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REVIEW ARTICLE

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State of the art review: Chemotherapy-induced cardiotoxicity in children

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Abstract

Chemotherapy-induced cardiotoxicity in adults and children is a topic with a growing interest in the cardiology literature. The ability to detect cardiac dysfunction in a timely manner is essential in order to begin adequate treatment and prevent further deterioration. This article aims to provide a review on the myocardial injury process, chemotherapeutic agents that lead to cardiotoxicity, the definition of cardiotoxicity, and the methods of timely detection and treatment.

KEYWORDS

anthracyclines, cardiotoxicity, chemotherapy, congestive heart failure, pediatrics

1 | INTRODUCTION

With the advent of new chemotherapeutic treatments, survival rates for childhood malignancies are at an all-time high, now exceeding 80% at 5 years.[1] This has led to the development of a large population of childhood malignancy survivors, who require multidisciplinary medical care related to the aftereffects of their disease and treatment. It is now estimated that there are over 400 000 survivors in the USA.[2] Other than recurrence of the patient's initial malignancy or a secondary malignancy, numerous studies have demonstrated that cardiovascular disease is the leading contributor to morbidity and mortality in survivors.[3] Relative to their healthy counterparts, survivors are at an eightfold higher risk of cardiovascular related deaths, including myocardial infarction with coronary artery disease, cardiomyopathy with congestive heart failure, and cerebrovascular events.[4] In childhood survivors with 30 years of follow-up, 8% had congestive heart failure.[5] These realities call for increased involvement of the pediatric cardiologist for the detection and treatment of chemotherapy-induced cardiotoxicity (CIC). The main objective of this review is to provide a background knowledge of the cause of CIC and the techniques employed to diagnose and treat CIC.

1.1 | Chemotherapeutic agents

Anthracyclines (AC), doxorubicin and daunorubicin, were originally used as antibiotics, but were considered too toxic. They later were used as mainstay drugs in the early treatment protocols for many childhood malignancies. Their mechanism of action includes inhibition of DNA replication and RNA transcription, particularly in rapidly dividing cells, and in the generation of free radicals and AC-iron complexes.[6–9] The free radicals can cause direct damage to the cell membrane in addition to their metabolism by the mitochondria, which triggers cellular apoptosis (Figure 1).

The cardiomyocyte is believed to be particularly susceptible for three reasons. First, there is a low concentration of free radical scavenger molecules, leading to increased susceptibility to free radicals generated by ACs and, second, the myocardial cell has one of the highest concentrations of mitochondria of any human cell, leading to increased apoptosis cascade activation.[10–13] There are two hypotheses for CIC: (1) "multiple mechanisms"[7] and (2) "multiple hits."[14] The multiple mechanisms hypothesis describes the formation of iron-AC metabolites, reactive oxygen species, and inhibition of topoisomerase B enhancing the damage each agent can do in combination on the myocyte. This would also be affected by genetic predisposition. The multiple hits hypothesis differs slightly, in that it describes the effect of sequential injuries done by a pharmacologic agent on the myocyte.

Initial use of ACs was often limited by the development of cardiotoxicity with acute congestive heart failure, which occurred in up to 10% of patients.[15,16] Cardiotoxicity was consistently noted with large cumulative doses of these medications, prompting further investigations on determining a safe dose. The first groups studied the effect of cumulative dose of doxorubicin on the overall incidence of congestive heart failure in adult cancer patients and demonstrated an exponential increase in congestive heart failure at dose ranges of 450–550 mg/m^2.[17,18] Further

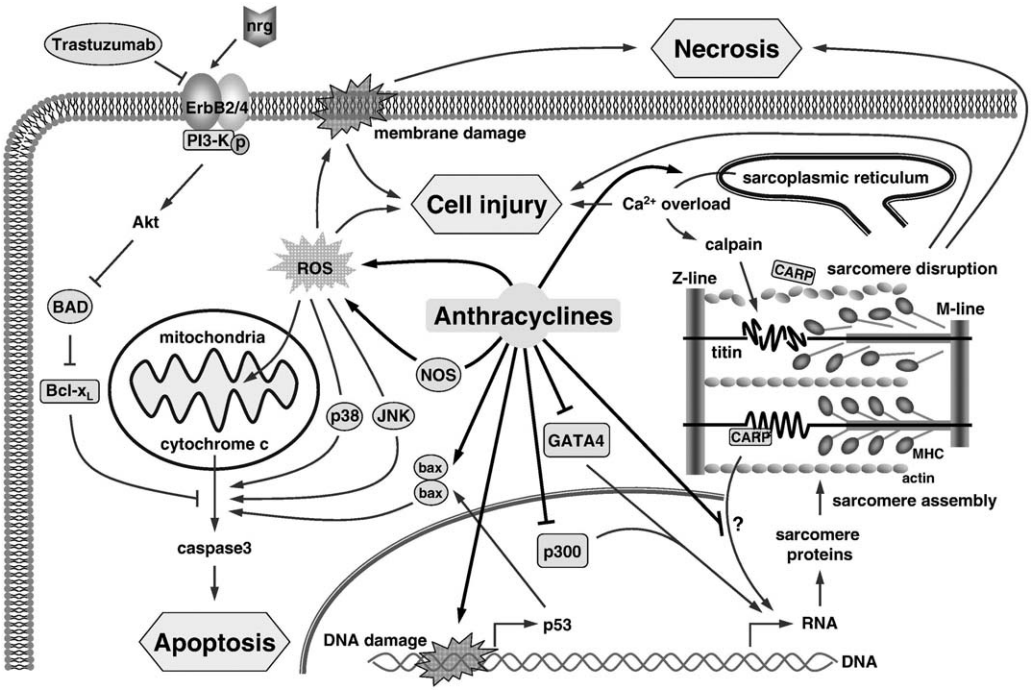

FIGURE 1 Schematic representing the many biochemical processes of anthracycline-induced cardiotoxicity within the cardiac myocyte. Reproduced with permission from Elsevier[9]

work showed that doses of 250–300 mg/m^2 carry a lower risk of CIC, although there is variation in susceptibility among individual patients.[19] In a study of children that received a heart transplant for CIC, 5 of the 17 patients had cumulative dosage less than 300 mg/m^2.[20] Even at doses as low as 45 mg/m^2, some patients have shown cardiac effects at 5 years or more of follow-up,[21] suggesting that development of CIC depends on more than just the dose given. This variation in dose-response has led many to conclude that there is no truly safe dose of AC and highlights the importance of close involvement of cardiologists and oncologists alike.

Over time, monitoring protocols for CIC have become more sophisticated. Billingham et al was the first group to report on the results of endomyocardial biopsies of adult patients exposed to ACs.[22,23] They developed a scoring system based on the histological changes of the myocardium, ranging from normal to vacuolar changes to fibrosis to necrosis. The histological appearance of the patient's biopsy specimen often provided the basis for decision on continuing AC therapy.

1.2 | Risk factors

Concomitant radiation exposure to the chest also adds to the risk of developing CIC. Radiation therapy damages the pericardium, coronary arteries, and conductive tissue in addition to the myocardium.[5,24–26] Similar to AC exposure, the risk is dose dependent. High doses (35–40 Gy) carry the greatest risk, but low doses (5 Gy) have also been associated with cardiovascular disease.[5,27] Other risk factors for CIC include younger age (<4 years), Down syndrome, female sex, African American ancestry, and features of metabolic syndrome (hyperlipidemia, hypertension, and obesity).[28] Carriers of certain genetic mutations are also more susceptible, such as with the hemochromatosis gene (*HFE C282Y* allele), which is thought to relate to higher concentrations of cellular iron leading to increased AC-iron complexes.[29] Patients with this mutation may be as much as nine times higher risk of CIC. Much research has focused on genetic polymorphisms relating to proteins that affect AC pharmacokinetics,[30–35] mechanisms of free radical deactivation,[36] or repair of myocardial damage.[37] Genetic testing of patients who will receive ACs may have the potential to inform medical decision making, in an effort to prevent CIC.[38]

In an effort to reduce the risk of CIC, structural analogs of doxorubicin and daunorubicin, called epirubicin and idarubicin, respectively, were developed. These agents have a higher therapeutic index with less toxicity but remain dose dependent.[28] Large trials and meta-analyses in adults and children have not demonstrated a reduction in CIC.[39] Other chemotherapeutic agents such as mitoxantrone, high-dose cyclophosphamide, bleomycin, and vinctristine have been hypothesized to potentiate the cardiotoxic effects of ACs in limited studies.[13,40,41]

1.3 | Definition of cardiotoxicity

CIC is categorized based on the timing of its occurrence into three groups: acute, early onset, and late onset.[40] The acute type is rare and occurs within 1 week of exposure to ACs. The risk factors for this subtype are unknown, but fortunately, the depression of contractility is fully reversible with removal of the inciting agent. Arrhythmias may also be seen. Early onset CIC occurs within 1 year of first AC exposure. It is characterized by left ventricular dilation and depressed contractility

(Supporting Information Video S1), and its course is progressive. A study of 115 children with acute lymphoblastic leukemia reported heart failure in 11 (~10%) within 1 year exposure.[42] Finally, late onset, or chronic CIC occurs more than 1 year out from first exposure. This form of toxicity also mimics a dilated cardiomyopathy, but often has restrictive features in addition.[21] Like early onset, this subtype is also progressive.

The focus of CIC research has been in the detection and recognition of early onset and late onset CIC. It can be present as subclinical ventricular dysfunction to overt heart failure and cardiomyopathy. Lipshultz et al found significant decreases in LV contractility, shortening fraction, LV mass, and wall thickness over time in pediatric patients.[21] There is no published, or agreed-upon, definition of CIC for pediatric patients. Rather, the definition of CIC has come from adult data, which has been variable. This variability has led to ambiguity in the actual incidence of CIC. Historically, CIC has been defined as a decrease in left ventricular ejection fraction (LVEF) by more than 10% to a value of less than 50%.[43] More recently, an expert consensus from the American Society of Echocardiography and European Association of Cardiovascular Imaging defined CIC as a decline in LVEF by more than 10% to a value of less than 53%.[44] An LVEF of 53%, based on large normal population data in adults, is now considered a normal value. When these findings are first recognized, a cardiology consult and a confirmatory imaging examination should be obtained 2–3 weeks later. If the ventricular function remains depressed to the same level, or beyond, then chemotherapy is halted and cardiac treatment is started.

2 | DETECTION

Prompt, early detection of CIC should be the primary goal of the cardio-oncology team, as doing so leads to treatment and a better chance at recovery.[45] In an ideal situation, CIC could be detected prior to the deterioration of ventricular dysfunction, and modern echocardiographic research has focused primarily on this goal. The challenge is in distinguishing between the expected and unavoidable myocardial injury inherent to AC exposure and when the same heart begins to change in a maladaptive manner, leading to cardiomyopathy (Figure 2). A large study of adult cancer patients receiving ACs assessed the LVEF at baseline and every 3 months during treatment and every 6 months after treatment completion.[46] The investigators defined CIC as LVEF decline of at least 10% to a value less than 50%. Once CIC was detected, patients were started on treatment. CIC occurred in 9%, with 98% of that group deteriorating within the first year after completing treatment. Only 11% of these adult patients experienced full recovery of LVEF, 71% had partial recovery, and 18% had no recovery at all. From this study, the two most noteworthy risk factors for the lack of recovery were (1) the LVEF at the end of chemotherapy and (2) the cumulative dose of AC with a 10% increase per additive 50 mg/m^2.

2.1 | Imaging protocols

A recent consensus publication on surveillance of childhood cancer survivors was issued to aid in standardizing screening protocols based on current available evidence.[47] This group has recommended that, in at-risk patients, (1) surveillance be lifelong and occur at least every 5 years, (2) at-risk patients that are pregnant require closer monitoring, (3) evaluation by a cardiologist is necessary in the presence of cardiomyopathy even when asymptomatic, and (4) at-risk patients should also be screened for modifiable cardiovascular risk factors such as dyslipidemia, diabetes, hypertension, and obesity. Patients considered to be at greater risk, based on cumulative exposure to ACs and concomitant radiation therapy, should be screened more frequently. In accordance with this, the Children's Oncology Group (COG) long-term follow-up guidelines recommend a screening echocardiogram for survivors annually, every other year, or every 5 years depending on age at diagnosis, cumulative AC dose, and radiation dose.[48] Employing these guidelines, Spewak et al. examined 1700 echocardiograms for 850 patients and reported an overall yield of cardiac dysfunction in 2.1%.[49] A positive echocardiogram was associated with AC dose >300 mg/m^2 and radiation exposure. No patients with a dose <100 mg/m^2 had abnormal imaging over the study period. The authors concluded that screening for low-risk patients should occur less frequently. At present, there are no guidelines for frequency of screening during chemotherapy treatment. An international task force recently produced a risk score in an effort to predict the development of cardiomyopathy in

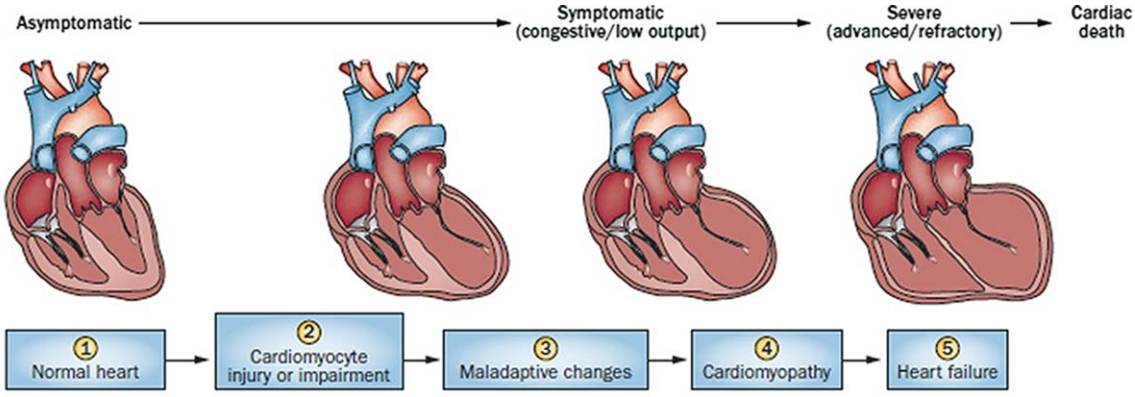

FIGURE 2 Schematic representing natural history of cardiotoxicity development. Reproduced with permission from Wiley[110]

childhood cancer survivors by the age of 40 years, with reasonably good accuracy.[50] Further studies of large cohorts are needed to guide screening strategies.

2.2 | Two-dimensional echocardiography

Two-dimensional echocardiography is considered the preferred test of choice because of its noninvasive nature, availability, and does not expose the patient to further radiation. However, standard echocardiographic parameters like LVEF may lack sensitivity for detection of systolic dysfunction. A significant decline in LVEF may be a late finding in CIC, further emphasizing the need and importance of early detection. In particular, measurement of LV function by shortening fraction should be done with caution as it only measures two of the walls of the LV for its calculation, and it is prone to high inter-observer variability.[51] Markers of diastolic dysfunction such as mitral E and A wave ratio, E to E′ ratio and deceleration time are of limited use in the pediatric population as well.[52] Furthermore, published normal for these diastolic parameters come from studies of small pediatric populations and the normal values have a wide range.[53]

Reproducibility of ventricular function has been examined in adult cancer patients. A study of 56 adult patients with stable function, defined as no significant change in LV global longitudinal strain, were followed over 1 year.[54] Two- and three-dimensional functions, with and without contrast enhancing agents, were analyzed for variability. Three-dimensional function assessment demonstrated the best temporal and intra- and interobserver variabilities. Another study of adult cancer survivors at risk for CIC compared LVEF via two-dimensional Simpson's biplane method to cardiac MRI.[55] The authors showed that two-dimensional LVEF was on average overestimated by 5% points. Furthermore, nearly 10% of patients had an abnormal LVEF <50% by cardiac MRI but were considered normal by two-dimensional analysis (Figure 3). LVEF is a good predictor of outcomes in the general population and in cardiomyopathies, but it has poor sensitivity in the detection of the subtle changes in LV function that are important for early detection of CIC. This is due to the numerous geometric assumptions made in calculation of LVEF by Simpson's biplane or bullet methods, the difficulty in adequately visualizing the endocardial borders, and the variability between operators in tracing these borders if they are seen. For instance, in a study of adult cancer patients, a group of investigators followed ASE guidelines for calculation of LVEF using Simpson's biplane method.[54] They reported differences in absolute LVEF of approximately 10%. Furthermore, detection of ventricular dysfunction in terms of LVEF may not come soon enough to begin treatment and fully reversible the damage.[46]

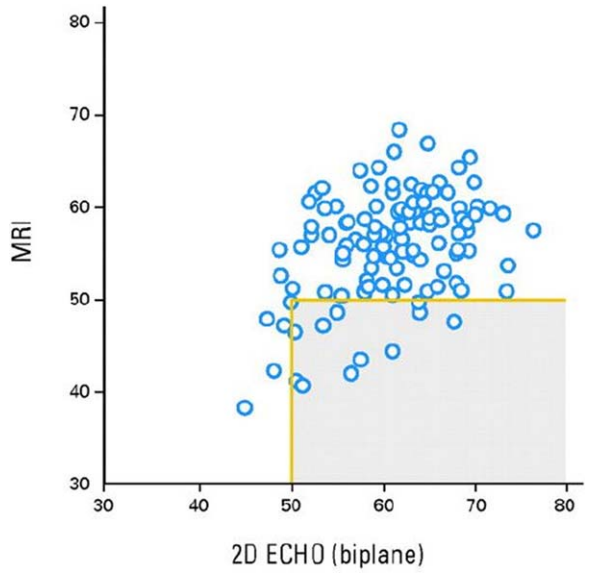

FIGURE 3 Graphical representation of the relationship of left ventricular ejection fraction measured by cardiac MRI and two-dimensional echocardiography. A significant proportion of patients' ejection fraction was overestimated by two-dimensional echocardiography, leading to false-negatives for detection of ventricular dysfunction. Reproduced with permission from the American Society of Clinical Oncology[55]

2.3 | Strain

In light of the poor sensitivity of 2D LVEF measurement, the use of LV strain analysis has become an area of interest. Strain obtained by speckle tracking two-dimensional echocardiography is angle independent and has been validated with low inter- and intraobserver variability.[56–58] Several studies in adult cancer patients have evaluated the use of LV strain as a detector of subclinical dysfunction.[59] In the majority of these studies, the myocardial deformation that strain measures is impaired prior to the development of decreased LVEF, and this persists throughout cancer treatment. Decreased deformation, in terms of strain values, lies between 10% and 20% in adults over the course of treatment.[43] Strain also offers the benefit of evaluating regional abnormalities and layers of myocardium (subendocardial, midmyocardial, or subepicardial). It has been shown that AC exposure does not discriminate towards one particular layer, rather all layers seem to be affected.[60,61] Experimental animal models have shown this as well, as apoptosis occurs in all myocardial layers.[62] The strongest strain predictor for detection of CIC is the relative change in global longitudinal strain (GLS).[60,63–67] A fractional change of >15% from baseline GLS appears to be a significant cutoff value.[65] An important consideration in the use of strain is consistency. Differences are seen across software vendors, and this is strain's greatest limitation.[68,69] When evaluating patients longitudinally using strain, efforts to be consistent are paramount.

Pignatelli et al. studied 25 pediatric cancer patients at risk for CIC, who had received 60–450 mg/m^2 and had a normal LVEF ≥55%.[70] Fifteen of the 25 (60%) had abnormal global longitudinal peak systolic strain, and 19 (76%) had abnormal peak circumferential strain, when compared to age-matched controls (Figure 4). The interobserver variability of the strain values was less than 5%. Another study by Moon et al evaluated pediatric survivors, with normal LVEF and shortening, after chemotherapy completion.[71] The study evaluated strain parameters for the posttreatment echocardiogram and to age-matched controls. Nearly all LV strain parameters were impaired. The favorable interobserver variability and ability to detect subclinical ventricular

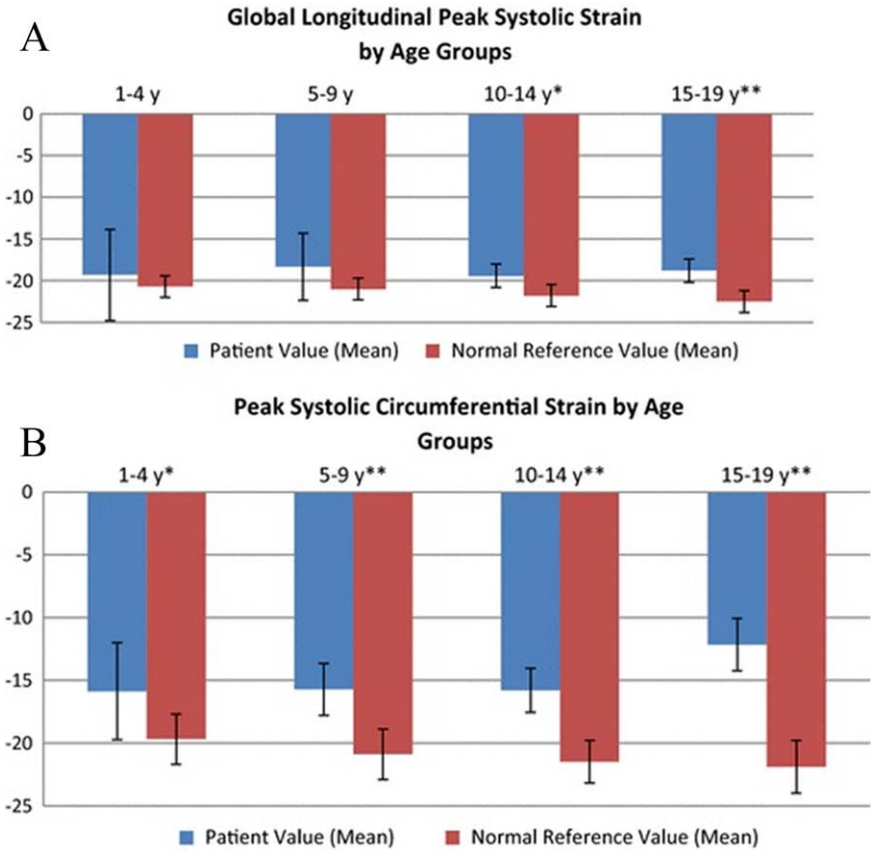

FIGURE 4 Bar graphs representing comparison of global longitudinal (A) and global circumferential strain (B) for the left ventricle in patients exposed to anthracyclines versus healthy controls. This demonstrates impaired ventricular deformation (strain) in those exposed to anthracycline across all age groups. Reproduced with permission from Springer[70]

dysfunction in the absence of systolic impairment on two-dimensional echocardiography point to strain analysis as a potential contributor for early detection in patients at risk of CIC. Although the use of strain is promising for children at risk, it is not known if the impairment of strain predicts future risk of CIC.

2.4 | Diastolic function

Diastolic function has been evaluated in adults undergoing cancer treatments. One study demonstrated a prolonged isovolumic relaxation time preceding a decline in LVEF, which occurred months later.[72,73] Another study of 52 breast cancer patients had impaired diastolic function by strain analysis immediately after (at 1 week) exposure to ACs.[61] These changes were associated with systolic impairment of strain at the end of the patients' chemotherapy treatments. These studies provide a basis for the theory that impaired diastolic function precedes systolic impairment. In pediatric CIC, interrogation of diastolic dysfunction has mostly been limited to transmitral Doppler indices such as the E/A ratio, E/e′ ratio, deceleration time, and isovolumetric relaxation time with reported tendency towards abnormal LV relaxation.[74] Dorup et al reported changes in diastolic indices of children treated with ACs, namely lower E wave velocity and prolonged isovolumetric relaxation time.[73] In general, the use of these standard transmitral indices have limitations as they are dependent on afterload and heart rate, and they lack sensitivity and specificity.[75] Newer modalities such as diastolic strain and strain rate have become more of a focus in CIC. In children, Moon et al. found that diastolic strain rate was the most discrepant variable between patients at-risk for CIC and healthy controls.[71] These findings may suggest that diastolic dysfunction occurs before the onset of systolic dysfunction, although more literature is certainly called for.

2.5 | Cardiac MRI

There should be an increasing role for cardiac MRI in the monitoring of these patients, as it offers some advantages over echocardiography. The reproducibility of LV function analysis is excellent and is not necessarily affected by poor imaging windows or altered ventricular geometry. MRI assessment of LV volume and function relies on a series of short axis cuts of the entire LV, which provides excellent definition of myocardial borders and is not handicapped by geometric assumptions that are inherent to two-dimensional echocardiography. These measurements have been shown to be more reproducible than two-dimensional echocardiography.[76–78] Measurement of LV mass may be of significant use as a diagnostic tool for CIC, as it has been shown to decrease with higher doses of ACs.[79] A study of 28 children at risk for

CIC found that end-systolic volume increased, and EF for both the LV and RV decreased after AC exposure using MRI.[79] MRI has been shown to detect ventricular dysfunction when two-dimensional analysis reports a normal LVEF in 10% of patients.[55] In light of this data, the use of cardiac MRI may be best suited in determining the true LVEF when echocardiography reaches a "threshold" or a value approaching 55%, when the decision to discontinue or pause chemotherapy needs to be made. Another use is in the patient with poor acoustic windows, or the patient that an accurate Simpson's biplane calculation of LVEF is impossible. CMR has also begun to emerge as a valuable entity for the identification of early changes in the cardiac myocardium by evaluating regional wall motion by myocardial strain assessment. This was demonstrated in a recent study by Drafts et al., whereby LV circumferential strain was decreased 6 months post treatment and correlated with decreased LVEF.[80] Myocardial tissue characterization by CMR is a recent development that has been utilized in several pathologies, and shows great promise for detection of early AC-induced cardiotoxicity. The myocardial injury from AC has an initial phase characterized by inflammation and myocardial edema. Magnetic resonance imaging with T2-weighting is able to quantify myocardial edema, and has shown an ability to identify this cardiac change during AC treatment.[81,82] Further along the histological continuum of cardiac injury is cell necrosis and fibrosis. Myocardial characterization by T1 mapping and extracellular volume quantification is able to similarly quantify these findings.[83] MRI is certainly more time-consuming than a follow-up echocardiogram and may not be as readily available at every pediatric center. Oftentimes, younger children or those with claustrophobic tendencies require sedation to obtain good MRI images and this is a significant limitation.

2.6 | Biomarkers

Biomarkers also may play a role in the detection of CIC. Advantages include good availability, minimal invasiveness, and limited assay variability. Cardiac troponins are the gold standard biomarker measures in any scenario involving myocardial injury. Troponin I (TnI) has been shown as an effective measure of myocardial injury in adults exposed to ACs.[84] Patients with persistent elevation of TnI seem to be at particular risk of developing CIC.[84–87] Other biomarkers like B-type natriuretic peptide and N-terminal pronatriuretic peptide have also been studied, but have shown conflicting results in predicting systolic impairment.[88–90] A study examined the use of GLS and TnI in adults and found cut-off values for a negative predictive value of 91% in patients at risk.[60,91] Troponin T (TnT) has been shown to be elevated in children treated with AC. Lipshultz et al demonstrated elevated N-terminal probrain natriuretic peptide and TnT in children exposed to ACs.[92] Elevations in both of these biomarkers within the first 90 days of chemotherapy treatment were associated with impaired LV function at medium-term follow-up. Although biomarkers appear promising, there remain some limitations. TnT is seen in skeletal muscle in addition to myocytes, and therefore may not be a direct reflection of cardiac injury. The appropriate timing of when to obtain and the number of tests needed are subject to debate. Regardless, there seems to be a role for cardiac biomarkers in monitoring of patient at risk of CIC, particularly when added to imaging.

3 | TREATMENT

3.1 | Cardioprotection

Several agents have been trialed as cardioprotectants, in the hopes of preventing CIC. However, the only agent approved by the US Food and Drug Administration is dexrazoxane, which is an iron-chelating agent and topoisomerase inhibitor 2B.[93,94] Through these mechanisms of action, dexrazoxane prevents the formation of iron-AC complexes limiting potential toxicity and inhibits AC-related DNA damage. One concern over its use is the theoretical inhibition of the ability to eradicate the cancer cell, leading to poorer malignancy cure rate. There is also a concern over the possibility of secondary malignancy. However, neither of these concerns have been proven.[94,95] There have been prospective studies examining the potential protective effects of dexrazoxane in children and have shown better preservation of shortening fraction and end-systolic dimension,[94,96] and reduced TnT levels.[93] The role of dexrazoxane is likely to expand in the treatment of childhood cancers, particularly in those patients who will require large cumulative doses of ACs over the course of their treatment.

3.2 | Medical therapy

Treatment of CIC is adapted from adult studies. The pediatric recommendations for treatment of systolic dysfunction list diuretics and angiotensin-converting enzyme (ACE) inhibitors as class I drugs.[97] Beta-blockers and aldosterone receptor antagonists are class IIa. Studies in adults have shown that ACE inhibitors both prevent further decline in LVEF and aid in recovering some function. One such study by Cardinale et al. showed that starting an ACE inhibitor after initiation of chemotherapy in those with an elevated TnI resulted in preservation of LVEF compared to the control group.[98] Another study by Cardinale et al. began treatment in 201 patients with LVEF $\leq$45%.[99] Patients responded better to heart failure treatment when initiated more promptly. In this study, all patients were started on enalapril, and carvedilol was added if the patient could tolerate it. The percentage of

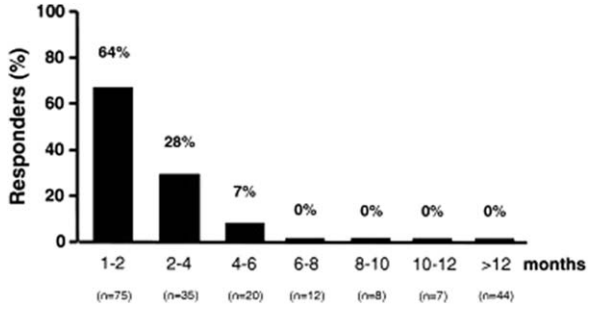

FIGURE 5 Percentage of patients who had ventricular dysfunction by two-dimensional echocardiography that responded to medical therapy with enalapril. With increasing time to initiation of enalapril, there is less of a response in recovering ventricular function. Reproduced with permission from Elsevier[99]

treatment responders decreased with time from end of chemotherapy to initiation of heart failure treatment (Figure 5). Interestingly, there were no responders after 6 months' time. There was no difference in patients receiving enalapril alone versus enalapril plus carvedilol. A very interesting study examined the differences between patients that were started on an ACE inhibitor prior to beginning chemotherapy versus those receiving a placebo. They were evaluated by echocardiography and MRI at baseline and again at 6 months into chemotherapy treatment.[100] Interestingly, there was no change LVEF in the enalapril group. This was significantly different than the placebo group, who experienced a 6.7% decline in LVEF over 6 months. A similar study employing strain imaging showed a significant decrease in systolic function as well.[101]

A retrospective study evaluated 18 children cancer survivors treated with an ACE inhibitor, and showed preservation of LV dimensions, shortening fraction, LV mass in the first 6 years of follow-up. In those with congestive heart failure at the start of ACE inhibitor treatment, all either died or went on to heart transplantation.[102] A study of 50 children randomized to receive carvedilol or placebo prior to each round of AC treatment found significantly better preservation of shortening fraction and LV strain in the carvedilol group 1 week after chemotherapy.[103] A randomized and controlled trial of 150 asymptomatic childhood cancer survivors examined the effect of enalapril versus placebo. The investigators found a difference in the reduction of LV wall stress.[104] However, it should be noted that a significant proportion of these patients experienced side effects from enalapril, such as dizziness or hypotension.

Finally, the AHA/ACC recommendations for patients with dilated and restrictive cardiomyopathies endorse restriction from competitive sports, with the exception of lower intensity sports (class 1A).[105] Patients with CIC should be incorporated into this group as well, as they have similar physiologic features of both dilated and restrictive cardiomyopathies. However, it is important for these patients to continue to be physically active, as modifiable risk factors for future cardiac events include diabetes mellitus, hypertension, obesity, and hyperlipidemia. Cardiologists can be leaned on for aiding in these decisions and to consider what would be safe.

3.3 | Advanced therapies

The same advanced heart failure therapies for children with heart failure are available to those with CIC, such as ventricular assist devices and orthotopic heart transplantation. Outcomes in adult CIC patients are comparable to those without.[106] Adult CIC patients are more likely to utilize mechanical circulatory support as destination therapy, due to the requirement that a patient be free of cancer for at least 5 years. Their survival on mechanical circulatory support is no different than the general population. However, CIC patients require right ventricular assist devices more frequently and have greater bleeding risk.[107] When these patients are transplanted, they have similar outcomes to their counterparts with 86%, 79%, and 71% survival at 1, 3, and 5 years, respectively. However, the cancer patients have higher rates of infection and malignancy after transplantation.

In children, the first study looking at orthotopic heart transplant was in 2004 by Ward et al., who reported on the outcomes of 17 patients.[20] Their AC dose ranged from 240 to 540 mg/m^2. The main purpose of the study was to report the incidence of cancer recurrence, which occurred in only one patient. A larger and more recent study of 80 transplanted CIC patients from the Pediatric Heart Transplant Study Group reported no difference in graft survival or malignancy.[108] However, the risk of infection and death from infection was higher in this population. From this study, one can calculate that approximately 10 heart transplants are performed for CIC annually.[109]

4 | CONCLUSIONS

Due to the improved survival outcomes of pediatric malignancy, the incidence of CIC will continue to rise, necessitating a strong knowledge of this problem for the pediatric cardiologist. Early detection of dysfunction is key, so as to begin treatment prior to maladaptive myocardial changes occurring. More advanced imaging techniques, such as strain and MRI, may play significant roles in this undertaking. Above all else, harmonious collaboration between the oncologist and cardiologist is essential to ensure patients are cured from their malignancy, with a watchful eye on preserving cardiac function over the course of their treatment and in long-term follow-up.

CONFLICT OF INTEREST

The authors have conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

All listed authors fulfilled authorship criteria: (1) substantial contributions to research design, or the acquisition, analysis or interpretation of data; (2) drafting the paper or revising it critically; and (3) approval of the submitted and final versions.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

VIDEO S1 Short axis view focused on the impaired left ventricular systolic function in a patient with acute myeloid leukemia after two rounds of anthracycline treatment. The left ventricle is dilated with normal muscle wall dimensions. The calculated ejection fraction by Simpson's biplane was 38%

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