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Managing Chemotherapy-Related Cardiotoxicity in Survivors of Childhood Cancers

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Abstract

In the US, children diagnosed with cancer are living longer, but not without consequences from the same drugs that cured their cancer. In these patients, cardiovascular disease is the leading cause of non-cancer-related morbidity and mortality. Although this review focuses on anthracycline-related cardiomyopathy in childhood cancer survivors, the global lifetime risk of other cardiovascular diseases such as atherosclerosis, arrhythmias and intracardiac conduction abnormalities, hypertension, and stroke also are increased. Besides anthracyclines, newer molecularly targeted agents, such as vascular endothelial growth factor receptor and tyrosine kinase inhibitors, also have been associated with acute hypertension, cardiomyopathy, increased risk of ischemic cardiac events and arrhythmias, and are summarized here. This review also covers other risk factors for chemotherapy-related cardiotoxicity (including both modifiable and non-modifiable factors), monitoring strategies (including both blood and imaging-based biomarkers) during and following cancer treatment, and discusses the management of cardiotoxicity (including prevention strategies such as cardioprotection by use of dexrazoxane).

Introduction

The 5-year survival rate of US childhood cancers has increased from around 60% in the mid-1970s to more than 80% [1]. This increase is attributed, in part, to treatment advancements [1]. Some treatments can cause multi-organ toxicities, including the heart. About 65% of anthracycline-treated childhood cancer survivors have subclinical myocardial dysfunction [2]. Among survivors of childhood cancer, cardiovascular disease is the leading cause of morbidity and mortality after cancer recurrence and secondary malignancies [3, 4]. With increasing numbers of childhood cancer survivors comes a focus on monitoring for treatment-related long-term morbidity and mortality.

We review cardiotoxic effects of anthracyclines and other antineoplastic agents used to treat childhood cancers. We describe the mechanisms by which cardiotoxicity develops, its cardiac risk factors, screening and monitoring techniques, and measures to prevent or reduce cardiotoxicity in these vulnerable patients. We recognize that the increased incidence of global cardiovascular morbidity and mortality in this population has multifactorial mechanisms.

1. Risk Factors

Modifiable risk factors for anthracycline-related cardiotoxicity include drug-related and behavioral factors, such as anthracycline cumulative dose and dose rate, concomitant treatments, physical inactivity, metabolic risk factors, and smoking [5]. Non-modifiable risk factors include age, sex, and genetics [5]. Besides anthracyclines, other potentially cardiotoxic cancer therapies are discussed (Section 4.0).

1.1 Therapy-Related Risk Factors

An established therapy-related risk factor for abnormal left ventricular (LV) function is the cumulative anthracycline dose [6–9]. Since cardiac damage can occur at doses less than 240 mg/m^2 [10], there might not be any “safe” dose of anthacyclines. Both cumulative dose and

length of follow-up are risk factors for anthracycline cardiotoxicity in survivors. Thus, it is important to understand that a paucity of evidence of cardiotoxicity after relatively short follow-up might not reflect the findings after longer follow-up of the same patient. Much of the cardiotoxicity is progressive in nature.

A long-standing question is whether cardiotoxicity can be attenuated by replacing high peak serum doxorubicin concentrations from bolus infusion with lower peak concentrations associated with continuous infusion [11]. In a multicenter, randomized clinical trial (RCT) of childhood high-risk acute lymphoblastic leukemia (ALL) patients, neither cardioprotection nor event-free survival was better in patients receiving continuous versus bolus infusion doxorubicin [12]. In the absence of cardioprotection, recommendations exist that continuous infusion be discontinued in children because it increases length of hospital stay, costs, and risks of thromboembolic events and mucositis [13].

Mediastinal radiation with or without anthracycline treatment is another risk factor for cardiotoxicity [14, 15]. Low-dose cardiac radiation has been associated with an increased lifetime risk of cardiovascular morbidity and mortality [14, 16]. Among 294 survivors of Hodgkin's Lymphoma exposed to mediastinal irradiation, 23 had coronary events, including 10 with myocardial infarctions after 6.5 years of follow-up [17]. Cranial irradiation is also a risk factor for cardiovascular disease and abnormalities [18], presumably mediated by growth hormone deficiency and related to lower LV mass [19, 20].

1.2 Behavioral Risk Factors

As in the general population, potentially modifiable cardiovascular risk factors in childhood cancer survivors include inactivity, hypertension, dyslipidemia, endocrinopathies, obesity, diabetes, illicit drug use, alcohol use, caffeine, and smoking, [20, 21, 22–25]. Survivors are more likely to be inactive and less likely to meet physical activity standards than siblings or age- and sex-matched healthy controls [25, 26].

Hypertension incidence in childhood cancer survivors is 7.8% after 15 years of follow-up [27]. Hypertension increases the risk for coronary artery disease (relative risk [RR], 6.1), heart failure (RR, 19.4), valvular disease (RR, 13.6), and arrhythmia (RR, 6.0), and is an independent risk factor for cardiac death (RR, 5.6; 95% CI, 3.2 to 9.7) [28].

Although the incidence of obesity rate among survivors is similar to that of general population [22, 23, 25], certain survivor sub-groups are at increased risk [29]. Those treated with cranial irradiation had lower mean blood insulin growth factor-1 concentrations than unexposed survivors, increasing obesity risk [19]. Obesity increases the risk of insulin resistance and diabetes mellitus [22–24]. Abdominal, brain, and total body irradiation results in an increased incidence of diabetes mellitus in long-term survivors [30]. Smoking prevention and cessation programs may improve long-term outcomes of survivors [31]. Survivors are not more likely than siblings to smoke (15% and 16%, respectively), but may have disproportionately increase risk of adverse health outcomes [32].

1.3 Non-Modifiable Risk Factors

Younger at the time of treatment is associated with anthracycline-related cardiotoxicity [33, 34], including a higher risk of increased LV afterload and decreased LV mass and LV wall thickness [7].

The risk of late-onset depressed LV contractility is higher in girls than in boys, even at the same cumulative doxorubicin dose [7, 33]. Because anthracycline dose calculation is based on body-surface area, and girls have a higher percentage of body fat than boys, and doxorubicin is poorly fat-soluble, the higher risk among girls might be related to lower fat doxorubicin concentrations and higher cardiomyocyte concentrations [7]. Similar sex-related outcome differences after dexrazoxane cardioprotection suggest the possibility of increased free-radical injury susceptibility in girls [35].

Children with pre-existing cardiovascular diseases are at increased risk of anthracycline-related cardiotoxicity, as are children with cancer and pre-treatment elevated cardiac troponin concentrations [36]. Those with family histories of premature cardiovascular disease and genetic susceptibilities to cardiovascular diseases are also at increased risk of cardiotoxicity [37]. Inter-individual variation in risk of anthracycline-related cardiotoxicity at a given dose suggests genetic predisposition [37–41]. Mutations of the hemochromatosis gene (HFE) associated with hereditary hemochromatosis can interfere with iron metabolism and lead to iron overload, increasing susceptibility to anthracycline-related cardiotoxicity [37, 42]. The 10% of children with acute lymphoblastic leukemia (ALL) carrying the HFE C282Y mutation had nine-times the risk of doxorubicin myocardial injury than that of non-carriers [37]. Patients who are homozygous for the G allele of the CBR3 gene, which encodes carbonyl reductase 3, also had an increased risk of cardiomyopathy [39]. These genetic variants may assist in screening, guiding treatment, and in post-chemotherapy monitoring [37]. African-American patients and those with trisomy-21 are also more susceptible to anthracycline-related cardiotoxicity [43].

2. Monitoring Chemotherapy-Induced Cardiotoxicity

Monitoring children treated with chemotherapy might detect early cardiotoxicity even when LV dysfunction is asymptomatic, thus providing opportunities to prevent, attenuate, or reverse pathologic LV remodeling.

2.1 Myocardial Injury and Cardiomyopathy Biomarkers

Cardiac-specific biomarkers detect early anthracycline-induced cardiovascular injury. Cardiac troponins (including serum cardiac troponin T [cTnT] and serum cardiac troponin I [cTnI]) are intra-cardiomyocyte contractile proteins detectable in the blood after active cardiomyocyte injury or necrosis. Highly-sensitive troponin assays predict cardiac structural abnormalities and mortality in the general population [44, 45].

Troponins identify anthracycline-induced cardiomyocyte injury and subsequent cardiomyopathy risk. Cardiac troponin I concentrations can predict the risk of cardiac events in adults receiving high-dose chemotherapy [46]. Adults with persistently elevated cTnI concentrations 1 month after anthracycline therapy had more cardiac events at 3 years (84%)

than patients with transient or no cTnI elevations (37% and 1%, respectively) [46]. A randomized clinical trial (RCT) of prophylactic enalapril revealed the short-term benefit of early cardioprotective intervention in high-risk adults with anthracycline-induced elevations in cTnI concentration(s) [47]. One year after anthracycline therapy, LV systolic function was preserved with fewer cardiac events in enalapril-treated patients than controls [47]. This study had a short follow-up but illustrates the potential use of biomarker concentrations to guide cardioprotective therapy for early anthracycline-induced heart disease [48].

Cardiac troponin T concentrations are associated with cardiac outcomes in children receiving moderate-dose anthracyclines for high-risk ALL. Among 134 children, cTnT concentrations were measured before, during, and at the end of anthracycline therapy [36, 49]. More than 15% of children presenting with ALL had elevated cTnT prior to receiving anthracyclines and were at higher risk for anthracycline cardiotoxicity [36]. Concentrations of cTnT were elevated (>0.01 ng/mL) in more than a third of children and, when present during the first 90 days of therapy, were associated with subsequent reduced LV mass, LV thickness-to-dimension ratio (increased pathologic LV remodeling), and LV end-diastolic posterior wall thickness [49].

N-terminal pro-brain natriuretic peptide (NT-proBNP) is an unspecified marker of ventricular wall stress that can be elevated in a number of cardiovascular and non-cardiovascular conditions. For example, elevated NT-proBNP concentrations may indicate cardiomyopathy with increased LV wall stress from pressure or volume overload, and has been shown to predict anthracycline-induced cardiotoxicity in children with high-risk ALL [49]. Concentrations were elevated in more than 90% of 156 children receiving moderate-dose anthracyclines for high-risk ALL and, when detected during the first 90 days of therapy, were associated with an abnormal LV thickness-dimension ratio 4 years later, suggesting pathologic LV remodeling [49]. Other studies have reported acute elevations of NT-proBNP or BNP concentrations during anthracycline therapy; however, they have not always been able to assess associations between biomarker concentrations and LV structural and functional parameters at follow-up [50–52].

These studies substantiate cTnT and NT-proBNP concentrations as markers of early anthracycline-induced cardiotoxicity and validate these during-therapy markers as surrogates of late LV structural status in long-term survivors [36, 49]. For all cardiac biomarkers validated as surrogates for late cardiotoxicity, biomarker-guided cancer chemotherapy should be compared to conventional therapy to determine which has the better oncologic efficacy-to-cardiotoxicity profile [49].

2.2 Other Cardiovascular Biomarkers

Other cardiac biomarkers associated with development or progression of heart failure have not been fully validated in survivors of childhood cancer.

Inflammatory mediators, including interleukin-6, tumor necrosis factor-alpha, and high-sensitivity C-reactive protein, may be useful cardiovascular biomarkers, given the importance of inflammation in the progression of heart failure [53]. These markers can independently predict heart failure and adverse outcomes in non-oncology patients with

heart failure [54–56]. High-sensitivity C-reactive protein measured during doxorubicin therapy for childhood ALL increased with higher cumulative doxorubicin doses and cTnT concentrations, but was not predictive of late cardiotoxicity [49]. In a small study of adults with cancer, elevated interleukin-6 concentrations after epirubicin administration correlated with impaired LV contractility even at 18-month follow-up [57].

Cystatin-C, a protease inhibitor from oxidative stress, promotes extracellular cardiac matrix remodeling [58]. Cystatin-C concentrations predict subclinical cardiac structural abnormalities and heart failure in asymptomatic individuals and mortality in patients with heart failure [59, 60]. Plasma cystatin-C concentrations are elevated in early murine doxorubicin-induced cardiomyopathy [58].

Galectin-3 is a β-galactoside-binding lectin that promotes cardiac fibroblast proliferation and collagen synthesis after myocardial injury [61, 62]. Elevated galectin-3 concentrations predict adverse outcomes in heart failure, but have not been evaluated in childhood cancer survivors [63].

MicroRNAs are post-transcriptional gene expression regulators involved in cardiac regeneration, repair, and pathologic remodeling associated with stress and disease [43]. However, this is still an evolving concept. Whether or not circulating myocardial-derived microRNA concentrations are sensitive and specific markers of cardiomyocyte injury and cardiovascular disease is still under debate [65]. MicroRNA dysregulation after anthracycline-induced cardiomyocyte injury was found in mice but not in patients receiving anthracyclines [66, 67].

2.3 Cardiac Imaging during Chemotherapy

Echocardiography is commonly used for monitoring cardiac structure and function. It is non-invasive, painless, and widely available. Early guidelines for monitoring chemotherapy cardiotoxicity involved assessing LV ejection fraction and LV fractional shortening [68]. These guidelines also recommended the frequency of monitoring and the criteria for discontinuing anthracycline therapy; however, these guidelines have been criticized for not being evidence-based [69]. The impact of these guidelines on detecting later cardiac outcomes and of dose-modification on cancer outcomes remains unclear.

LV fractional shortening was evaluated in doxorubicin-treated children with ALL and has not correlated with elevations cTnT. Yet, in that study, cTnT elevations were validated as surrogates of late-occurring abnormalities of LV structure [36, 49]. Thus LV fractional shortening measured during therapy to predict long-term cardiovascular status was not supported by longitudinal studies [36, 49]. Such measurements ascertained during therapy may be abnormal from many causes unrelated to anthracycline-induced myocardial injury. Thus, the fact that these abnormalities do not relate to long-term cardiac status is not surprising [49]. End-therapy measurements of LV structure and function have predictive value for late cardiac status [33]. Both LV ejection fraction and LV fractional shortening are load-dependent, may not be sensitive to detect restrictive anthracycline-related cardiomyopathy, nor reflect changes in LV contractility or mass.

Data on the utility of other echocardiographic techniques for monitoring of children during chemotherapy is limited. The results of 2-dimensional, speckle-tracking-derived longitudinal strain measurements in 19 children at baseline, 4 and 8 months during chemotherapy demonstrate that changes in LV global longitudinal peak systolic strain preceded changes in LV ejection fraction and segmental deformation in mid- and apical-segments and correlate with decreases in LV ejection fraction at later follow-up [70].

Doppler speckle-tracking-derived longitudinal strain echocardiography has been useful in assessing adults for cardiac damage [71]. Comparing the sensitivity of strain-rate imaging using Doppler techniques with conventional echocardiograms in 16 elderly women with breast cancer at baseline and after 3 and 6 cycles of liposomal doxorubicin showed that LV dimensions, ejection fraction, and systolic myocardial velocities were similar between modalities; longitudinal and radial strain and strain-rate were markedly lower, with radial strain showing greater and earlier changes [72].

Similarly, LV 2-dimensional longitudinal and radial systolic strain measured by speckle-tracking were significantly reduced 1 week after chemotherapy in women with breast cancer without LV ejection fraction changes [73]. Measurements of peak systolic myocardial longitudinal, radial and circumferential strain using speckle-tracking in 43 patients with breast cancer at baseline, and at 3 and 6 months during chemotherapy indicated that longitudinal strain-rate predicted the development of lower LV ejection fraction at 6 months [74]. These studies had a short follow-up duration [74].

Evaluation of serum biomarkers and the myocardial performance index (MPI), a global index of LV systolic and diastolic function thought to be shape- and load-independent, at diagnosis and 24 hours after each anthracycline course in 19 children with standard-risk ALL showed that the MPI was increased at higher cumulative anthracycline doses. Similarly, 13 children had increased LV end-diastolic wall thickness, higher MPIs, and reduced LV wall thickening 2 hours after initial anthracycline dosing [75]. Diastolic LV function variables, such as E/A ratio and isovolumic relaxation time, changed markedly, as did longitudinal and radial systolic strain and strain rates [75].

Cardiac MRI may characterize myocardial tissue and assess perfusion abnormalities independent of a good transthoracic window to obtain acceptable echocardiographic images. Of 10 non-Hodgkin's lymphoma patients with cardiac MRI before and 3 months after doxorubicin-based chemotherapy, 5 had a greater than 10% decreases in LV ejection fraction, and three had at least one new or progressive segment of gadolinium-delayed enhancement at follow-up [76]. Global circumferential strain was lower after chemotherapy, suggesting that MRI detected early functional changes [76]. Myocardial contrast enhancement increased by day 3 of anthracyclines, which predicted a decrease in LV ejection fraction at 28 days [77]. The end-systolic LV volume index increased, and LV and RV ejection fraction decreased to below 55% in 15 of 28 young cancer patients during therapy [78].

The optimal timing, modality, measures, and impact of cardiotoxicity monitoring during chemotherapy need to be investigated further.

Radionuclide ventriculography is also used as a modality to detect cardiac dysfunction, which is reliable, reproducible and may be less operator dependent as compared to 2D echocardiography. In patients with limited windows for clear imaging by echocardiography radionuclide ventriculography is a useful option for monitoring ventricular function in this population. For young children, however, the radiation exposure and occasional need for sedation limit the use of radionuclide ventriculography.

2.4 Cardiac Imaging after Chemotherapy

Consensus-based guidelines for cardiotoxicity monitoring following chemotherapy using echocardiography exist [79]. Optimal timing and cost-effectiveness for such monitoring needs further investigation [80]. Left ventricular fractional shortening and ejection fraction are common measures for cardiotoxicity surveillance among children who have received chemotherapy. Six years after chemotherapy, about 30% of 115 children had reduced LV fractional shortening [2]. This has been assessed by others [75, 81]. Both measures are load-dependent, have measurement variability, lack sensitivity for subtle changes in function and have not been tested for long-term clinical outcome correlation. Although measuring LV ejection fraction by 3-dimensional echocardiography or the biplane method may improve reproducibility, and the results may correlate with the LV ejection fraction measured by MRI, there is no “gold-standard” for LV fractional shortening or ejection fraction measurement technique in terms of being a validated surrogate predictive of late clinically significant cardiovascular disease [82, 83]. Other indices, such as LV mass and LV end-diastolic posterior wall thickness, have been greatly reduced at 3, 6, and 8 years of follow-up [12, 33].

Serial myocardial performance, or the Tei index, in 26 children who received chemotherapy showed the index increased before other conventional LV systolic and diastolic functional variables did, even at low doses and as early as a year after chemotherapy [84]. Changes [0.53 (SD 0.08) vs. 0.37 (SD 0.06) in controls] in MPI were noted in as many as 83% of survivors on follow-up, despite normal LV fractional shortening, LV mass, and LV wall thickness [85]. The MPI is affected by LV afterload, preload, contractility, conduction disorders, activation synchrony, and is abnormal whenever any of these factors are abnormal so has not been a good predictor.

Longitudinal LV diastolic function measurements in survivors correlate with anthracycline dose. After chemotherapy, the ratio of early (E) and late (A) mitral inflow velocity (E/A) decreases, isovolumic relaxation time (IVRT) is prolonged, and the pulmonary venous Doppler pattern is abnormal [75, 85]. The ratio of E to the early velocity as measured by tissue Doppler imaging (E') (E/E’) was significantly higher in 32 survivors of childhood cancer than in healthy controls [86]. The clinical importance of the small difference in E/E' between the groups is unclear and the ratio in both groups was normal [86]. The E/A ratio is also load-dependent and only weakly correlated with other diastolic variables and subsequent impaired LV systolic function [87].

Tissue Doppler imaging, in addition to standard echocardiography, was studied in 63 children treated with anthracyclines [88]. Right ventricular wall thickness and LV fractional shortening were lower, and LV diameter was higher than in healthy controls. Tissue Doppler

measures of peak late diastolic myocardial velocities and transmyocardial systolic and diastolic velocities were also significantly lower in treated children than in controls. The authors postulated that the transmyocardial velocity differences were secondary to wall stiffness [88]. Twenty-percent of anthracycline-treated children had local paradoxical myocardial movements of the basal and mid LV wall [88].

Speckle-tracking echocardiography can detect subtle changes in cardiac dysfunction, but reproducibility has been a problem. Myocardial strain and strain-rate, as measured by speckle-tracking echocardiography, are dimensionless, angle- and load-independent global measures of LV function. Two-dimensional speckle-tracking echocardiograms in 47 survivors of Hodgkin's lymphoma 22 years after receiving chemotherapy demonstrated global longitudinal and circumferential strain and LV ejection fraction were lower than those of healthy controls [89]. Further, patients treated with anthracyclines had lower global longitudinal strain than that of those treated with radiotherapy. Left ventricular ejection fractions did not differ between groups.

Torsion analysis using speckle-tracking echocardiography in 25 adults before and at 1 and 3 months after treatment showed at 1 month torsion and twisting and untwisting rates had markedly deteriorated, and torsion measures were inversely correlated with cumulative anthracycline dose [90]. At 3 months follow-up, the isovolumic relaxation time was prolonged but all other Doppler indices were unchanged [90]. Another evaluation of torsion variables in 36 children confirmed markedly lower apical twisting and lower peak LV torsion, compared to controls, even in the absence of an abnormal LV ejection fraction [91].

Speckle-strain imaging is time-consuming and usually performed offline. Although many techniques appear sensitive in detecting cardiotoxicity, whether their results correlate with longitudinal cardiac outcomes in children who have received chemotherapy is unknown. The impact and cost of incorporating these techniques into the routine surveillance of children receiving chemotherapy needs study.

Cardiac MRI may provide quality images in echo-poor windows (e.g. in obese patients) to measure LV function; but is time-consuming, may be unavailable, requires trained physician interpretation, and in younger patients, may require sedation. T2-weighted imaging can detect edema and active myocardial inflammation. Gadolinium contrast-infused delayed enhancement can detect patchy sub-endocardial fibrosis in patients after myocardial infarction; it is not as effective for detecting diffuse fibrosis. Because doxorubicin cardiotoxicity may cause myocardial necrosis and fibrosis, cardiac MRI monitoring may be useful. Cardiac MRI found mid-myocardial delayed enhancement in 10 women with breast cancer treated with doxorubicin, all of whom had poor LV function [92].

Myocardial T1 mapping uses the T1 relaxation time to calculate the volume and distribution of gadolinium in the myocardium. Relaxation time is increased in the presence of diffuse myocardial fibrosis [77]. Whether cardiac MRI abnormalities in children can predict cardiac outcomes after chemotherapy remains unknown. Further, experimental imaging techniques using molecular probes designed to image areas of apoptosis are being developed [93].

3 Managing Cardiotoxicity

3.1 Prevention of Cardiotoxicity

There is strong evidence for dexrazoxane as a cardioprotectant. Dexrazoxane is an EDTA-like bis dioxopiperazine that decreases oxygen free radicals through intracellular iron chelation, among other actions, including being a weak topoisomerase inhibitor [94]. In two meta-analyses, dexrazoxane was associated with 60% to 80% fewer clinical and subclinical cardiac events during and after anthracycline-based therapy [95, 96]. Overall, toxicity and measures of tumor response were similar between patients exposed and unexposed to dexrazoxane [95]. Currently, the US FDA approves dexrazoxane for women with metastatic breast cancer who have received 300 mg/m^2 of doxorubicin and who may receive additional anthracycline-based therapy. The American Society of Clinical Oncology also recommends considering dexrazoxane for adults with any history of cancer who have already received 300 mg/m^2 of doxorubicin-based therapy [97]. Neither of these recommendations to start dexrazoxane after initial anthracycline-induced cardiomyocyte toxicity comports with our current understanding of the mechanism of cardioprotection.

Intermediate or surrogate endpoints in multiple RCTs of children show that dexrazoxane reduces cardiotoxicity [35, 36, 98]. Among 38 children with sarcoma, the rate of subclinical heart failure was lower among children receiving dexrazoxane than in those who did not (22% vs. 67%; $P<0.01$). Further, the dexrazoxane group received greater cumulative anthracycline doses before cardiotoxicity developed (410 vs. 310 mg/m^2, $P<0.05$) [98].

Among 206 children with ALL, those receiving dexrazoxane had fewer episodes of elevated cTnT concentrations after anthracycline treatment (21% vs. 50%, $P<0.001$; Figure 2) [36]. Longer-term follow-up data from 134 of the 206 children demonstrated various echocardiographic indices of LV structure and function were worse in those not receiving dexrazoxane [35]. Girls benefited from dexrazoxane more than boys, particularly with respect to changes in the LV end-diastolic thickness-to-dimension ratio, a marker of pathologic LV remodeling. Other large studies have found dexrazoxane to be cardioprotective in children treated with doxorubicin for T-cell ALL and lymphoma [99], in children with osteosarcoma [100], whose treatment also included the known cardiotoxic drug traztusamab; and in children with osteosarcoma treated with doxorubicin dose escalations to 600 mg/m^2 cumulative dose [101].

In all five of these trials, neither recurrence rates nor overall survival differed between treatment groups [98–102]. Moreover, earlier concerns that dexrazoxane may be associated with an increased risk of second cancers in children with Hodgkin’s lymphoma [103] have not been borne out, although such concerns have limited its widespread use among children [104, 105].

The long-term cardiac outcomes of patients treated on 2 Hodgkin’s lymphoma clinical trials remain unknown [103, 106, 107]. An ongoing Children’s Oncology Group study is following these children to determine whether dexrazoxane exposure is associated with longer-term effects on cardiac outcomes and to update the data on second cancers and overall mortality (National Clinical Trial #01790152) [108].

Cardioprotectants tested in RCTs, include amifostine [109], acetylcysteine [110, 111], calcium channel blockers [112, 113], carvedilol [114], coenzyme Q10 [115], and L-carnitine [116] (Figure 1). However, evidence of efficacy from these mostly smaller trials is not compelling. None of these agents is considered standard-of-care [95–97, 117]. Data on the potential cardioprotection associated with liposomal formulations of anthracyclines in children is limited. A Phase 1 study of liposomal daunorubicin in 48 children reported no cardioprotection with substantial cardiotoxicity, although all had been exposed to conventional anthracyclines [118].

3.2 Treatment of Cardiotoxicity

Cardiac dysfunction should be treated as early as possible (Figure 3) [119]. Many patients are treated only when cardiotoxicity becomes symptomatic [120].

Chemotherapy-induced cardiotoxicity can be categorized as acute, early-onset, or late-onset [14]. Acute cardiotoxicity is rare, occurring in less than 1% of patients. It is characterized by the onset of heart failure and sinus tachycardia within 1 week of starting anthracycline therapy and usually resolves after stopping anthracycline therapy. Early-onset cardiotoxicity occurs within the first year after completing therapy, and late-onset cardiotoxicity occurs any time thereafter [14]. Early- and late-onset cardiotoxicity may be subclinical, or present as symptomatic restrictive or dilated cardiomyopathy. All manifestations can persist and progress [14, 33].

Cardiac dysfunction in children and adolescents may present as subclinical dilated cardiomyopathy, but later develop into a restrictive cardiomyopathy [33]. Treatments for anthracycline cardiomyopathy depend, in part, on LV preload and LV afterload abnormalities, and the progression of cardiac fibrosis. The goal for treatment at early stages is to prevent pathologic LV remodeling using drugs that target LV preload (diuretics) and LV afterload (angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers; Figure 1). The use of angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers is based on extensive research that goes beyond simply LV afterload reduction. The beneficial effects of angiotensin-converting-enzyme inhibitors for childhood cancer survivors are transient. In a retrospective study of 18 children started on enalapril about 7 years after completing doxorubicin therapy, LV structure and function transiently improved during the first 6 years but this benefit was subsequently lost. For those with heart failure, initial benefits were short-lived. Subsequent management, including heart transplant, failed by 3–5 years in all patients [121]. Effective therapies for anthracycline-associated heart failure have not been tested. Drug regimens might include diuretics (furosemide) for volume overload; inotropes (dobutamine, milrinone, dopamine) to improve contractility and hemodynamics; vasopressors (epinephrine, norepinephrine); vasodilators (sodium nitroprusside); and calcium sensitizers (levosimendan). These are drugs to treat acute, severe heart failure and cardiogenic shock, not just heart failure.

Because anthracycline-related structural changes progress over time from dilated cardiomyopathy to a restrictive cardiomyopathy, it is of critical importance to understand the type of cardiomyopathy causing the heart failure in these patients. Many therapies appropriate for heart failure from dilated cardiomyopathy would be inappropriate for heart

failure from restrictive cardiomyopathy. We frequently employ tailored precision therapy based on hemodynamic monitoring of these symptomatic patients.

Beta-adrenergic blocking drugs have been used to treat cardiotoxicity [122]. Carvedilol, a non-selective beta-blocker, has improved LV function and mortality in adults [122–124], but its effects in childhood cancer survivors is unknown.

Clinical heart failure in childhood cancer survivors can rapidly progress to functional impairment that is refractory to drug therapy. In this situation, mechanical support, such as pacemakers, implantable defibrillators, extracorporeal membrane oxygenation, and implantable pulsatile or continuous-flow ventricular assist devices, may be considered. However, evidence for efficacy in children is still limited and is based on studies of general heart failure management. Adverse events, including infection, thrombosis, bleeding, and neurological complications occur in about 40% of patients requiring mechanical assist devices [125].

For those few patients who do not respond well to all other cardiac treatments, heart transplantation is an option for end-stage anthracycline cardiomyopathy [122]. In one multicenter study of 17 children (mean age at cancer diagnosis, 6 years) who underwent heart transplantation at a median of 9.2 years after cancer diagnosis, five underwent heart transplant within 5 years from the end of treatment. There was only one recurrent cancer and the 1-, 2-, and 5-year survival rates were 100%, 92%, and 60%, respectively [126].

Growth hormone therapy has also been used to treat cardiotoxicity. Additionally, LV mass and LV dimension are markedly lower in exposed survivors than in unexposed ones [19]. Together, these findings suggest that growth hormone therapy may help prevent cardiotoxicity, at least among growth-hormone-deficient survivors. In one longitudinal observational study of childhood cancer survivors with somatic growth deficiency, improvements in LV structure and blood pressure occurred with growth hormone therapy, but were lost after therapy was discontinued [127]. Additional studies are still needed to determine the clinical use, timing, dosage, and risks of growth hormone therapy to treat or prevent cardiotoxicity in these survivors.

4 New Chemotherapeutic Agents and Associated Cardiotoxicity

Several molecularly-targeted agents have been developed to improve anti-cancer efficacy and reduce side effects [128]. Although these agents have expanded therapeutic options, some have unanticipated and serious adverse cardiovascular effects [129, 130]. Many are not yet used in children.

A few of the more commonly used molecular agents and their cardiovascular side effects are reviewed below.

4.1 Imatinib

Imatinib, a tyrosine kinase inhibitor, acts against the BCR-ABL fusion gene product found in chronic myeloid leukemia and Philadelphia-positive ALL and is used to treat those two leukemias in both adults and children [131–133]. Imatinib also inhibits other tyrosine

kinases, such as KIT and platelet-derived growth factor receptor, which may be mutated in gastrointestinal stromal tumors. Imatinib, FDA-approved since 2001, is rarely associated with congestive heart failure, likely because of the effects of ABL inhibition on cardiomyocytes [134]. With a median follow-up of 4 years, only 22 of 1300 (1.7%) adults enrolled in imatinib clinical trials developed heart failure, and in only 8 cases of the 22 was considered to be related to imatinib [135]. Imatinib cardiotoxicity has not been a concern with children [136, 137].

Second- and third-generation derivatives of imatinib (e.g., dasatinib, nilotinib, bosutinib) are being used as first-line agents for chronic myeloid leukemia (CML) because of their greater molecular efficacy [138]. Ponatinib, efficacious against CML in patients with the T315I mutation, which renders CML resistant to the other current tyrosine kinase inhibitors was associated with a nearly 12% incidence of serious arterial thrombotic events in adults resulting in withdrawal from the market [139]. The vascular toxicity of nilotinib [140] has raised concerns about the safety of this class of agents, particularly as first-line agents for CML and other cancers [130].

4.2 Trastuzumab

Trastuzumab has cardiovascular side effects. An inhibitor of the human epidermal growth factor receptor (HER2, also known as ErbB2), trastuzumab is primarily used to treat breast cancers with HER2 overexpression [141]. Trastuzumab interferes with cellular repair, leading to increased apoptosis, particularly in the context of concurrent anthracycline therapy, and has been associated with LV systolic dysfunction and heart failure [142]. Anthracycline treatment and chest radiotherapy are risk factors for trastuzumab-associated LV systolic dysfunction [143]. In contrast to anthracycline-associated LV systolic dysfunction, trastuzumab-associated dysfunction is often reversible after discontinuing the drug; patients with LV systolic dysfunction may tolerate trastuzumab re-treatment [144].

Over-expression of HER2 has been found on osteosarcoma cells and is associated with a poorer prognosis. Although a Phase 2 trial of 41 patients with metastatic osteosarcoma found that trastuzumab could be safely given in conjunction with anthracycline-based chemotherapy and the cardioprotectant dexrazoxane (none experienced clinical heart failure and markers of cardiotoxicity were normal), its efficacy remains unclear [110]. Newer anti-HER2 agents, such as lapatinib and pertuzumab, may be less cardiotoxic than trastuzumab [142, 145]. Data with these agents in children are emerging [146, 147].

4.3 Bevacizumab

Antibodies and inhibitors against vascular signaling pathway proteins are also commonly used. Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor (VEGF) receptors, is approved for treating several metastatic cancers in adults [148, 149]. Heart failure was reported with bevacizumab in patients with metastatic breast cancer who also received anthracyclines or taxanes; bevacizumab is no longer approved for this indication [150].

A meta-analysis associated bevacizumab with a 2-fold higher relative risk of ischemic cardiac events but not of arterial thromboembolic events or stroke [151]. Bevacizumab has

been tested in children with high-grade central nervous system tumors [152, 153]. As well is in children with retinopathy of prematurity [154].

4.3 Other Inhibitors of Vascular Endothelial Growth Factor Receptors

Other VEGF receptor and tyrosine kinase inhibitors include sunitinib, sorafenib, axitinib, pazopanib, regorafenib, and vandetanib. These agents affect several signaling pathways and share similar cardiovascular side effects, particularly hypertension and, less commonly, cardiomyopathy. Sunitinib and sorafenib are most used in children, sunitinib in Phase 1 and 2 trials treating solid tumors [155] and sorafenib in Phase 1 trials treating both leukemia and solid tumors [156, 157].

Hypertension caused by VEGF receptor inhibitors is usually acute, occurs within 2 weeks of administration, and may relate to decreased nitrogen oxide concentrations, which increases vascular tone and endothelial cell apoptosis [149]. In adults, the incidence of hypertension has been as high as 40% for sorafenib and 81% for sunitinib [158–161]. In adults with metastatic renal cell carcinoma, hypertension may even increase sunitinib's anti-cancer efficacy; patients with hypertension have better overall survival than patients without hypertension, regardless of anti-hypertensive therapy [162]. Drug-related hypertension is often controlled with standard anti-hypertensive agents and has not necessitated stopping VEFG receptor inhibitors.

Episodes of cardiomyopathy have been rare, with the incidence of symptomatic heart failure (United States National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] grade 3 or higher) ranging from 1.5% to 15% among adults and the incidence of any LV systolic dysfunction ranging from 7% to 28% [158–161, 163]. Left ventricular systolic dysfunction, like that seen with trastuzumab, is often reversible and has not resulted in discontinuations. These agents have been associated with increased ischemic cardiac events and arrhythmias, including QT-interval prolongation [159, 160].

Experience with these agents in children is limited. Among 12 children with solid tumors treated with sunitinib, 2 experienced CTCAE grades 2–3 dose-limiting reductions in LV ejection fraction, leading to exclusion of subsequent patients with a history of anthracycline or cardiac radiation exposure [155]. Among 11 children subsequently enrolled in the same study, none experienced cardiotoxicity, none had remarkable issues with hypertension, and only 2 had grade 1–2 QT-interval prolongation (i.e. a subclinical corrected QT interval >500 milliseconds no more than once) [155]. In another study, among 12 children with relapsed or refractory leukemia treated with sorafenib, none experienced adverse cardiotoxicity, aside from one instance of hypotension [156]. A sorafenib study with 65 children with refractory solid tumors and leukemia reported at least 3 instances of non-dose-limiting hypertension requiring anti-hypertensive medications without sorafenib dose reduction [157].

Given that these agents are usually tested in adults before children, and assuming they are effective, determining their long-term cardiovascular safety in children may require years, if not decades, of close follow-up. An FDA survey of 19 pediatric Phase 1 trials of molecularly-targeted agents approved for adults found cardiotoxicity only with sunitinib [164].

Comparing late-onset cardiotoxicity is difficult because most trials do not typically use cardiovascular measures as primary or secondary endpoints, often exclude patients with a history of cardiovascular diseases or findings, and define cardiotoxicity differently. Even when common definitions are used, such as the CTCAE [165], these definitions, particularly earlier versions, are usually oriented to grading acute toxicities and may not be detailed enough to capture more chronic or late-onset toxicities. Finally, these trials often do not include prospective longer-term monitoring, when important late outcomes may become more detectable [21].

Conclusions

Advancements in treatment have increased survival of children with cancer. These treatments come with a high cost of cardiotoxicity. Research dedicated to preventing, detecting, predicting, and treating cardiotoxicities in survivors of childhood cancer has been informative. Significant gaps in knowledge remain, including the influence of genetic predisposition, the optimal use of both blood- and imaging-based biomarkers both during and following cancer-therapy, the efficacy of potential cardioprotectants, optimal management strategies once subclinical cardiotoxicity has been detected, and the long-term cardiotoxicity of newer chemotherapeutics. Recognizing these opportunities to increase our understanding in these areas should result in continuing progress toward improving life-spanning quality of life by maximizing the efficacy of cancer treatment while minimizing its short- and long-term adverse effects.

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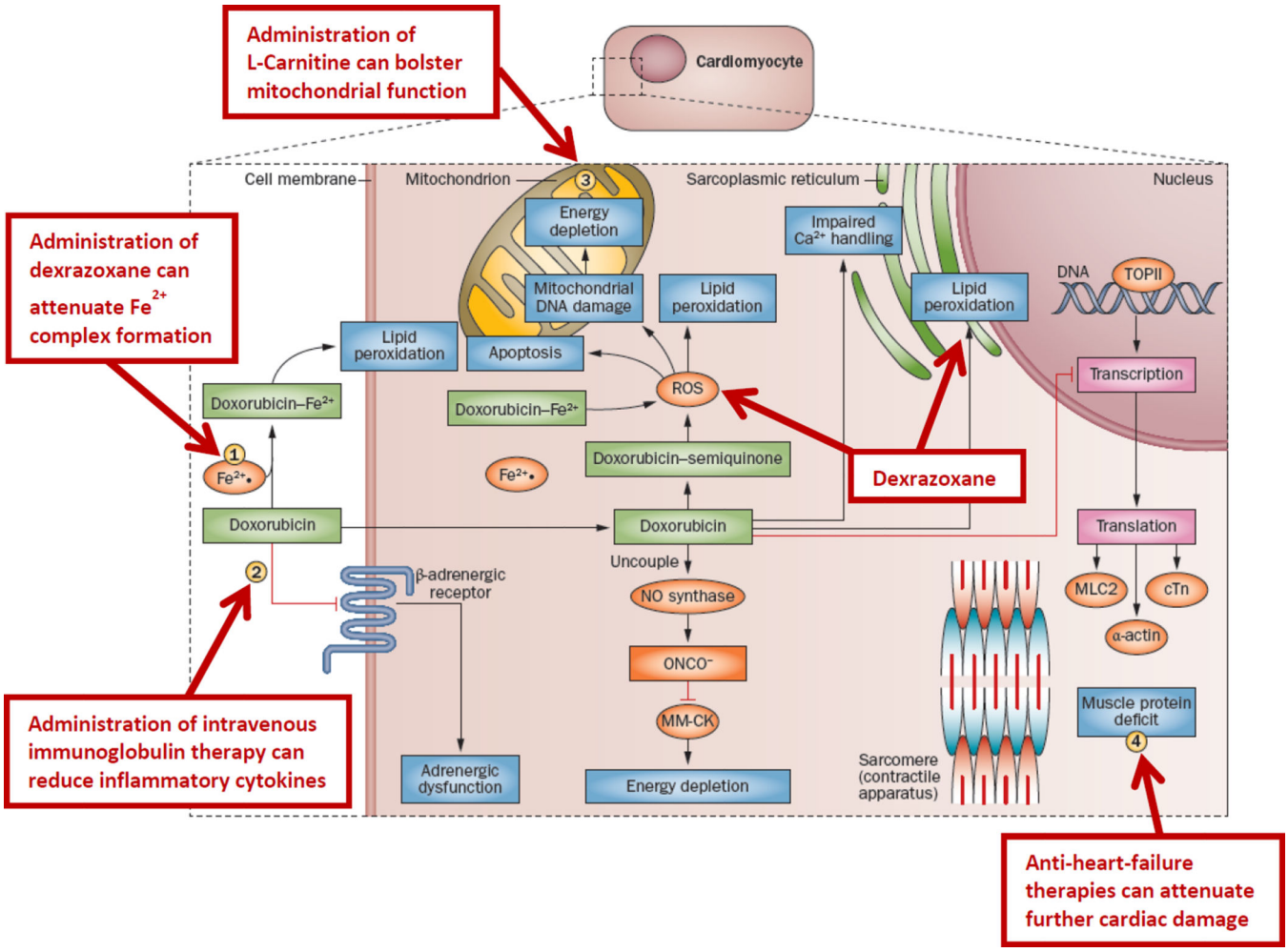

Figure 1. Potential Opportunities for Cardioprotection

Doxorubicin chemotherapy has a range of effects on cardiomyocytes. It induces lipid peroxidation at the cell and mitochondrial membranes by way of complexing with Fe^{2+} and induces apoptosis, mitochondrial DNA damage and energy depletion through its production of reactive oxygen species. Furthermore, it impairs Ca^{2+} processing in the sarcoplasmic reticulum and inhibits the transcription of important muscle elements, weakening the heart muscle. It also downregulates adrenergic receptors and interrupts cell signaling. (1) Administration of dexrazoxane can prevent Fe^{2+} complex formation. (2) Intravenous immunoglobulin therapy can reduce inflammatory cytokines. (3) L-carnitine can bolster mitochondrial function. (4) Anti-heart-failure therapies, such as angiotensin-converting-enzyme inhibitors and β-blockers, can prevent further damage. Abbreviations: cTn, cardiac troponin; MLC2, myosin light chain 2; MM-CK, myofibrillar isoform of the CK enzyme; ROS, reactive oxygen species; TOPII, topoisomerase 2. (Reprinted with permission from Nature Publishing Group [21].)

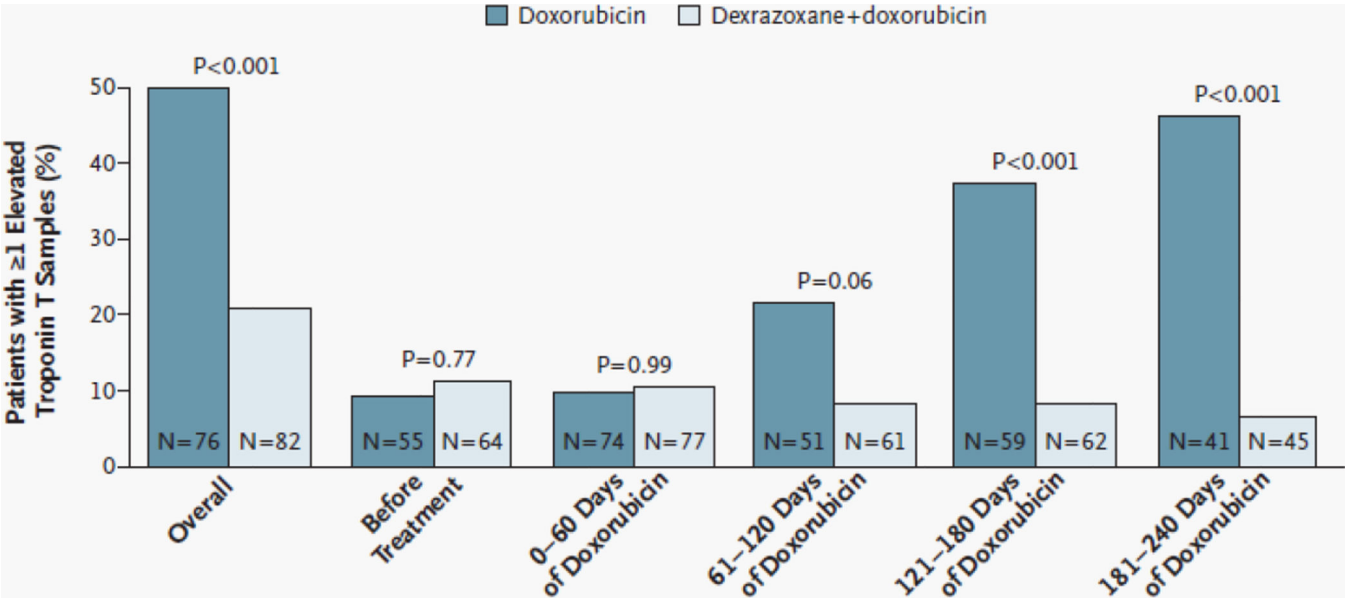

Figure 2. Percentage of Patients With at Least One Elevated Serum Cardiac Troponin T Measurement Overall, Before Treatment with Doxorubicin, and During Treatment

An elevated level of troponin T was defined as one that exceeded 0.01 ng per milliter. The number of patients in whom troponin T was measured at least once during the specified intervals is shown in each bar. (Reprinted with permission from Massachusetts Medical Society [36].)

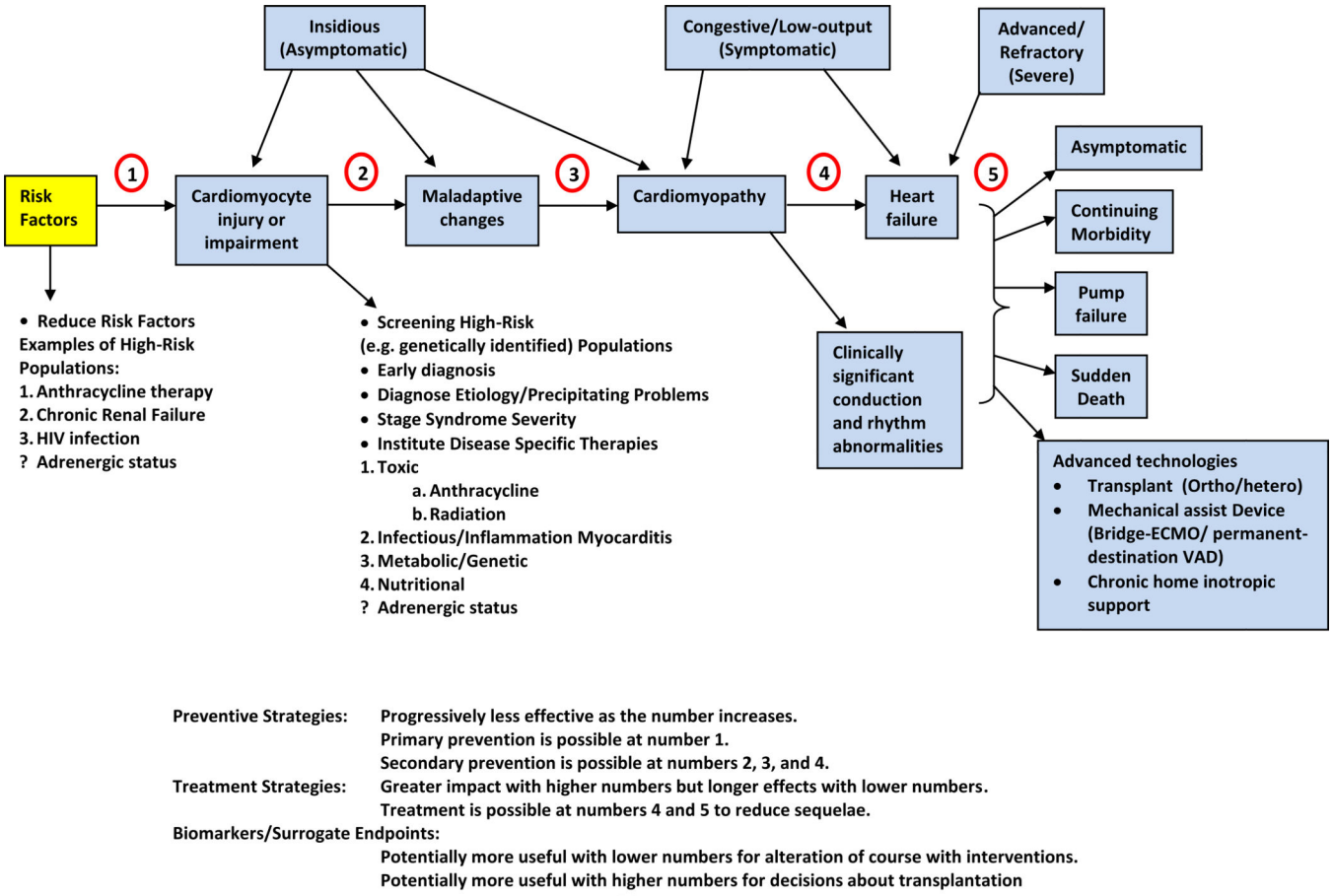

Figure 3. Stages in The Course of Pediatric Ventricular Dysfunction

(1) Primary prevention is possible at this stage by reducing risk factors in high-risk populations (such as those receiving anticancer therapy). (2) Secondary prevention is possible at this stage to reduce the effects of the treatment-induced injury. (3) Secondary prevention is also possible at this stage. (4) Clinically significant conduction and rhythm abnormalities might be observed. (5) Radical therapies might be required at this stage (such as heart transplant) if there is failure of medical management. Preventive strategies are progressively less effective as the toxicity increases. Treatment strategies have a greater impact when used to treat the more-diseased heart, but have longer effects if initiated early. Biomarkers and surrogate end points are potentially useful at early stages to alter the course with interventions, and are potentially useful at later stages to aid decisions about transplantation. (Reprinted with permission from Elsevier [166].)