Paediatric cardio-oncology: epidemiology, screening, prevention, and treatment

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Received 10 November 2018; revised 18 January 2019; editorial decision 24 January 2019; accepted 13 February 2019; online publish-ahead-of-print 7 March 2019

Abstract

With 5-year survival of children with cancer exceeding 80% in developed countries, premature cardiovascular disease is now a major cause of early morbidity and mortality. In addition to the acute and chronic cardiotoxic effects of anthracyclines, related chemotherapeutics, and radiation, a growing number of new molecular targeted agents may also have detrimental effects on the cardiovascular system. Survivors of childhood cancer also may have earlier development of conventional cardiovascular risk factors such as hypertension, dyslipidaemia, and diabetes, which further increase their risk of serious cardiovascular disease. This review will examine the epidemiology of acute and chronic cardiotoxicity relevant to paediatric cancer patients, including genetic risk factors. We will also provide an overview of current screening recommendations, including the evidence regarding both imaging (e.g. echocardiography and magnetic resonance imaging) and blood-based biomarkers. Various primary and secondary prevention strategies will also be discussed, primarily in relation to anthracycline-related cardiomyopathy. Finally, we review the available evidence related to the management of systolic and diastolic dysfunction in paediatric cancer patients and childhood cancer survivors.

Keywords

Paediatric • Cardio-oncology • Anthracycline • Cardiomyopathy • Prevention • Survivorship

This article is part of the **Spotlight Issue on Cardio-oncology**.

1. Introduction

Five-year survival of children with cancer is now ~85% in developed countries.¹ With the growing number of long-term survivors, premature heart disease is an increasingly important cause of late morbidity and mortality.² While changes in therapy over the past several decades have resulted in reduced radiation exposures, more patients now receive potentially cardiotoxic chemotherapy, and the overall effect on long-term cardiovascular morbidity and mortality has been mixed. For example, a major update from the North American Childhood Cancer Survivor Study (CCSS) found that, among over 30 000 long-term survivors of childhood cancer, the cumulative incidence of cardiac death 15 years

after cancer diagnosis decreased from 0.5% for those diagnosed in the 1970s to 0.1% for those diagnosed in the 1990s.³ However, the cumulative incidence of specific serious conditions such as heart failure and ischaemic heart disease have not significantly changed.⁴

While cardiomyopathy, ranging from subclinical dysfunction to overt congestive heart failure, has been the most commonly described acute and late serious cardiovascular sequela in childhood cancer survivors, ischaemic heart disease remains relevant, particularly among aging survivors.^{2,5} Furthermore, other cardiovascular risk factors such as hypertension, dyslipidaemia, and glucose intolerance, appear to present earlier than in siblings or the general population.^{6–8} In general, while therapeutic protocols have evolved over time, many of the same agents used

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Table 1 Reported cardiac toxicities associated with the most common conventional and targeted or immunotherapeutic agents used in paediatric cancer

Reported cardiac toxicities	Conventional agent	Targeted or immunomodulatory agent
Left ventricular systolic dysfunction, heart failure	Alkylators (e.g. cyclophosphamide, melphalan, busulfan, and carmustine) Anthracyclines (e.g. daunorubicin, doxorubicin, epirubicin, idarubicin, and mitoxantrone)	ABL targeting TKI (e.g. imatinib and nilotinib) Chimeric antigen receptor T cells Immune checkpoint inhibitors (e.g. ipilimumab, nivolumab, and pembrolizumab) MEK inhibitor (e.g. trametinib) Proteasome inhibitor (e.g. bortezomib) VEGF inhibitor (e.g. sorafenib, sunitinib, and bevacizumab)
Myocarditis/pericarditis	Alkylators (e.g. cyclophosphamide) Anthracyclines (rarely in the acute setting) Antimetabolites (e.g. cytarabine): pericarditis	Immune checkpoint inhibitors (e.g. ipilimumab, nivolumab, and pembrolizumab)
Arrhythmia	Alkylators (e.g. melphalan): atrial fibrillation and ventricular arrhythmia Anthracyclines: atrial fibrillation, long QT, and ventricular arrhythmia Antimetabolites (e.g. 5-fluorouracil): atrial fibrillation and long QT Arsenic: long QT Platinums (e.g. cisplatin): atrial fibrillation and ventricular arrhythmia	ABL targeting TKI (e.g. dasatinib and nilotinib): atrial fibrillation and long QT ALK inhibitor (e.g. crizotinib): long QT and bradycardia Anti-CD20 (e.g. rituximab): atrial fibrillation Anti-EGFR (e.g. cetuximab): long QT BRAF kinase inhibitor (e.g. vemurafenib and dabrafenib): atrial fibrillation and long QT Bruton's TKI (e.g. ibrutinib): atrial fibrillation Histone deacetylase inhibitor (e.g. panobinostat and vorinostat): long QT Proteasome inhibitor (e.g. bortezomib): long QT and ventricular arrhythmia
Coronary, cerebral, or peripheral vascular events	Alkylators (e.g. carmustine) Antimetabolites (e.g. 5-fluorouracil) Platinums (e.g. cisplatin) Vinca alkaloids (e.g. vincristine, vinblastine)	ABL targeting TKI (e.g. nilotinib and ponatinib) BRAF kinase inhibitor (e.g. vemurafenib and dabrafenib) Proteasome inhibitor (e.g. bortezomib) VEGF inhibitor (e.g. sorafenib, sunitinib, and bevacizumab)
Hypertension	Platinums (e.g. cisplatin)	ABL targeting TKI (e.g. ponatinib) BRAF kinase inhibitor (e.g. vemurafenib and dabrafenib) VEGF inhibitor (e.g. sorafenib, sunitinib, and bevacizumab)
Metabolic effects	Retinoic acid: dyslipidaemia	ABL targeting TKI (e.g. nilotinib): hyperglycaemia mTOR inhibitor (e.g. temsirolimus): dyslipidaemia and hyperglycaemia
Other	Retinoic acid: pericardial effusion	ABL targeting TKI (e.g. dasatinib): pulmonary hypertension

historically continue to be used for children newly diagnosed with cancer today, and thus these lessons from the past will continue to be informative for the foreseeable future.^{9,10}

In this review, we provide an overview of the epidemiology and risk factors associated with acute and chronic cardiotoxicity, with a focus on anthracycline-related cardiotoxicity (ACT), including genetic risk factors. We also review current screening recommendations, primary and secondary prevention strategies, and cardiotoxicity treatment considerations. While the overwhelming evidence available at present relates to conventional cytotoxic chemotherapy (primarily anthracyclines) and radiotherapy, the toxicities observed with newer molecularly targeted agents will also be discussed where applicable.

2. Acute cardiotoxicity

While the focus of much of the paediatric cardiotoxicity literature has centred on late cardiovascular complications occurring in long-term survivors, there can be acute and early onset (within the first year of cancer

therapy) cardiovascular complications of cancer therapy. These complications are particularly relevant with some of the newer targeted therapies. These toxicities vary by agent and manifest as arrhythmia, transient or progressive left ventricular systolic dysfunction (LVSD), myocarditis, pericarditis, arrhythmia, and vascular complications, such as hypertension and ischaemia (Table 1).

Acute toxicities described in children include transient, largely subclinical arrhythmias (seen in up to 24% of adults within 24 h of infusion; prevalence unclear in children),¹¹ and subclinical troponin elevations related to myocardial injury (seen in nearly 50% of children receiving moderate dose anthracyclines for acute lymphoblastic leukaemia).¹² In adults, rare cases of reversible acute myopericarditis and acute life-threatening left ventricular failure have also been reported.¹³ Recently, the Children's Oncology Group (COG) reported a striking incidence of early ACT manifesting as LVSD during and soon after therapy, in children receiving high-dose anthracyclines for acute myeloid leukaemia.¹⁴ Cumulative LVSD incidence reached 12% within 18 months of therapy, with those experiencing LVSD during protocol therapy demonstrating a 12-fold increased risk for LVSD following therapy (95% confidence interval

4.2–34.8). Importantly, the occurrence of LVSD had significant implications on treatment outcomes, with a >15% decrement in 5-year event-free and overall survival in those with LVSD (Figure 1). Thus, early ACT has significant implications on both cardiac health and cancer survival.

Other conventional chemotherapeutic agents such as alkylating agents, platinum, and antimetabolites have been infrequently associated with a range of cardiac effects, including arrhythmias such as prolonged QTc, myocardial ischaemia, and/or hypertension (Table 1).¹⁵ Differentiating agents, such as arsenic used for acute promyelocytic leukaemia and tretinoin used for both acute promyelocytic leukaemia and neuroblastoma, are also associated with arrhythmias (e.g. prolonged corrected QT interval) and dyslipidaemia, respectively.^{15,16}

Newer targeted oncologic therapies hold promise for reduced toxicities due to focused targeting of specific proteins or receptors.¹⁷ While paediatric oncology continues to rely heavily on conventional agents, a number of targeted therapies have entered paediatric Phase 3 clinical trials (Table 2). However, as the use of these agents have increased, both on- and off-target cardiotoxic effects of these new agents have been increasingly recognized, with reports primarily in the adult setting. For example, sorafenib, a small molecule inhibitor targeting FLT3 in patients with acute myeloid leukaemia, has off-target effects on vascular endothelial growth factor that contribute to significant hypertension

and, particularly when given in combination with anthracyclines, significant LVSD.¹⁸ A meta-analysis of adults receiving sorafenib or other therapies that target vascular endothelial growth factor also demonstrated higher risks for hypertension and LVSD, as well as QTc prolongation and cardiac ischaemia (relative risks 1.7–6.3, $P < 0.01$).¹⁹

The targeting of most tyrosine kinase inhibitors against multiple on- and off-target kinases leads to hypertension, QTc prolongation (incidence ranging between 2 and 10% in those inhibitors commonly employed in the paediatric setting), and in later generation agents, an increased risk of pulmonary hypertension (e.g. dasatinib) and vascular events, including myocardial ischaemia, peripheral arterial occlusive disease, and stroke (e.g. ponatinib).²⁰ Crizotinib has been associated with arrhythmia in adults.²⁰ Metabolic complications, such as dyslipidaemia and hyperglycaemia, have been seen with mechanistic targeting of rapamycin inhibitors (e.g. temsirolimus).²¹

Proteasome inhibitors have been associated with a higher risk for LVSD, arrhythmia, and arterial or venous thrombo-embolic events in adult studies (1.5- to 2.4-fold increased risk vs. controls).²² However, these side effects appear to be less common with bortezomib, a reversible proteasome inhibitor (first inhibitor of this class US Food and Drug Administration-approved, in 2003), and in groups free from cardiovascular comorbidities.²³

The use of immune checkpoint inhibitors, such as nivolumab, pembrolizumab, and ipilimumab, is becoming increasingly prevalent in adult oncology and being studied in numerous trials of paediatric haematologic and solid tumour malignancies.²⁴ Immune-mediated myocarditis and associated heart failure has been reported in <1% of adult patients receiving single agent checkpoint inhibition and in those receiving combination therapy with programmed cell death protein 1 and cytotoxic T lymphocyte associated protein 4 inhibition.²⁵ Although typically reversible, numerous cases of fulminant myocarditis have been described.²⁶

Overall, the lower prevalence of conventional cardiac risk factors in paediatrics may decrease the incidence of the acute cardiac effects described with many molecularly targeted agents in the adult setting.^{17,20} However, treating oncologists must be mindful of these potential toxicities and have a low threshold for detailed cardiac evaluations and cardiology referral when utilizing these agents.

3. Chronic cardiotoxicity

The prevalence of late cardiomyopathy reported among paediatric cancer survivors is varied due to different definitions used to define this outcome, along with differences in screening methodologies, patient populations, and study designs. A series of systematic reviews have suggested a frequency of symptomatic cardiac dysfunction in up to 16% of anthracycline exposed survivors but subclinical disease in over 50%.^{27,28}

The risk of cardiomyopathy is increased among all childhood cancer survivors but particularly greater among groups heavily exposed to cardiotoxic agents, such as high-dose anthracyclines and radiation fields involving the heart.²⁹ While an anthracycline dose–response has been demonstrated, more recent studies have suggested no safe dose but a clear increased risk beyond 250 mg/m² (Figure 2a).³⁰ Cardiac radiation exposure can further increase the risk, particularly beyond 15 Gy, and higher yet at doses exceeding 35 Gy.³⁰ Other risk factors may include female sex, younger age at exposure, and traditional age-related cardiovascular risk factors such as hypertension, obesity, dyslipidaemia, and diabetes.^{2,8}

Table 2 Phase 3 clinical trials of novel targeted agents including children (age <18 years) and their associated cardiotoxic effects

Target	Drug	Clinical trials in paediatric oncology	Known toxicity (on therapy or after completion of therapy) ^a
ALK	Crizotinib	Neuroblastoma, high risk <ul style="list-style-type: none"> • NCT03126916 	Bradycardia, QT prolongation
BCR-ABL1, KIT PDGFR, SRC, EGFR, BRAF, DDR1, DDR2, Ephrin receptors	Dasatinib	Acute lymphoblastic leukaemia <ul style="list-style-type: none"> • NCT00549848 • NCT00720109 • NCT02883049 • NCT03020030 • NCT03117751 	Pulmonary hypertension Vascular events
BTK	Ibrutinib	Graft vs. host disease prophylaxis <ul style="list-style-type: none"> • NCT02959944 Graft vs. host disease treatment <ul style="list-style-type: none"> • NCT03474679 Non-Hodgkin lymphoma, relapsed <ul style="list-style-type: none"> • NCT02703272 	Atrial fibrillation
CTLA4, PD-1	Ipilimumab Nivolumab	Glioma, high-grade <ul style="list-style-type: none"> • NCT02017717 	Fatal myocarditis
HDAC	Vorinostat	Acute lymphoblastic leukaemia <ul style="list-style-type: none"> • NCT03117751 Glioma, high-grade: <ul style="list-style-type: none"> • NCT01236560 	QT prolongation
PI3K-AKT-mTOR	Everolimus Sirolimus	Astrocytoma and subependymal giant cell <ul style="list-style-type: none"> • NCT00789828 Graft vs. host disease prophylaxis <ul style="list-style-type: none"> • NCT00382109 • NCT00406393 • NCT01106833 • NCT01231412 	Hypercholesterolaemia, hyperglycaemia, hypertriglyceridaemia
	Temsirolimus	Hepatoblastoma <ul style="list-style-type: none"> • NCT00980460 Rhabdomyosarcoma and intermediate risk <ul style="list-style-type: none"> • NCT02567435 	
Ubiquitin-proteasome system	Bortezomib	Acute lymphoblastic leukaemia <ul style="list-style-type: none"> • NCT02112916 • NCT03117751 • NCT03643276 Acute myeloid leukaemia <ul style="list-style-type: none"> • NCT01371981 	Arrhythmia, cardiomyopathy/heart failure, hypertension, thrombo-embolic events
VEGF, VEGFR, PDGFR	Bevacizumab	Glioma, high-grade <ul style="list-style-type: none"> • NCT01236560 • NCT02017717 Neuroendocrine tumour, high risk <ul style="list-style-type: none"> • NCT00569127 	Cardiomyopathy/heart failure, hypertension, proteinuria, thrombo-embolic events
	Pazopanib	Angiosarcoma, advanced stage <ul style="list-style-type: none"> • NCT02979899 Soft tissue sarcoma <ul style="list-style-type: none"> • NCT02049905 • NCT02180867 	
	Sorafenib	Acute myeloid leukaemia <ul style="list-style-type: none"> • NCT01371981 Hepatoblastoma <ul style="list-style-type: none"> • NCT03017326 • NCT03533582 Renal cell carcinoma <ul style="list-style-type: none"> • NCT00111020 	

Per Clinicaltrials.gov, as of 23 December 2018, and not limited to trials being conducted in the USA.

^aDerived from adult oncology literature.

It is important to note that cardiomyopathy does not occur in isolation among childhood cancer survivors. A quarter of CCSS survivors reported more than one cardiac disorder and 10% reported two or more modifiable cardiovascular risk factors, compared to 10% and 7.9% of the siblings, respectively.^{8,30} Concomitant cardiovascular sequelae, may further impair cardiac function among cancer survivors. The incidence of premature coronary artery disease is also increased, particularly among those with cardiac irradiation (Figure 2b).³⁰ By age 40, rates may exceed 10%.^{5,29} Exposure to chest radiation is thought to cause increased vessel wall permeability, generation of reactive oxygen species leading to endothelial damage, fibrointimal hyperplasia, thrombus formation, and accelerated atherosclerosis.²

While exposure to anthracyclines and/or chest radiation are well-established risk factors, newer targeted agents may have the potential to mitigate cardiovascular complications due to fewer off-target effects. However, as their use in adult oncology increases, so do the number of publications reporting complications during and after the completion of therapy.^{17,20} Most of these reports have focused on acute toxicities experienced during and soon after therapy. The incidence of side effects associated with these agents in paediatrics remains unclear, and longitudinal monitoring will be critical to systematically ascertain the magnitude of their long-term toxicity profiles.

4. Molecular and genetic factors

The pathophysiology of ACT remains incompletely understood. Initially thought to be related to free radical formation resulting in oxidative stress on the cardiac myocytes, a lack of protection from anti-oxidant

Table 3 Published genetic associations for anthracycline-related cardiomyopathy in cancer survivors, adapted from Chow et al.¹⁷

Gene, alphabetical ^{a,b}	First author, alphabetical (PMID) ^{c,d}
ABCB1, ABCB4, ABCC1 ^a , ABCC2, ABCC5 ^a	Armenian (23927520) Aminkeng (26237429) ^d
CAT	Blanco (18457324 and 22124095) ^d
CBR3 ^a	Cascales (23576480)
CELF4 ^{a,b}	Hertz (26799497)
CYBA	Krajinovic (26345518) ^d
FMO2	Leger (26968791)
HAS3 ^{a,b}	Lipshultz (23861158) ^d
HFE ^a	Rajic (19863340) ^d
HNMT	Rossi (19448608)
NCF4 ^a	Schneider (27993963)
NOS3	Semsei (21929509) ^d
PRDM2 ^a	Visscher (21900104, 23441093, and 26230641) ^d
RAC2	Vulsteke (26017071)
RARG ^{a,b}	Wang (24470002 and 26811534) ^d
SLC10A2	Wells (28542097)
SLC22A17 ^a , SLC22A7 ^a , SLC28A3 ^a	Wojnowski (16330681)
SPG7	
UGT1A6 ^a	
rs28714259 (intergenic) ^a	

Studies based on human samples as identified from PubMed as of 1 October 2018; studies based only on cell lines or drug pharmacokinetics are not listed.
^aPolymorphism in the gene has been associated with the phenotype in at least one separate sample/population.
^bEvidence for an association from in vitro (i.e. functional) experiments.
^cIncludes studies that reported null findings.
^dStudies where the population was >50% survivors of childhood cancer.

therapies gave rise to hypotheses of other potential mechanisms.³¹ Doxorubicin, the most widely used anthracycline, acts on topoisomerase-II (Top2) to bind DNA and induce cell death. While the Top2α isoform is overexpressed in tumours, the Top2β isoform is expressed on cardiomyocytes. Recent studies have demonstrated a role for Top2β in a mouse model of ACT and in human induced pluripotent stem cell-derived cardiomyocytes.^{31,32}

Separately, the wide range of inter-individual susceptibility to ACT has led to the hypothesis that genetic variation may contribute to individual susceptibility. To date, genetic variation in ~25 genes have been associated with ACT (Table 3).^{17,33} Many of these associations require further validation through replication and/or functional and mechanistic studies to confirm and better understand the roles of these associated variants in ACT. Two genes with strong evidence for involvement in ACT that have been identified from genome-wide studies include RARG and UGT1A6. The RARG S427L variant (rs2229774) is highly associated with ACT in paediatric patients from various worldwide populations (odds ratio 4.1–7.0).³⁴ This gene variant alters RARG function and was found to increase Top2β.^{31,32} Finally, genetic variation in the UGT1A6*4 haplotype (e.g. rs17863783) has been associated with ACT in multiple patient cohorts from various worldwide populations (odds ratio 3.7–19.5).^{35,36} UGT1A6 is involved in drug glucuronidation and the UGT1A6*4

haplotype has been associated with significantly reduced enzyme activity which hypothetically could reduce the elimination of anthracyclines or anthracycline metabolites.³⁷ If validated, genetic predictors of ACT could eventually be incorporated as part of clinical risk predictors and screening algorithms (further discussed below).

5. Screening

While it is anticipated that advances in our understanding of the pathophysiology of ACT may pave the way for personalized delivery of cancer care, there will continue to be a growing number of long-term survivors who remain at risk for ACT due to past exposure to cardiotoxic therapies. Monitoring of ACT in these at-risk survivors has historically relied upon serial echocardiographic screening, primarily based on resting left ventricular ejection fraction (EF) or shortening fraction (SF).³⁸ However, limitations in conventional echocardiography have raised interest in novel parameters, alternative imaging modalities such as cardiac magnetic resonance imaging (cMRI), and blood-based biomarkers. These various screening strategies are discussed below, including a review of current screening guidelines.

5.1 Imaging

Echocardiography is the most common, low cost, easily accessible, non-invasive method of monitoring the cardiac status in at-risk survivors.³⁹ Nearly all treatment protocols that include anthracyclines, now require a pre-treatment echocardiogram to collect baseline measurements of cardiac structure and function.³⁹ Two-dimensional echocardiographic measurements of left ventricular systolic functions like SF and EF, continue to be the most widely used screening methods for monitoring cardiotoxicity both during and years after anthracycline treatment. However, they may not detect early and subtle myocardial dysfunction, and lack the predictive value in identifying children at higher risk of developing symptomatic cardiovascular disease in the future.

Other measures to detect early cardiac dysfunction have been investigated, such as tissue Doppler imaging, myocardial performance index, two-dimensional strain, strain rate, end-systolic wall stress, and velocity of circumferential fibre shortening.^{27,40,41} Two-dimensional speckle tracking echocardiography provides a sensitive measure of left ventricular systolic function and may aid in the diagnosis of cardiotoxicity.⁴² Using this method, the European Association of Cardiovascular Imaging and American Society of Echocardiography recommend assessing global longitudinal strain (GLS) as a routine component of clinical echocardiograms in adult cancer patients at risk for cardiotoxicity.⁴³ GLS has also been shown to be more prevalent than alterations in EF in survivors of childhood cancer with early subtle signs of cardiac dysfunction.⁴⁴ In a cross-sectional study of 134 patients (mean age: 31 years) previously treated with anthracyclines with or without radiotherapy, GLS was worse ($P=0.003$) and prevalence of abnormal GLS was higher ($P=0.004$) in patients treated with mediastinal radiotherapy.⁴² Thus, strain imaging may be a powerful tool to identify early myocardial injury in survivors of childhood cancer.⁴⁵ Recently, three-dimensional echocardiography, especially three-dimensional strain imaging, has shown potential superiority in diagnosing subclinical cardiotoxicity in adult-onset cancers.⁴⁶

As an alternative to echocardiography, cMRI has been used to monitor early and late cardiotoxicity in paediatric cancer patients and survivors.^{47,48} cMRI has superior intra- and inter-observer reproducibility and

accuracy compared with conventional two-dimensional echocardiography.⁴³ Moreover, cMRI is able to measure myocardial fibrosis associated with myocardial damage via late gadolinium enhancement, subendocardial damage, and subclinical late cardiac complications.^{48,49} Cardiac T1 mapping sequences in cMRI, which are a marker of interstitial fibrosis, have been used to follow these patients. In 46 long-term childhood cancer survivors with a cumulative anthracycline dose $\geq 200 \text{ mg/m}^2$, the mean T1 mapping values of the myocardium were significantly lower than that of control subjects ($P=0.01$).⁴⁹ This suggests that asymptomatic post-chemotherapy paediatric patients have abnormal myocardial characteristics and strain parameters by cMRI despite normal global cardiac function. Compared with echocardiography, the current disadvantages are that cMRI is more time-consuming, not widely available, and may require sedation, especially in younger patients. However, with advancing techniques and its ability to detect early myocardial fibrosis, cMRI may become the screening modality of choice in the future for high-risk patients.

5.2 Blood biomarkers

Elevated troponin concentrations indicate cardiomyocyte damage; however, the long-term implications of acute cardiomyocyte injury are less clear.⁵⁰ Anthracyclines cause cardiomyocyte injury with release of intracellular troponin into the circulation. Serum troponin concentrations have been reported to be acutely increased following anthracycline therapy in children.^{12,51} In these studies by Lipshultz *et al.*, acute serum troponin elevations correlated with left ventricular end-diastolic dimension and left ventricular wall thickness measurements up to 4 years later. However, other studies have not necessarily found an association between acute or chronic troponin release and left ventricular dysfunction in childhood cancer survivors.^{52,53}

Brain natriuretic peptide (BNP) is produced by the ventricles in response to increased cardiac stress and is an attractive option for monitoring survivors because of the physiologic relationship with cardiac function along with the low cost and wide availability of assays. The N-terminal peptide of BNP (NT-proBNP) is simultaneously secreted but has a longer half-life. Serum NT-proBNP concentrations measured after treatment has been associated with increased concentrations of serum troponin and abnormal left ventricular fractional shortening.¹² Elevated serum concentrations of NT-proBNP during the first 90 days of treatment has also correlated with abnormal left ventricular thickness-to-dimension ratios 4 years later.¹² In childhood leukaemia survivors receiving even low-dose anthracycline, higher concentrations of NT-pro-BNP may detect cardiotoxicity earlier than echocardiographic changes.⁵⁴

While troponin and BNP have shown promise in the detection of subclinical cardiotoxicity during cancer treatment, these blood-based biomarkers may be affected by cytokine-mediated myocardial depression and abnormal left ventricular loading conditions, which can often vary greatly in children receiving chemotherapy.⁵¹ As such, their sensitivity, specificity, and predictive value in relation to both acute and chronic cardiomyopathy may be limited. Besides troponin and BNP, other blood-based biomarkers may be relevant. Recently, alterations in plasma microRNA expression in children receiving anthracycline or non-cardiotoxic chemotherapy were found to correlate with the microRNA expression of markers of cardiac damage (elevated cardiac troponin concentrations).⁵⁵ However, the utility of these more novel biomarkers still need to be validated in additional populations. In summary, while blood-based biomarkers remain an attractive area for cardiotoxicity screening, at present, data remain limited with regards to the optimal

biomarker(s), timing, and how best to combine with an imaging-based screening strategy. Finally, regular histories and physical examinations remain essential in closely monitoring childhood cancer survivors at risk for ACT.

5.3 Current guidelines

The aforementioned associations between cancer treatment exposures and cardiotoxicity have prompted leading organizations to develop cardiovascular surveillance guidelines specific to childhood cancer survivors.⁵⁶ In North America, COG has issued the Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers.⁵⁷ These guidelines were developed to inform specialty and primary care providers regarding the risks for late-adverse health effects in survivors and to simultaneously provide a standardized surveillance approach. To account for the variability of evidence to guide surveillance strategies, the COG guidelines have adapted a hybrid approach, aligning evidence of risk for cancer treatment-related adverse health outcomes with consensus screening recommendations. Where able, developers have adapted a value framework surveillance model reliant on three leading concepts.⁵⁸ The first is that screening involves a cascade of events rather than a single test, and that the downstream impact of this cascade must be considered when making screening recommendations. Second, the availability and efficacy of treatment for identified lesions should be considered, a notable challenge when developing cancer survivorship guidelines given the often decades long latency from treatment exposure to onset of disease. Lastly, a 'one-size fits all' approach is rarely appropriate, supporting a need for personalized screening strategies in individuals at varying degrees of risk.

The COG and other endorsed guidelines make several recommendations specific to cardiovascular late effects. While many aforementioned studies inform risk for late occurring cardiovascular events in cancer survivors, few report yield from screening, and none address treatment efficacy specific to these events. With respect to yield from screening, Landier et al.⁵⁹ assessed the screening yield of the COG guidelines in 370 individuals for whom >98% of recommended evaluations were completed. In this study, performing screening echocardiograms in accordance with the COG guidelines resulted in a two-fold increase in the diagnosis of underlying cardiomyopathy or valvular disorders. Similarly, Hudson et al.⁶⁰ screened 1713 prospectively evaluated survivors who were considered at risk for cardiomyopathy, also as outlined by the COG guidelines. They demonstrated a greater than two-fold increase in the prevalence of cardiomyopathy (2.6% vs. 6.2%, respectively) and a greater than nine-fold increase in the prevalence of valvular abnormalities (6.2% vs. 56.7%, respectively) from before, compared to after risk-based screening. While both studies identify an enhanced ability to detect cardiovascular disease in childhood cancer survivors by screening, they do not circumvent the need for longitudinal investigations to inform the frequency and duration of screening.

Two studies have estimated the cost-effectiveness of cardiomyopathy surveillance strategies using microsimulation models within the economic infrastructure of United States healthcare system.^{61,62} The first, by Yeh et al., estimated the cost-effectiveness of a variety of screening strategies approximating those put forth by the COG in at-risk survivors. The second, by Wong et al., specifically addressed the cost-effectiveness of the existing risk stratification and corresponding screening strategies endorsed by the COG. Both found that although compelling arguments could be made to support the use of existing strategies, a modified, less frequent approach would likely be more cost effective. Importantly, Wong et al. suggested that the most influential variable in determining

cost-effectiveness of a given cardiomyopathy surveillance strategy was the efficacy of the subsequent pharmacologic intervention. Unfortunately, data informing treatment efficacy for ACT in childhood cancer survivors are largely limited to acute, rather than late occurring cardiac dysfunction.⁶³ As a result, the benefits of cardiomyopathy surveillance have, to date, assumed similar treatment efficacy for anthracycline-related heart failure to that of heart failure in the general population, highlighting a key knowledge gap for future investigation.

In 2010, the International Late Effects of Childhood Cancer Guideline Harmonization Group was established to create a single, unified set of recommendations more broadly applicable to the global population of childhood cancer survivors. Comprised of international experts with public health and disease-specific expertise, this group has applied rigorous methodology to assess existing guidelines for concordances and discordances and to construct and perform exhaustive literature searches surrounding a number of clinical queries. In 2015, this work resulted in a comprehensive review and consensus guideline regarding the utility of screening for treatment-related cardiomyopathy in childhood cancer survivors, providing a rich resource for clinicians across a number of clinical practice environments.³⁸

6. Prevention

Successful prevention of cardiotoxicity in childhood cancer patients requires a multifactorial approach (Figure 3).⁶⁴ Primary prevention strategies include the evolution of oncology treatment protocols to reduce the exposure to anthracyclines, radiation, and other agents known to be cardiotoxic, as well as development of effective cardioprotective strategies. Secondary prevention strategies are directed towards survivors who have already been exposed to cardiotoxic agents but in whom clinical changes and symptoms have not yet occurred. While this includes testing the potential of pharmacologic agents to reverse pathologic cardiac remodelling, lifestyle changes including exercise, may also have an important role. Finally, tertiary prevention among those with structural heart disease is also important and is covered in further detail in the Section 7.

6.1 Primary prevention strategies

Given the high overall survival of many children now diagnosed with cancer, there is growing interest in testing regimens that reduce anthracyclines and radiation exposure to normal tissue while maintaining oncologic efficacy. It is estimated that more than half of children treated on contemporary protocols receive some anthracyclines and more than 20% receive radiation exposure to the chest.⁴ As mentioned earlier, a growing number of molecularly targeted agents are now being tested in both adult and paediatric settings, with the hope that they may begin to supplant conventional agents, including anthracycline and radiotherapy.¹⁷ Improvements in radiotherapy, in the form of intensity-modulated therapy and the use of protons (instead of photons), offer the promise of maintaining the therapeutic dose to the tumour volume while reducing the dose delivered to adjacent normal tissues. In theory, these refinements should reduce both acute and long-term side effects associated with radiotherapy, although long-term data for these modalities are still extremely limited.¹⁷

Alternative primary prevention strategies include the use of cardioprotectants and novel formulations of existing anthracyclines that may be associated with reduced cardiotoxicity. While several cardioprotective strategies have been tested in randomized clinical trials (RCTs; e.g.

amifostine, acetylcysteine, calcium channel blockers, coenzyme q10, and L-carnitine), none have been clearly efficacious, and currently none of these agents are recommended as standard of care.^{65,66} Only dexrazoxane (DRZ) has been approved by the US Food and Drug Administration and the European Medicines Agency as a cardioprotectant, with the indication reserved for adults with advanced/metastatic breast cancer who have already received a cumulative doxorubicin dose of 300 mg/m². Meta-analyses of DRZ-containing RCTs in general (primarily in adult breast cancer patients) showed a 60–80% risk reduction of clinical and subclinical heart failure.⁶⁵ Overall, DRZ did not appear to be associated with more side effects and anti-tumour efficacy did not seem to be compromised.⁶⁵ The American Society of Clinical Oncology has recommended considering DRZ for any adult cancers when more than 250 mg/m² of doxorubicin will be given.⁶⁶

Paediatric data regarding DRZ have been more limited. Paediatric RCTs published suggest that DRZ can ameliorate cardiotoxicity in children based on those exposed having less acute troponin release and/or changes in left ventricular wall thickness-dimension ratio (as a marker of pathologic remodelling) after 3–5 years.^{67–69} Among these paediatric trials, the primary cancer outcomes did not appear to differ by DRZ randomization status. COG is now attempting to prospectively assess long-term cardiac function in paediatric cancer survivors treated on prior DRZ-containing RCTs 15–20 years after exposure (NCT01790152). Finally, the potential efficacy of alternative anthracycline formulations such as liposomal versions also remains understudied in paediatric cancer patients.⁷⁰

6.2 Secondary pharmacologic prevention

Strategies for pharmacologic interventions in long-term cancer survivors who have been exposed to cardiotoxic therapies have mostly been adapted from studies in adults with asymptomatic LVSD due to causes other than anthracyclines (e.g. post-myocardial infarction). These include early screening and initiation of angiotensin-converting enzyme (ACE)-inhibitors and β -blockers to prevent the progression of asymptomatic LVSD to symptomatic disease.⁷¹ However, conventional measures of LVSD such as low EF and SF have increasingly been recognized as

inadequate for detecting subtle changes in cardiac function.⁷² Often, at the point when clinically significant changes in these parameters are detected, functional deterioration is irreversible, emphasizing the importance of prevention strategies in high-risk survivors prior to onset of LVSD.⁶³

Clinicians caring for childhood cancer survivors have been hesitant to use secondary pharmacologic strategies in asymptomatic ‘at-risk’ populations, due to the paucity of well-conducted RCTs that would provide the evidence to support such an approach. Data from adult cancer patients suggest that early pharmacologic intervention (e.g. enalapril) in high-risk patients, defined by an increased cardiac troponin-I value (>0.07 ng/mL) during treatment, can result in a decreased risk of cardiac dysfunction.⁷³ The only paediatric RCT to date evaluating efficacy of secondary intervention to prevent heart failure was a placebo-controlled trial of the ACE-inhibitor enalapril in survivors with a history of transient LVSD during cancer treatment.⁷⁴ While the study failed to demonstrate clinically significant improvement in cardiac function, Silber *et al.* suggested that those previously treated with high dose (≥ 250 mg/m²) of anthracyclines benefited most from the intervention. Due to small numbers in the high-dose arm and short follow-up of 2 years, investigators were unable to make more definitive recommendations regarding prevention in long-term survivors. Since β -blockers may be more likely to reverse the chronic cardiac remodelling than ACE inhibitors,⁷⁵ an ongoing RCT (NCT02717507) being conducted by COG is assessing the impact of carvedilol (vs. placebo) on prognostic markers of cardiac remodelling in ~ 250 childhood cancer survivors previously treated with high-dose (≥ 250 mg/m²) anthracyclines.

6.3 Conventional cardiovascular conditions

Besides attempting to directly alter the trajectory of pathologic cardiac remodelling, control of conventional cardiovascular conditions such as hypertension, dyslipidaemia, and diabetes is also critical. As reviewed earlier, at least in adult studies, the presence of these conditions may increase the risk of acute cardiotoxicity, including those seen with molecularly targeted agents. Multiple studies have also shown that these modifiable conditions are more common in survivors of childhood

Figure 4 Relative risk of serious cardiovascular outcomes in long-term childhood cancer survivors ($n = 10\,724$) in relation to cancer treatment exposures (ANTH, anthracycline; CRT, chest radiotherapy) and hypertension (HTN) status. Adapted from Armstrong et al.⁸ * $P < 0.01$ vs. referent. †Relative excess risk due to interaction [RERI] = 24 (95% CI 12–40); RERI > 0 indicates interaction was more than additive. ‡RERI = 45 (95% CI 17–106).

cancer compared with age-matched peers.^{6–8} Importantly, in combination with anthracycline and radiation exposures, hypertension (Figure 4), as well as dyslipidaemia and diabetes appear to further increase the risk of serious cardiovascular disease in more than additive fashion.⁸

Given that these conditions tend to present at younger ages compared with the general population, there is also a greater risk of underdiagnosis and undertreatment of these conditions in young adult-aged survivors. Furthermore, available survey data suggest that primary care providers tend to have limited knowledge of survivor-specific screening guidelines and survivors themselves also have reported low self-knowledge of past treatment exposures and health-related risks.^{76,77} However, remotely delivered counselling interventions may be effective in improving knowledge and healthcare surveillance. In a CCSS-based RCT ($n = 472$) testing advanced-practice nurse-led telephone counselling vs. printed survivorship educational materials only, Hudson et al.⁷⁸ demonstrated a 30% greater rate of cardiomyopathy screening in those who received counselling after 1-year (52% vs. 22%; $P < 0.001$). The CCSS is now conducting a follow-up RCT to see if undertreatment of hypertension, dyslipidaemia, and diabetes among high cardiovascular risk survivors can also be reduced following a remote nurse-led intervention (NCT03104543).

6.4 Exercise interventions

While pharmacologic interventions directed towards cardiac function and remodelling along with tighter control of modifiable cardiovascular risk factors are important, the global nature of cardiovascular toxicity provides a strong rationale for other treatment strategies with the capacity to augment or preserve cardiovascular function. Exercise therapy, a pleiotropic intervention with the unique capacity to improve function across multiple organs, is the first-line treatment for adult patients with coronary artery disease, chronic stable angina, and heart failure.⁷⁹ Research into the application of exercise following a cancer diagnosis—a

field now known as ‘exercise-oncology’—has increased dramatically over the past two decades.⁸⁰ National organizations (e.g. COG)⁵⁷ have published exercise guidelines for childhood cancer survivors following treatment (i.e. ≥ 150 min of moderate-intensity or ≥ 75 min of vigorous-intensity exercise/week). However, compared to extant exercise evidence in patients with adult-onset cancers, the potential cardioprotective properties of exercise in paediatric oncology have received limited attention.⁸¹ Here, we provide an overview of the evidence investigating the efficacy of exercise therapy on cardiovascular toxicity during and after cancer treatment.

During cancer therapy, both prior and ongoing investigations in exercise-oncology focus predominantly on the efficacy of exercise to offset the acute adverse effects of anticancer therapy on physical functioning and patient-reported outcomes.^{82,83} Research examining the potential cardioprotective properties of exercise during therapy are primarily explorative, descriptive pilot studies.⁸⁴ In a recent systematic review, Morales et al.⁸⁵ reported that among eight RCTs of exercise during therapy, four assessed cardiorespiratory fitness (an integrative assessment of global cardiovascular function), with two demonstrating a significant improvement in fitness after 12–52 weeks of home-based aerobic exercise intervention. However, in general, limited attention has been given to determining whether exercise during therapy is an effective intervention to prevent and/or mitigate acute or chronic treatment-induced cardiovascular toxicity.

Following the cessation of cancer therapy, epidemiological studies have investigated whether exposure to exercise lowers long-term risk of late serious cardiovascular events among long-term childhood cancer survivors. In these studies, featuring upwards of 15 000 survivors, there was a dose-dependent association between baseline activity levels (0–21 metabolic equivalent task-h/week) and subsequent cardiovascular disease, as well as all-cause mortality after 8–12 years of follow-up (Figure 5).^{86,87} Supportive data are also available from several single arm studies that examined 12–16 week-long home-based aerobic and resistance interventions.^{88,89} Alternatively, several small RCTs have evaluated home-based mobile health interventions, but reported no significant differences in physical activity levels after 10–24 weeks, suggesting that structured exercise and/or supervised exercise may be required to improve cardiovascular endpoints.^{90,91} An RCT evaluating the efficacy of a 12-month home-based aerobic and resistance exercise on cardiovascular risk factors among 150 childhood cancer survivors is ongoing.⁹²

7. Treatment considerations

The wide spectrum of cardiotoxicity of currently employed conventional and targeted agents demand a multi-disciplinary approach to the management of children with cancer. Once a patient has evidence of ACT as defined by echocardiographic changes including left ventricular dilation, wall thinning, and systolic dysfunction, it is important to separate those patients who have heart failure symptoms with those who remain asymptomatic. There are robust, large RCTs in the adult literature that support the treatment of heart failure with reduced EF using a regimen of reverse remodelling medications including ACE inhibitors, beta blockers, and aldosterone receptor antagonists.⁷¹ These medications are considered standard of care in adult heart failure management, both in symptomatic and asymptomatic patients. There are newer medications that have also been studied in adult heart failure patients including the combination drug sacubitril/valsartan that have shown greater survival compared to enalapril.⁹³ Unfortunately, patients with cardiomyopathy

Figure 5 Cumulative incidence of all-cause mortality according to quartiles of vigorous exercise at study entry. Adapted from Scott *et al.*⁸⁷ MET, metabolic equivalent task.

secondary to anthracyclines and chest radiation were excluded from these large adult trials, so the evidence is not as clear regarding the efficacy of these medications among cancer survivors (of any age).

Given the significantly lower incidence of heart failure in paediatrics compared to adults, it has not been feasible to conduct large-scale definitive RCTs looking at the same heart failure medications that are currently in use in the adult population.⁹⁴ Despite this, the consensus among the paediatric heart failure community has been to utilize these same standard heart failure therapies including ACE inhibitors, beta blockers, and aldosterone receptor antagonists to treat children with LVSD.⁹⁵ This has been translated to those paediatric patients who develop ACT as well.

There are limited paediatric studies examining the effectiveness of ACE inhibitors in paediatric patients with ACT. One such retrospective study reviewed 18 children who had developed left ventricular dysfunction following treatment of their childhood cancer with a mean time between completion of doxorubicin treatment and initiation of enalapril of 7 years and a median follow-up time of 10 years.⁶³ While Lipshultz *et al.* saw improvement in LV dimension, SF, and mass in the first 6 years of enalapril treatment, those improvements were only temporary as further decline was seen between 6 and 10 years of starting enalapril. As mentioned earlier (see Section 6),

Silber *et al.*⁷⁴ examined 135 survivors of paediatric cancer with at least one cardiac abnormality including echocardiographic abnormalities (left ventricular SF < 29% or a 10% decrease from a prior study), gated nuclear angiography abnormalities (EF < 55%, decrease in EF with exercise, or a 10% decrease in EF from a prior study), a decreased maximal cardiac index on cycle ergometry at peak exercise, or a prolonged QTc interval. These patients were randomized and blinded to receive enalapril or placebo. After 1 year of treatment, LV end-systolic wall stress was reduced in the enalapril group vs. the placebo group, although no differences were seen in the maximal cardiac index or SF, which presumably are more indicative of functional cardiac status. The conclusion from the authors was that while there may be theoretical benefit in wall stress reduction, it is still unproven what clinical benefit is achieved with enalapril.

Diastolic dysfunction is often an earlier echocardiographic finding before evidence of systolic dysfunction is detected both from anthracycline exposure⁹⁶ and chest radiation.⁹⁷ Unlike systolic dysfunction, there has been no data to support medical therapies in improving survival in patients with diastolic dysfunction. The mainstay of treatment for diastolic dysfunction is symptomatic relief including diuretics for volume overload and antihypertensives for blood pressure control.⁷¹ The standard reverse modelling medications for reduced systolic function include

ACE inhibitors and beta blockers, which can also be used for hypertension management. This will generally also improve diastolic and systolic dysfunction. Therefore, diligent screening for hypertension and medical management once hypertension is recognized is vital to preventing further complications of cardiovascular disease.

8. Conclusion

Significant advances in understanding the epidemiology and risk factors related to acute and late cardiovascular toxicities have occurred in the past decade. This knowledge has greatly informed the creation of national and international guidelines related to ACT and more general cardiovascular health screening among childhood cancer survivors. In addition, there is a growing body of evidence supporting the importance of controlling modifiable cardiovascular risk factors, particularly as cancer survivors age, and the cardioprotective role of exercise. However, many evidence gaps remain. These include: (i) the role for genetic risk factors, a growing number of which have been reported, but many of which require further validation and integration as predictive risk factors; (ii) similarly, the validity and integration of blood biomarkers with imaging biomarkers to detect individuals at risk for ACT earlier; and (iii) a more robust evidence base for the efficacy of primary and secondary cardioprotective strategies, as well as treatment for those diagnosed with clinical cardiomyopathy. Finally, as cancer therapy evolves with the adoption of new agents and technology, it remains a challenge to conduct long-term follow-up of survivors given the long average latency between cancer treatment and cardiotoxicity development. Given the relative rarity of paediatric cancers, adequate resources and international collaborations to facilitate follow-up and to pool data are critical. Increased collaboration between cardiologists, epidemiologists, exercise and behavioural scientists, and oncologists are also critical to design robust studies that further advance the field and improve the quality of life of all childhood cancer survivors.

Authors' contributions

All authors jointly conceived the work, participated in its writing, critically reviewed the content, provided final approval of the work, and agree to be accountable for the work.

Conflict of interest: none declared.

Funding

This work was supported by the US National Institutes of Health (CA204378 and CA211996 to E.J.C. and CA008748 to J.M.S.); AKTIV Against Cancer and Kavli Trust to J.M.S.; Leukemia and Lymphoma Society (2315-17 to S.A.H.); and the Michael Smith Foundation for Health Research and the Canadian Cancer Society to C.J.R.

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