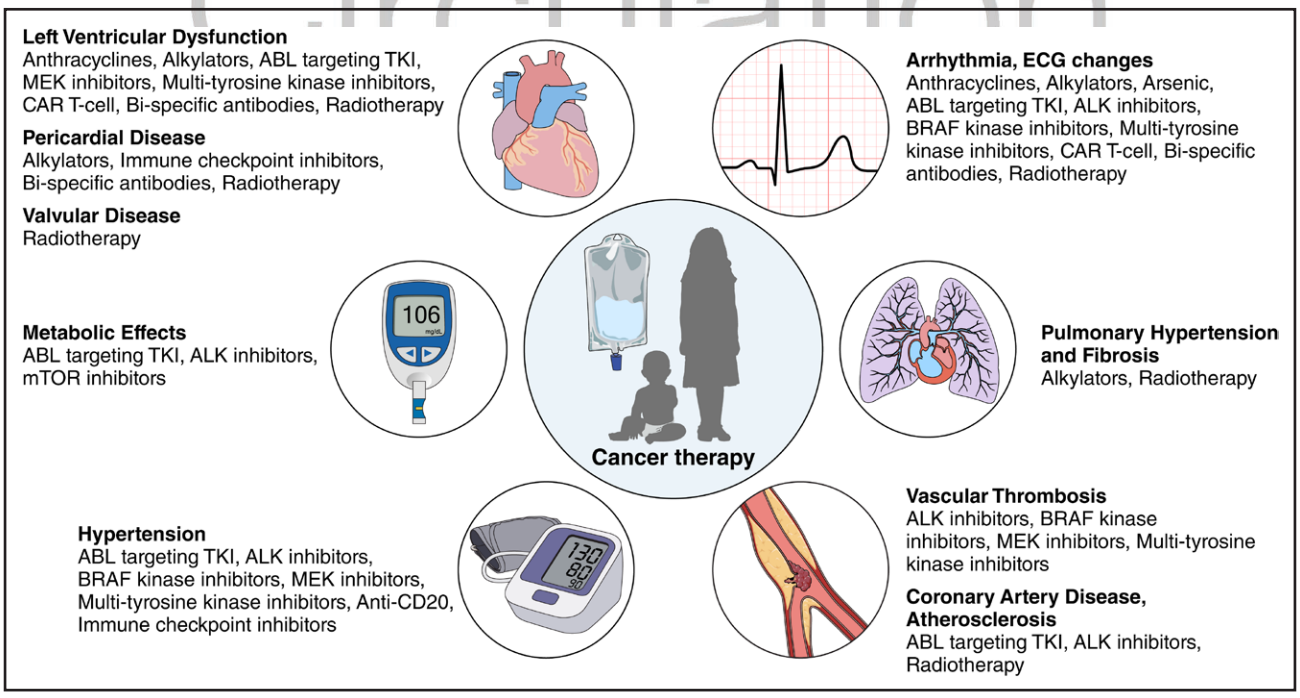

Figure 1. Pharmacological and nonpharmacological cancer therapies with reported effects on the cardiovascular system in pediatric patients.

ALK indicates anaplastic lymphoma kinase; BRAF, B-Raf proto-oncogene, serine/threonine kinase; CAR, chimeric antigen receptor; MEK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; and TKI, tyrosine kinase inhibitor.

Table. Pharmacological and Nonpharmacological Therapies Used to Treat Pediatric Patients With Cancer, Including Selected Indications and Cardiotoxic Effects

	Selected pediatric malignancies treated	LV dysfunction	Myocarditis	Pericardial disease	Valvular disease	Arrhythmia, electrocardiographic changes	Hypertension	Pulmonary hypertension, pulmonary fibrosis	Vascular thrombosis	Atherosclerosis, CAD	Metabolic effects (hyperglycemia, hyperlipidemia)
Conventional chemotherapy agents											
Anthracyclines (eg, daunorubicin, doxorubicin, epirubicin, idarubicin, and mitoxantrone)	Sarcomas, metastatic solid tumors, acute myeloid leukemia, lymphoma, recurrent cancers	X		X*		X					
Alkylators (eg, cyclophosphamide, melphalan, busulfan, and carmustine)	Sarcomas, solid tumors, leukemia, lymphoma, recurrent cancers, stem cell transplantation	X		X		X		X	X*		
Antimetabolites (eg, 5-fluorouricil and cytarabine)	Hepatoblastoma, acute leukemias					X	X*				
Arsenic	Acute promyelocytic leukemia			X*							
Retinoic acid	Acute promyelocytic leukemia	X		X*		X					
Small-molecule kinase inhibitors											
ABL-targeting TKI (eg, imatinib, dasatinib, and nilotinib)	Chronic myelogenous leukemia, Philadelphia chromosome–positive acute lymphoblastic leukemia	X				X	X	X*	X*	X	X
ALK inhibitor (eg, crizotinib, lorlatinib)	Anaplastic large-cell lymphoma					X	X		X	X	X
FLT3 inhibitor (eg, gilteritinib and midostaurin)	Acute myeloid leukemia	X*				X*	X*				
RET inhibitor (eg, selpercatinib)	Recurrent cancers, thyroid cancer					X*	X*				X*
BRAF kinase inhibitor (eg, vemurafenib and dabrafenib)	Low-grade glioma, Langerhans cell histiocytosis					X	X		X		
MEK inhibitor (eg, trametinib)	Low-grade glioma, Langerhans cell histiocytosis	X					X		X		
Bruton TKI (eg, ibrutinib)	Lymphoma, GVHD	X*				X*	X*				
Multi-TKI (eg, sorafenib, sunitinib, pazopanib, lenvatinib, cabozantinib, and regorafenib)	Sarcomas, thyroid cancer, acute myeloid leukemia, recurrent cancers	X				X	X		X		
Small-molecule nonkinase inhibitors											
Proteasome inhibitor (eg, bortezomib)	Non-Hodgkin lymphoma	X*				X*	X*	X*	X*		
Histone deacetylase inhibitor (eg, panobinostat and vorinostat)	Recurrent cancers					X*					
mTOR inhibitor (eg, temsirolimus)	Recurrent cancers						X*				X
BCL2 inhibitor (eg, venetoclax)	Acute myeloid leukemia		X*								
Antibody conjugates											
Anti-CD20 (eg, rituximab)	Non-Hodgkin lymphoma	X*				X*	X				X*
Anti-CD22 (eg, inotuzumab)	Relapsed acute lymphoblastic leukemia					X*					
Anti-EGFR (eg, cetuximab)	Pediatric solid tumors (squamous cell carcinoma of the head and neck, colorectal cancer)	X*				X*	X*				
Anti-VEGF (eg, bevacizumab)	Pediatric solid tumors, CNS tumors, thyroid cancer, recurrent cancers	X*				X*	X*		X*		
Immunotherapies											
Chimeric antigen receptor T cells (eg, tisagenlecleucel)	Recurrent/refractory acute lymphoblastic leukemia, non-Hodgkin lymphoma	X				X	X*		X*		X*
Immune checkpoint inhibitors (eg, ipilimumab, nivolumab, and pembrolizumab)	Recurrent/refractory lymphoma, metastatic melanoma, Hodgkin lymphoma, alveolar soft part sarcoma, hepatocellular carcinoma, pediatric rare tumors		X*	X		X*	X		X*		X*
Bispecific antibodies (eg, blinatumomab and dinutuximab)	Recurrent/refractory acute lymphoblastic leukemia, neuroblastoma	X		X		X	X*				X*

(*Continued*)

Table. Continued

	Selected pediatric malignancies treated	LV dysfunction	Myocarditis	Pericardial disease	Valvular disease	Arrhythmia, electrocardiographic changes	Hypertension	Pulmonary hypertension, pulmonary fibrosis	Vascular thrombosis	Atherosclerosis, CAD	Metabolic effects (hyperglycemia, hyperlipidemia)
Nonpharmacological											
Radiotherapy	Multiple	X		X	X		X*	X	X*	X	

Presence of an X indicates reported cardiotoxic effect.[9–39]

ALK indicates anaplastic lymphoma kinase; BCL2, B-cell lymphoma 2; BRAF, B-Raf proto-oncogene, serine/threonine kinase; CAD, coronary artery disease; CNS, central nervous system; EGFR, epidermal growth factor receptor; FLT3, fms-like tyrosine kinase 3; GVHD, graft-vs-host disease; LV, left ventricular; MEK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; RET, rearranged drug transfection; TKI, tyrosine kinase inhibitor; and VEGF, vascular endothelial growth factor.

*Data based largely on adult patients with cancer.

beneficial in adults, prolonged infusion of doxorubicin to decrease peak plasma concentration did not demonstrate a reduction in the risk of developing cardiomyopathy in children with acute leukemia.[61] In contrast, concomitant administration of dexrazoxane has demonstrated consistent efficacy in reducing early and late cardiotoxicity in children and adults without compromising cancer-related outcomes.[45–47,62,63] The cardioprotective effect of dexrazoxane is mediated through its inhibition of the binding of anthracycline to topoisomerase IIb.[64] Concerns for higher rates of second malignant neoplasms in dexrazoxane-treated patients initially limited its use, although more recent studies with longer follow-up have confirmed its safety and efficacy.[65] As a result, recent international consensus guidelines recommend administration of dexrazoxane in children expected to receive ≥250 mg/m^2 of cumulative doxorubicin equivalents.[63] Liposomal encapsulation of doxorubicin has been investigated as an alternative cardioprotective strategy because it provides reduced drug penetrance into cardiac tissue.[66] Adult studies have demonstrated lower cardiomyopathy/heart failure risk with liposomal compared with standard anthracyclines, although definitive data in pediatrics are lacking.[67,68] Recent preclinical and early clinical studies of the anthracycline derivatives aclarubicin and diMe-doxorubicin demonstrate how selection of anthracyclines with a more narrow mechanism of action specific to chromatin damage, without the characteristic topoisomerase II–mediated DNA damage, may achieve comparable antitumor efficacy without cardiotoxicity, making this a promising approach for future study.[69]

RADIOTHERAPY CARDIOTOXICITY

Chest-directed radiotherapy is a well-established risk factor for late CVD in childhood cancer survivors (Figure 1 and Table).[70] This includes heart failure, CAD, valvular disease, arrhythmia, and pericardial disease.[51,71,72] Initial studies linking radiotherapy exposures to CVD typically used prescribed dose or calculated mean dose to the entire heart.[73,74] Adult data suggest that among breast cancer and Hodgkin lymphoma survivors, there is no threshold dose below which the risk of cardiac disease is absent.[75,76] Similar findings have not been replicated in children, with multiple studies suggesting that mean whole-heart doses of <5 to 10 Gy do not appear to significantly increase the risk of late cardiac disease.[51,72] However, it is noteworthy that in current studies of even long-term survivors of childhood cancer, the majority are only in their fourth or fifth decade of life, a time before which cardiac disease becomes prevalent in the general population.

More recently, calculation of mean radiotherapy doses to cardiac substructures, including coronary arteries, cardiac valves, and the 4 chambers of the heart, has allowed improved prediction of late CVD risk in childhood cancer survivors, demonstrating no threshold radiotherapy dose below which there is no increase in late cardiac risk. This is most pronounced in investigations into the relationship between mean radiotherapy dose and risk of CAD: For each 1-Gy increase in mean dose to the right coronary artery, there was a 28.7% increase in the risk of CAD.[77] This is an important finding given that modern radiotherapy techniques such as intensity-modulated radiotherapy or proton therapy are much more conformal than classic 2- or 3-dimensional approaches on which the vast majority of currently available literature focuses.[78,79] Modern techniques are better able to spare the heart and potentially preferentially spare specifically vulnerable substructures. How these more conformal techniques will affect the burden of CVD in the next generation of childhood cancer survivors remains to be seen because they have been widely used for only 10 to 20 years.

Beyond cardiac disease, radiation also increases the risk for cerebrovascular disease. Data from adult patients

treated for Hodgkin lymphoma and for head and neck cancers show that long-term survivors are at a markedly increased risk of stroke, especially those who received radiotherapy to the mediastinum and neck.[80,81] Analysis of survivors of childhood cancer showed that radiotherapy increased endothelial dysfunction, which likely mediates this risk.[82]

NOVEL THERAPIES

Although small-molecule and immunological cancer therapies generally offer a more tolerable toxicity profile, their on- and off-target effects result in various potential cardiovascular complications (Figure 1 and Table). Small-molecule kinase inhibitors modulate a range of dysregulated signaling pathways that drive malignant transformation and progression across cancer subtypes in both children and adults.[83] BCR-ABL–targeting tyrosine kinase inhibitors, used in the treatment of Philadelphia (Ph+) chromosome–positive or Ph-like leukemias, are associated with off-target cardiovascular effects, which vary depending on the spectrum of non-ABL kinases inhibited by each agent.[84] QTc prolongation is specific to second-generation tyrosine kinase inhibitors (eg, dasatinib, nilotinib), whereas vascular toxicities are most common with nilotinib and ponatinib.[84] FMS-like tyrosine kinase 3 inhibitors (eg, midostaurin, gilteritinib), effective in the treatment of FMS-like tyrosine kinase 3 inhibitor–mutant acute myeloid leukemia, are most commonly associated with QTc prolongation (incidence, 5%–10%).[85] Vascular endothelial growth factor–targeting kinases or antibody drug conjugates lead to an array of cardiovascular complications, including hypertension (high grade, 6%),[86] heart failure (3%),[87] QTc prolongation, and, less commonly, acute vascular events.

Fibrosarcoma B-type and mitogen-activated extracellular kinase inhibitors are indicated for the treatment of low-grade glioma, thyroid cancer, and Langerhans cell histiocytosis.[26] The combination of fibrosarcoma B-type and mitogen-activated extracellular kinase inhibitors, as well as MEK inhibitors alone, has been reported to cause cardiotoxicity in studies of pediatric and adult patients (Figure 1 and Table).[88–90] Although LV dysfunction is generally reversible in patients who receive these agents, the long-term cardiovascular effects of targeting these pathways remains unknown. Selectively rearranged during transfection receptor tyrosine kinase inhibitors are indicated for the treatment of thyroid cancer and recurrent pediatric solid tumors with an activated mutation or fusion in this proto-oncogene. The main cardiovascular effects of these agents are hypertension and prolongation of the QTc interval.[11]

A number of immunotherapies have received US Food and Drug Administration approval for pediatric malignancies over the past decade (Figure 1 and Table).[91] In adult cohorts, immune checkpoint inhibitors targeting cytotoxic T-lymphocyte–associated protein 4 and programmed death-1/programmed death-ligand 1 are associated with arrhythmia and, rarely, fatal myocarditis, with the incidence of the latter in pediatrics unknown.[92–94] For chimeric antigen receptor T-cell therapies, cardiotoxicity (eg, cardiomyopathy, arrhythmia, hypotension/shock, and cardiac arrest) can occur in up to one-third of pediatric, young adult, and adult patients, associated primarily with cytokine release syndrome.[18,95–97]

SURVEILLANCE AND SURVIVORSHIP

Early recognition of CVD is integral to optimizing the health of young patients from diagnosis through survivorship (Figure 2). This is of particular importance given that data from the Childhood Cancer Survivor Study show that adult survivors of childhood cancer have a higher risk of mortality after major cardiovascular events (heart failure, CAD, and stroke).[98] Risk-based cancer care delivery allows primary CVD prevention (eg, avoidance of cardiotoxic therapy, use of cardioprotectants) and secondary prevention (eg, cardiovascular imaging and blood biomarker–based surveillance/intervention, reduction of cardiovascular risk factors). These considerations differ across the continuum of treatment into survivorship.

During and Shortly After Cancer Treatment

Cardiac Imaging

Pediatric-specific, consensus-based guidelines and modern cooperative group clinical trials recommend echocardiographic monitoring for patients receiving anthracyclines, starting before treatment, repeated every 1 to 2 cycles, and at end of therapy (Figure 2).[99,100] The American Society of Echocardiography recommends the use of 2-dimensional echocardiography to estimate LVEF by the biplane Simpson method or 5/6 area-length method to assess LV function both during pediatric cancer therapy and in survivorship.[101,102] When feasible, 3-dimensional echocardiography may be a superior method to assess LVEF in adolescents and young adults, although its utility has not been established in younger children.[103,104] Global longitudinal strain has diagnostic and prognostic associations in adults during chemotherapy.[105–108] Although cardioprotective strategies based on decline in global longitudinal strain during cancer therapy did not demonstrate efficacy in adults at 1 year, 3-year follow-up has demonstrated superiority over ejection fraction–based interventions.[109,110] This finding is supported by similar studies of strain by cardiac magnetic resonance imaging.[111] Pediatric-specific strain data continue to be lacking; thus, initiation of cardioprotective strategies based on global longitudinal strain alone during cancer treatment in children is not currently supported.

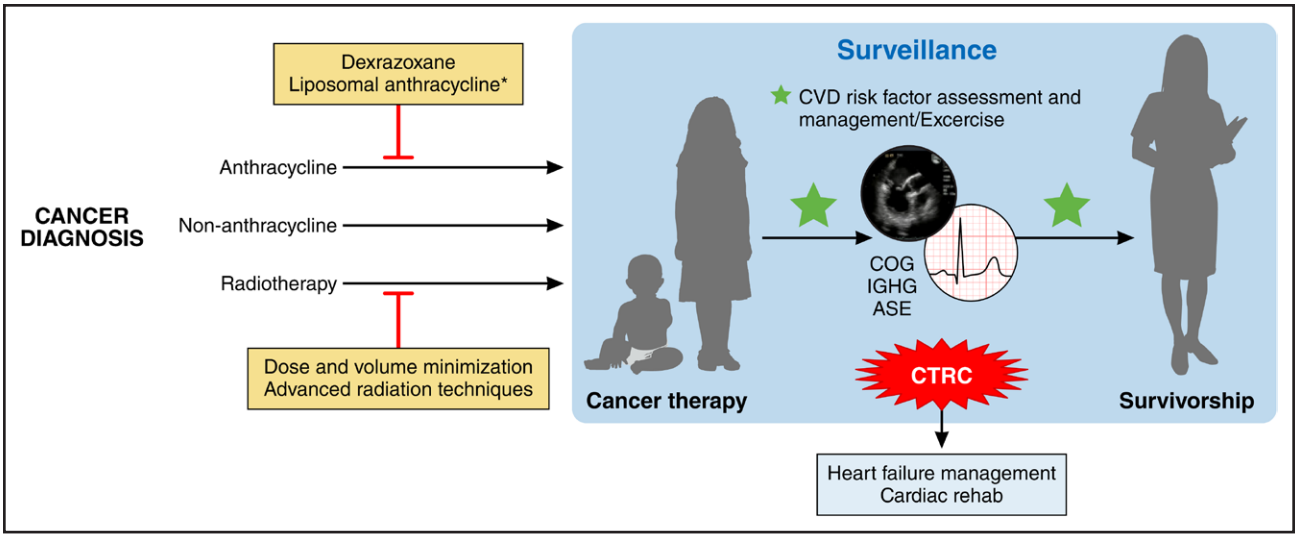

Figure 2. Care of the patient with pediatric CTRC through the age spectrum.
ASE indicates American Society of Echocardiography; COG, Children's Oncology Group; CTRC, cancer treatment–related cardiotoxicity; CVD, cardiovascular disease; and IGHG, International Guideline Harmonization Group. *Adult studies have demonstrated lower cardiomyopathy/heart failure risk with liposomal compared with standard anthracyclines, although definitive data in pediatrics are lacking.

Cardiac magnetic resonance imaging, considered the gold standard for assessing LV function,[103] has improved accuracy and reproducibility compared to echocardiography, and may be used to confirm echocardiogram-derived borderline LVEF or when there are poor acoustic windows.[102,112] When performed with gadolinium-based contrast, T1 mapping–derived extracellular volume may provide an additional marker of cardiotoxicity, although clinical utility has not been established.[113,114] In addition, it more accurately measures cardiac mass, which is a predictor of outcome in adult cancer populations,[115] and is the gold standard to echocardiography in assessing right ventricular function, which can also be affected by anticancer therapy. The primary limitations of cardiac magnetic resonance imaging include lack of widespread availability and the need for sedation in younger children. As an alternative, contrast echocardiography can assess LV volumes and function in the setting of poor echocardiographic windows.[116,117]

Cardiac Biomarkers

Adult cardio-oncology guidelines recommend troponin and natriuretic peptide monitoring throughout cancer therapy (at baseline, during therapy, and in early follow-up) for cardiac risk assessment; this recommendation may not be applicable to children.[84] A meta-analysis of 27 studies including 1651 children found an association between anthracycline-induced natriuretic peptide elevations after anthracycline exposure and LV dysfunction (odds ratio, 7.1; P=0.003), but the sensitivity of this biomarker was limited.[118] Although not associated with cardiac dysfunction in this analysis, troponin elevations have been observed early in anthracycline therapy and have been associated with echocardiographic markers of adverse cardiac remodeling in children with acute lymphoblastic leukemia.[119] Other novel biomarkers such as myeloperoxidase, galectin-3, growth differentiation factor-15, and microRNAs have been explored for cardiotoxicity risk assessment[120,121]; however, existing data are limited.

Integration of Cardiotoxicity Monitoring Into Clinical Decision-Making

Interruptions and dose modifications in anthracycline delivery, based on the detection of subclinical cardiotoxicity by imaging and blood biomarkers, should be pursued with caution given the potential to compromise cancer outcomes.[122] The threshold for anthracycline dose modifications is controversial and should be informed by the efficacy of alternative regimens and individualized, interdisciplinary decision-making aimed to maintain cancer therapy effectiveness while limiting short- and long-term cardiac deterioration. Early implementation of neurohormonal antagonist medications may improve long-term cardiac function in adult patients with cancer,[123] but there are limited data in pediatrics.

Considerations During Survivorship

The latency and heterogeneity of CVD in long-term childhood cancer survivors pose challenges to the development of comprehensive evidence-based surveillance guidelines. However, since the publication of the last American Heart Association scientific statement,[6] investigations have helped refine screening recommendations for cardiac dysfunction and included guidelines for CAD and valvular disease.

Using microsimulation modeling, Ehrhardt and colleagues[124] estimated the benefits and cost-effectiveness

of screening recommendations proposed by the International Guideline Harmonization (IGHG) group.[125] Investigators classified the risk for developing heart failure, based on treatment exposure, as low (anthracycline 1-99 mg/m^2 or radiotherapy <15 Gy, or both), moderate (anthracycline 100 to <250 mg/m^2 or radiotherapy 15 to <35 Gy), and high (anthracycline ≥250 mg/m^2 or radiotherapy ≥35 Gy, or both anthracycline ≥100 mg/m^2 and radiotherapy ≥15 Gy).[126] The lifetime risk of heart failure in each group was 16.9% (95% CI, 11.2%–23.8%), 24.7% (95% CI, 17.3%–33.5%), and 36.7% (95% CI, 28.7%–43.9%), respectively.[124] Screening was determined to be cost-effective for high- and moderate-risk survivors at 2- and 5-year intervals from completion of cancer treatment, respectively. However, no screening interval was found to be cost-effective for survivors in the low-risk category. On the basis of this and other emerging studies, both an IGHG expert panel and the Children's Oncology Group (COG) recommended a screening frequency of every 2 years for high-risk survivors and every 5 years for moderate-risk survivors. No recommendations for routine screening could be made for low-risk survivors, representing ≈40% of survivors who would have otherwise undergone routine echocardiographic surveillance. This does not, however, equate to a lack of risk, and individualized screening based on clinical signs/symptoms, modifiable cardiovascular risk factors, and medical judgement is recommended.[126]

Two-dimensional echocardiography remains the preferred imaging modality, and its use is recommended by the American Society of Echocardiography for cardiotoxicity surveillance in children. The sensitivity and specificity of blood biomarkers for the detection of asymptomatic cardiac dysfunction during long-term survivorship are mixed.[108,127] Emerging studies suggest that these biomarkers may have a role when they are used in conjunction with advanced cardiac imaging measures such as global longitudinal strain,[108,128] when standard 2-dimensional echocardiographic imaging results are borderline, or when suspicion is high for ventricular dysfunction. The IGHG panel also recommended surveillance before or in the first trimester of pregnancy for women in the moderate- or high-risk group. However, women with a history of cardiac dysfunction that has resolved, regardless of risk group, may be at higher risk for recurrent dysfunction. Therefore, continued surveillance during pregnancy is recommended.[125] Evidence remains limited on optimal screening for survivors treated with cardioprotectants (eg, dexrazoxane), those with germline genetic risk factors or cardiovascular comorbidities, and those treated with newer cardiotoxic therapies or radiotherapy approaches.

Screening recommendations for CAD and valvular disease in survivors of pediatric cancer remain largely understudied. Chow and colleagues[129] developed and validated risk prediction formulas modeling varying radiotherapy doses to the heart. The cumulative incidence of CAD at 50 years ranged from 2.3% (95% CI, 1.5%–3.1%) to nearly 20% (95% CI, 15.0%–24.7%) for the group with the highest calculated risk score. However, a systematic review conducted by the IGHG found insufficient evidence to support routine CAD screening beyond monitoring and management of modifiable cardiovascular risk factors, similar to the general population.[130] The prevalence of valvular disease, strongly associated with radiotherapy exposure, has varied widely due to differences in diagnoses and classification of valve disease.[71,131,132] Largely studied among survivors of Hodgkin lymphoma, a direct dose response has been described, with a cumulative 30-year risk of 12.4% for Hodgkin survivors treated with >40-Gy radiotherapy.[133] Although contemporary therapies typically avoid such high cardiac doses, newer studies that have included dose/volume metrics suggest that low to moderate doses (5–20 Gy) to large volumes (>90%) of the heart increase the risk for valve disease (hazard ratio, 3.9 [95% CI, 1.15–13.49]).[51] Having access to mean cardiac exposure is beneficial in stratifying risk but in reality can be difficult in many patients.

Transition of Care and Equitable Access to Health Care

Studies show that ≈60% to 90% of long-term survivors will develop ≥1 chronic health conditions, including cardiovascular, reproductive, and endocrine disorders, with a majority having severe or life-threatening conditions.[134] These risks do not reach a plateau but rather increase across the age spectrum. Thus, the long-term health of these survivors depends on the successful transition of their care from pediatric to adult settings. Historically, pediatric oncology transition practices have been limited and insufficient; fewer than half of childhood cancer survivors remain engaged in survivorship-focused care.[135]

To improve organizational health care transition from early adolescence to young adulthood, the US Center for Health Care Transition (Got Transition)[136] developed and reported a set of core components of health care transition.[137] Subsequently, in 2023, Marchak et al[138] reported a survey on the transition practices for survivors of childhood cancer. With ≈73% of the invited 209 COG institutions responding, two-thirds indicated that in accordance with their institutional policies, they transitioned survivors from pediatric programs to adult-focused cancer survivorship care. Most of the institutions reported introducing the transition plan during survivorship (usually by survivorship care clinicians) rather than during cancer treatment.

A significant obstacle identified to systematic transition programs is the burden placed on underresourced survivorship programs.[2] These findings indicate that there is a lack of uniformity in transitional survivorship care standards among COG institutions and underscore

the need to establish best practices to inform the development of transition programs for childhood cancer survivors. Therefore, the American Academy of Pediatrics has made efforts to disseminate recommendations encouraging primary care physicians to incorporate the evidence-based COG long-term follow-up guidelines into their practice for surveillance of cancer survivors[139] and to partner with oncology subspecialists to educate survivors and facilitate a smooth transition to adult-focused care.

Equitable Access to Transition Care

As in the general population, health disparities, including the development of CTRC, are evident among cancer survivors and manifest by race or ethnicity, income, age, geographic location, cognitive capacity, physical disability, or comorbidity status.[140–142] Data from the Childhood Cancer Survivor Study detail a higher burden of CVD risk factors in non-Hispanic Black and Hispanic adult survivors of childhood cancer, similar to that found in the general population.[143] Although disparities are increasingly recognized in the field of childhood cancer survivorship, practitioners often struggle to effectively address them. The absence of robust methods to reduce barriers and the fragmented state of current research hinder the development of suitable equity policies across various levels. Some of the proposed strategies to help address these disparities include a strategic focus on communities at greatest risk, access to quality health care, increasing workforce capacity, and support for standardized research to identify and address disparities.[140] In response, a growing area of investigation has emerged to address inequities in survivorship care. Because survivors of childhood cancer often require transition of complex, multidisciplinary care as they enter the adult health care system, educating adult cardiologists on the risks faced by this group may bolster the successful establishment of cardiac surveillance in adulthood.

CARDIOMETABOLIC CONSIDERATIONS

Studies in long-term childhood cancer survivors have shown that conventional CVD risk factors such as hypertension, diabetes, and dyslipidemia are more prevalent and manifest earlier compared with control subjects without cancer.[144–146] A recent large cohort study reported that Hispanic and non-Hispanic Black survivors had a much higher rate of cardiovascular risk factors, particularly diabetes and obesity, compared with non-Hispanic White survivors.[143] These findings are especially concerning given the high rates of underdiagnosis and undertreatment of these risk factors for survivors compared with control subjects without cancer, contributing to greater disparities in care for this population. These comorbidities have significant implications given data showing that anthracycline-treated survivors who develop hypertension and diabetes have a >35-fold risk of developing clinically significant cardiovascular complications such as heart failure compared with survivors without these risk factors.[50]

Several cancer treatments are associated with the development of cardiovascular risk factors. Radiotherapy (cranial, chest, abdominal, total body) has been linked to hypertension, dyslipidemia, and type 2 diabetes.[147–154] The treatments (eg, corticosteroids, calcineurin inhibitors) used for graft-versus-host disease can place stem cell transplantation survivors at a 9-fold risk of hypertension, 5-fold risk of diabetes, and 3-fold risk for dyslipidemia compared with those who are unaffected.[155] Last, acquired endocrine abnormalities such as growth hormone deficiency and hypogonadism contribute to alteration of lipid levels and the metabolic syndrome if left untreated.[156,157]

Screening of childhood cancer survivors for CVD risk factors is recommended by the COG long-term follow-up guidelines (Figure 2).[158] Childhood cancer survivors who have been treated with total-body irradiation or abdominal radiotherapy should have a fasting lipid profile and fasting glucose or hemoglobin A1c test every 2 years and blood pressure checked yearly. Height, weight, and body mass index should be evaluated yearly or every 6 months until growth is completed in those noted to have growth hormone deficiency.[158] If a childhood cancer survivor develops any criteria for metabolic syndrome, health care professionals should screen for associated components. Treatment should include lifestyle counseling on maintenance of appropriate weight, consumption of a heart-healthy diet, participation in adequate physical activity (discussed later), and avoidance of smoking.[158]

During the past 4 decades, a growing body of literature has characterized the epidemiology of CVD in patients with cancer and survivors, identified associations between treatment exposures and resultant cardiovascular complications, and highlighted important modifiers of CVD risk. These accomplishments have allowed the development of risk-based screening and intervention recommendations for CVD and cardiovascular risk factors that differ from those established for the general population because risk scores developed for the general population do not take into consideration unique treatment-related exposures in childhood cancer survivors.

Exercise and Cardiac Rehabilitation

Limited randomized trials have evaluated the impact of unsupervised behavioral interventions on improving physical activity and cardiometabolic health in children with cancer and survivors. Most have shown little or no effect on physical activity levels or cardiopulmonary

fitness outcomes,[159] suggesting that supervision is required to deliver the appropriate frequency, intensity, and duration to promote sustained movement and to achieve a cardiorespiratory response. Exercise prescription in children during cancer therapy and through survivorship should consider cardiopulmonary fitness and should be adapted to accommodate other cancer treatment–related impairments (eg, amputation, neuropathy, balance disorder), with progression based on response to initial and subsequent exercise stimulus. A traditional cardiac rehabilitation approach[160] delivered by an exercise professional with specific cancer and exercise knowledge[161] is suggested in which exercise testing identifies targets (low muscle mass and weakness, poor respiratory support, suboptimal cardiac responses) for improvement.[162] Recent studies show that individually prescribed aerobic exercise is safe,[163] demonstrates a positive impact on LV function,[164] and improves cardiopulmonary fitness among children during cancer therapy and after exposure to anthracyclines.[165] Supervised interventions also improve muscle strength and daily physical activity in survivors <18 years of age.[166] Conversely, 12 months of monthly personalized coaching (6 months in person, 6 months by phone) in adult survivors of childhood cancer only decreased composite CVD risk (*Z* score difference, −0.18) compared with control subjects. Although this difference was statistically significant, there was no effect of the intervention on individual components of the CVD risk score (average *Z* score of waist circumference, blood pressure, fasting glucose, inverted high-density lipoprotein cholesterol, triglycerides, and inverted cardiorespiratory fitness) and no difference in physical activity levels between the intervention and control groups at study completion,[167] again suggesting that more frequent supervision, perhaps with telehealth-based technology to increase access,[168,169] is needed to achieve sustained effects in this population. Because exercise decreases cardiovascular events, second malignant neoplasms, and mortality in survivors of childhood cancer,[170–172] early referral for appropriate exercise training is warranted. On the basis of the overwhelming positive benefits of exercise and activity throughout the continuum of cancer care, the American Cancer Society has promoted the Moving Through Cancer initiative, with the goal to "ensure that all individuals living with and beyond cancer are assessed, advised, referred to, and supported to engage in appropriate exercise and rehabilitation programming."[173]

CLINICAL MANAGEMENT OF CARDIOTOXICITY

Standard heart failure therapies have scarcely been studied in the management of children with CTRC, and no formal guidelines exist beyond those for heart failure in the general pediatric population, although the recent American Heart Association scientific statement on the treatment of pediatric cardiomyopathy does include a discussion of cardio-oncology (Figure 2).[174–176] In the adult realm, studies support the use of angiotensin-converting enzyme inhibitors and β-blockers in the management of CTRC.[177,178] Conversely, in small pediatric studies, although there was short-term benefit of the use of angiotensin-converting enzyme inhibitors for CTRC, particularly enalapril,[179,180] the long-term risk-to-benefit ratio has been called into question.[181] This is based, in part, on a potentially unique remodeling profile seen in survivors of pediatric cancer compared with survivors of adult cancer.[182] Similarly, the primary end point, standardized LV wall thickness–dimension ratio *Z* score, was not significantly different among childhood cancer survivors treated with low-dose carvedilol with the goal of preventing anthracycline-induced LV dysfunction, leading the authors to conclude that the "results do not support the use of carvedilol for secondary heart failure prevention in anthracycline-exposed childhood cancer survivors."[183] The mineralocorticoid receptor antagonist spironolactone is regularly used in pediatric patients with heart failure, but there are no data specific to pediatric CTRC. Similarly, although the safety of sacubitril-valsartan has been established in adults with CTRC,[184,185] it has not been evaluated in children. Despite the lack of formal guidelines, the IGHG recommends consideration of conventional pharmacological intervention in patients with cardiac dysfunction,[125] and recent surveys show that health care professionals regularly use these therapies, including in cases of mild reduction in LVEF.[186–188] That said, additional studies are needed to evaluate the role of phenotypically informed interventions for the secondary treatment of CTRC in childhood cancer survivors because many of the traditional heart failure management approaches may not be as applicable to this population.[189]

Advanced Heart Failure Therapy

Data in adult patients demonstrate that LV assist devices are a reasonable option to support patients with heart failure not responsive to oral therapies both during chemotherapy and afterward.[190,191] Use of such devices in children can be limited by the smaller patient size and restrictive ventricular physiology seen more frequently in this group. For pediatric patients in need of support after anthracycline therapy, the only data currently available come from case reports or small case series.[192,193] In a study of 80 patients <18 years of age transplanted for end-stage CTRC, long-term graft survival, risk of secondary malignant neoplasms, time to first infection, time to first rejection, and time to coronary graft vasculopathy were similar to those in patients with other dilated cardiomyopathies, suggesting that transplantation may be a

viable path for some patients with cancer and survivors with advanced heart failure.[194] The revised 2016 International Society for Heart and Lung Transplant listing criteria now permit individuals with a history of cancer to be considered for heart transplantation, contingent on determination of their risk of tumor recurrence in consultation with oncology experts and after a designated monitoring period.[195]

FUTURE DIRECTIONS

During the past 4 decades, a growing body of literature has characterized the epidemiology of CVD in patients with cancer and survivors, identified associations between treatment exposures and resultant cardiovascular complications, and highlighted important modifiers of CVD risk. This has allowed the development of risk-based screening and intervention recommendations for CVD and cardiovascular risk factors that differ from those established for the general population because risk scores developed for the general population do not take into consideration unique treatment-related exposures in childhood cancer survivors.[129,196,197] Risk-based screening has facilitated consideration of secondary prevention trials to reduce the burden of CVD. However, these CVD prevention trials have focused largely on broad clinical risk groups (eg, history of transient LV dysfunction,[180] high-dose [≥250 mg/m^2] cumulative anthracycline exposure[183]), providing mixed results to date. Recent studies have highlighted the prognostic role of NT-proBNP (N-terminal pro-B-type natriuretic peptide) in refining heart failure risk determination in asymptomatic survivors,[108,127] and this may provide the impetus to consider combined clinical and biomarker-based (imaging, blood) approaches to screen for survivors who may derive the most benefit from future secondary prevention efforts.

There have been parallel efforts to further refine CVD risk before the initiation of cardiotoxic therapy, driven largely by studies focusing on germline genomics.[53] Although these studies initially focused on candidate genes, they have expanded to include customized arrays and genome-wide approaches, providing insights into the pathogenesis of cardiotoxicity associated with chemotherapies such as anthracyclines.[53] There are ongoing efforts to integrate findings from these genomic studies with transcriptomics, proteomics, and metabolomics, which would allow more precise risk determination, facilitate the development novel blood biomarkers, and identify therapeutic targets.[53] Investigators may also need to consider the role of acquired somatic mutations (eg, clonal hematopoiesis of indeterminate potential) associated with CVD in nononcology populations given the higher prevalence of clonal hematopoiesis of indeterminate potential in childhood cancer survivors compared with community control subjects.[198] The success of these efforts will be strengthened by continued transdisciplinary collaborations and a steadfast commitment to bench-to-bedside translation. The emergence of specialized pediatric cardio-oncology clinics[199,200] may provide the means to translate these findings, allowing optimization of cardiovascular health outcomes across the cancer care delivery continuum.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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†Significant.

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†Significant.

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