Chapter 5

Evaluation and Long-Term Outcomes of Cardiac Toxicity in Paediatric Cancer Patients

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Additional information is available at the end of the chapter

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Abstract

Paediatric cancer survival rates have increased dramatically in the last 20 years. With decreased mortality comes increased long-term morbidity. Cardiovascular disease is the leading cause of secondary morbidity and mortality of childhood cancer survivors. The most common chemotherapeutic agents in treatment regimens are implicated in chemotherapy-induced cardiomyopathy. The clinical presentation is rarely uniform and may manifest in symptoms besides chest pain, shortness of breath or decreased exercise tolerance. In addition to symptomatic patients, asymptomatic patients are especially important to screen as the effects of cardiac toxicity are reversible if caught early. There are new techniques more sensitive than traditional 2D echocardiography ejection fraction that may lead to earlier detection of cardiac dysfunction. Treatment methods have changed little in the recent past with the exception of miniaturization of support devices allowing for cardiac recovery or bridge to cardiac transplant.

Keywords: cardiomyopathy, cardio-oncology, heart failure, cardiotoxicity, anthracyclines

1. Introduction

Cardiovascular compromise is the leading cause of morbidity and mortality of childhood cancer survivors [1]. As paediatric cancer treatment improves and survival increases, there is a significant amount of that population with resultant secondary morbidities who need to be monitored. Paediatric cancer survivors have been found to have an eight-time greater risk of dying from a cardiovascular event compared to their peers [2]. Routine monitoring is paramount because progressive cardiac dysfunction in children may not be present in typical fashion [3]. Children may also be too young to effectively communicate what they are feeling, requiring the provider to obtain a specific history from the caretaker, a detailed physical

exam and often adjunct imaging and laboratory studies. When cardiac dysfunction is found early, working with the oncology team to limit further cardiotoxic medications, if possible, as well as implementing heart failure management strategies may lead to full cardiac recovery.

2. Clinical presentation and initial assessment

Depending on the chemotherapeutic agent used, heart failure can present in 0.5–28% of patients [2], and a larger percentage can have other cardiac-related dysfunctions. The typical presentation of heart failure is dyspnoea, oedema and chest pain [4]. However, more than half of patients who present to an emergency department for cardiomyopathies have a primary complaint of gastrointestinal symptoms such as abdominal pain, decreased appetite, nausea or vomiting. Symptoms can be often vague, and a high index of suspicion is needed to prompt further evaluation. In babies, the history should include questions such as changes in feeding patterns, decreased tolerance of feeds, tiring or sweating with feeds and poor weight gain. In older children, the history should include questions about keeping up with peers, changes in weight (either increased or decreased), puffiness, nausea or vomiting, decreased appetite, overall level of energy and if they're needing more pillows to sleep on at night. Asymptomatic patients may also have small decreases in cardiac function that can be clinically important.

The physical exam should include vital signs such as heart rate, blood pressure, pulse oximetry, respiratory rate, weight and height. A thorough cardiac exam includes palpation of the chest wall for chest wall abnormalities as well as feeling for a point of maximal impulse. When auscultating it is important to assess for murmurs, an abnormally split S2, an S3 or S4, a P2, as well as a rub or distant heart sounds. Jugular venous distension should be noted as well as any carotid bruits. The extremities should be examined for pulses, oedema, capillary refill or nodules. The nail beds should be examined looking for splinter haemorrhages as a sign of endocarditis. The abdomen should be palpated for liver and spleen size if able.

These patients have accelerated coronary artery disease [5] that can have a varying presentation from being asymptomatic to acute coronary syndrome and myocardial infarction. Hypertension manifests in this patient population secondary to reduced nitric oxide production, and screening blood pressures should be obtained during clinic visits [6]. Longstanding hypertension can lead to left ventricular hypertrophy and ultimately dysfunction. Paediatric cancer survivors are also at risk for increased thromboembolic events and may present with tachycardia, chest pain, shortness of breath and symptoms, which could be due to pulmonary embolism. Patients with unilateral leg pain should be worked up for deep vein thromboses.

3. Common cardiotoxic agents

Many conventional forms of chemotherapy are aimed at causing cancer cell injury and death; however, they can also induce myocardial cell damage. This injury from agents such

http://dx.doi.org/10.5772/67043

as anthracyclines, antimetabolites and cyclophosphamide can lead to acute or chronic left ventricular dysfunction [2]. Right ventricular dysfunction is rare, but some drugs such as anthracyclines, cyclophosphamide and 5-fluouracil can cause right ventricular systolic and diastolic function [7]. It is important to be aware of the offending agents in order to minimize exposure, if clinically possible, in a failing heart. Left ventricular dysfunction from anthracycline exposure has been well studied and is dose dependent. Thus, it is important to have a clear record of the lifetime dosage a patient receives of chemotherapeutic agents. **Table 1** lists the most common cardiotoxic agents and their toxic dose ranges.

Every patient is different, which is why routine screening of cardiac dysfunction is recommended even below the toxic level range as well as with drugs not typically associated with cardiac dysfunction. Radiation can also be cardiotoxic leading to myocardial oedema, fibrosis and necrosis, and total radiation dose as well as the area radiated should be recorded.

Drug	Toxic dose range	Cardiac toxicity	Frequency
Doxorubicin	>450 mg/m^2	LV dysfunction	>5% [6]
Epirubicin	>900 mg/m^2	LV dysfunction	>5% [6]
Idarubicin	150–290 mg/m^2	LV dysfunction, heart failure	5–18% [8]
Docetaxel		Arrhythmia, heart failure	5% [9]
Cyclophosphamide	>100–120 mg/kg	LV dysfunction	2–10% [9]
Ifosfamide	>10 mg/m^2	Arrhythmias	Unknown
Capecitabine	Conventional dose	Cardiac ischemia	1–18% [10]
Fluorouracil	Conventional dose	Arrhythmias, myocardial ischemia	1–18% [10]
Arsenic trioxide	Conventional dose	QTc prolongation	>5% [6]
Cisplatin		Diastolic dysfunction, myocardial ischemia, hypertension [11]	>6% (major cardiac event)

Table 1. Common cardiotoxic chemotherapeutic agents and their cardiotoxicity.

4. Screening

4.1. Electrocardiography

A baseline electrocardiogram (ECG) should be obtained on all patients before undergoing chemotherapy. ECGs are relatively inexpensive, quick and noninvasive screening tests that give information about chamber sizes, depolarization abnormalities, rhythm disturbances and conduction abnormalities. Some of the chemotherapeutic agents or supportive medications prolong QT intervals so it is important to manually calculate a QTc before initiating therapy as well as while on QT-prolonging medications. ECGs can be repeated during imaging follow-up or with any concerning symptoms. Twenty-four hour Holter monitors should be ordered as clinically indicated.

4.2. Echocardiography

Echocardiography is the most widely used imaging modality for screening cardiac dysfunction and is an important noninvasive manner to follow up cardiac function over time. The advantages of echocardiography are that it is widely available in paediatric cardiology clinics, can usually be performed without sedation and is noninvasive, and a targeted function exam can be performed relatively quickly in the inpatient and outpatient setting. It is recommended that all patients have a complete paediatric echocardiogram before the initiation of chemotherapy. All structures of the heart should be visualized including coronary arteries, the pulmonary veins and the aortic arch during the first echocardiogram. If all structures are seen adequately during the first echocardiogram, subsequent echocardiograms can be targeted function exams. The cardiac valves should be visualized on all exams as these patients have an increased risk of endocarditis, nonbacterial thrombotic endocarditis as well as radiation-induced heart disease affecting valves [7]. Transthoracic echocardiography is acceptable for looking for endocarditis if there are clear windows to the heart valves; otherwise depending on the index of suspicion, transoesophageal echocardiography is indicated as the gold standard.

Surveillance echocardiograms, or equivalent cardiac imaging, should be performed anywhere from yearly to every 5 years depending on doxorubicin isotoxic equivalent dosing, age and radiation for asymptomatic children with stable function [12]. It is recommended that any decrease in serial function should be assessed yearly. Also, patients with clinical changes should be assessed more frequently.

Historically, left ventricular ejection fraction (EF) has been used to quantitate cardiac function over time. While EF is an adequate gross marker of cardiac function, it may not be sensitive enough to detect early cardiac dysfunction [13–15]. Zito et al. demonstrated that there is enough variability in EF measurements that it is not sensitive to detect a decrease in EF less than 10% [7]. If one is using EF as their main determinant of cardiac function, they may miss patients who have a significant decrease in cardiac function that may alter the course of therapy.

Some centres rely on indices of cardiac function other than EF. Strain and strain rate have been found to detect cardiac dysfunction earlier than a decrease in LV systolic function [16]. Strain is a measure of myocardial deformation or the fractional change in the length of a myocardial segment. Strain can be measured by tissue Doppler imaging (TDI) as well as speckle-tracking echocardiography (STE). Each of these methods requires adequate 2D echocardiographic imaging windows in order to process the image. TDI is angle dependent, requiring the plane of the ultrasound to be in line with the tissue being interrogated. One benefit of STE is that it is not angle dependent. Speckle tracking can determine peak systolic global longitudinal strain (GLS), which is becoming a commonly accepted method for evaluating myocardial function [17]. **Figures 1** and **2** demonstrate examples of normal vs abnormal global and regional strain, respectively. This method is quite useful for early detection of cardiotoxicity. It is likely that all of these indices used in conjunction with one another will provide the best insight to the cardiac status of the patient.

Diastolic function must also be evaluated during an echocardiographic evaluation of a paediatric cancer patient. Diastolic dysfunction may proceed to systolic deterioration and can indicate a need for closer follow-up as it has been reported that it can be a predictor of subsequent deterioration [18]. Diastolic dysfunction can be detected with a decrease in early to

http://dx.doi.org/10.5772/67043

late ventricular filling velocities (E/A ratio), an increased E/e′ ratio, enlargement of the atria and an increase in isovolumic relaxation time. TDI-derived peak early and late diastolic myocardial velocities of the right ventricular free wall, left ventricular lateral wall and septum are decreased in patients with myocardial dysfunction when compared with controls [19].

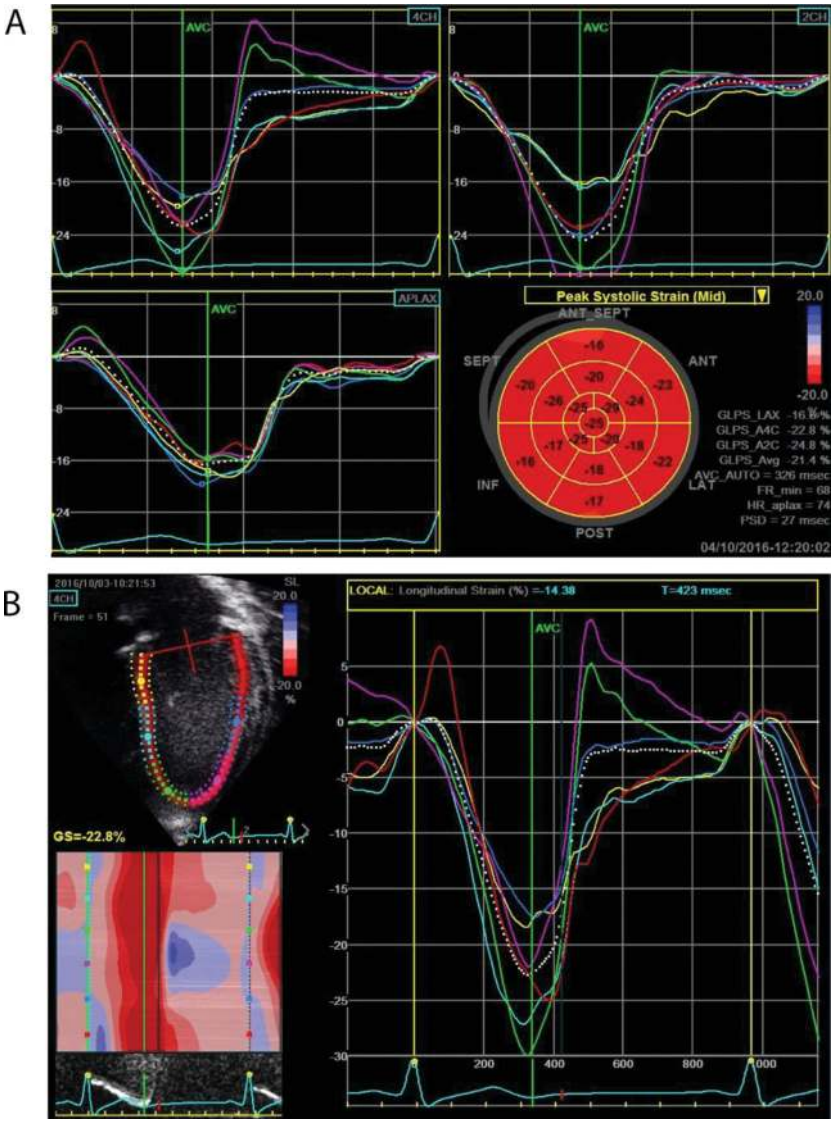

Figure 1. (A) Longitudinal strain analysis of the left ventricle, with both regional and global longitudinal strain reported. The six segment strain curves from the apical 4-chamber, apical 2-chamber and apical long axis are shown, as well as a "bullseye" view overlaying the longitudinal strain for each segment. (B) Segmental strain for the apical 4-chamber view, including contours of the left ventricle. Global longitudinal strain of the entire 4-chamber slice is normal at −22.8%.

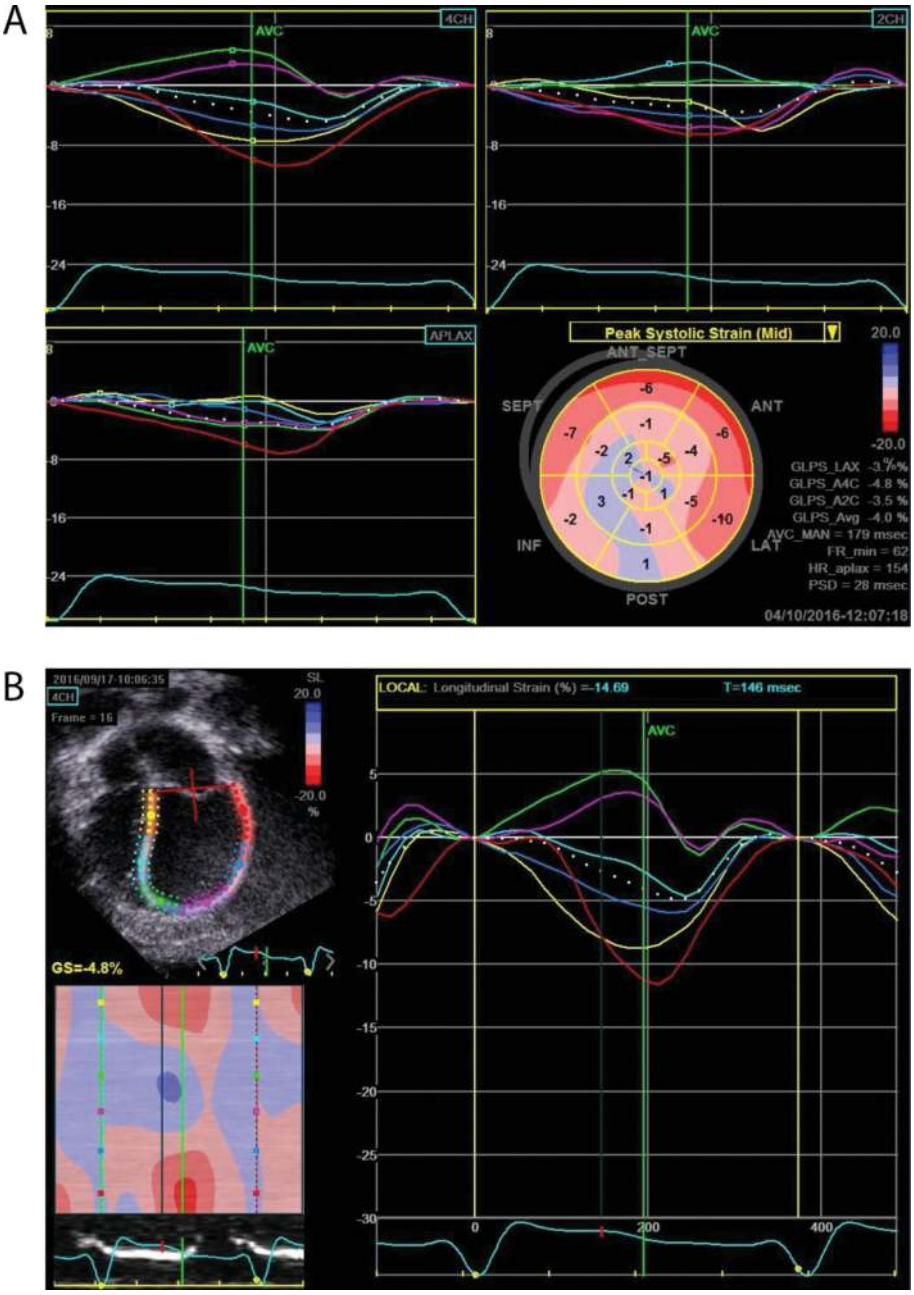

Figure 2. (A) Abnormally diminished regional and global longitudinal strain in a patient who has anthracycline-induced cardiomyopathy. Note the decreased regional strain values in nearly every segment, including positive strain (stretch of the muscle) during systole, indicating dyssynchrony. (B) Abnormally diminished global longitudinal strain of the entire 4-chamber slice at −4.8%. Note the strain waveforms above baseline which represent segments stretching during systole instead of contracting (indicative of dyssynchrony).

http://dx.doi.org/10.5772/67043

Three-dimensional echocardiography is being increasingly used as a more accurate measurement of left ventricular systolic function. Where, as previously described, 2D EF may be an inadequate measurement of systolic function, 3D echocardiography is a more sensitive method to detect decreased LV contractility than fractional shortening by M-mode or EF by 2D [20]. **Figure 3** shows an example of how 3D echocardiography is used clinically in patients receiving anthracyclines. If the patient has poor acoustic windows, however, 3D measurements will be unsatisfactory as these measurements rely on clear 2D acquisition. Besides EF, 3D speckle-tracking echocardiography is an emerging technique [4]. A 3D evaluation avoids the geometric assumptions of 2D imaging and shows good correlation of decreased myocardial contractility compared to MRI findings. At this time, 3D STE is largely experimental and not widely available in most echo laboratories.

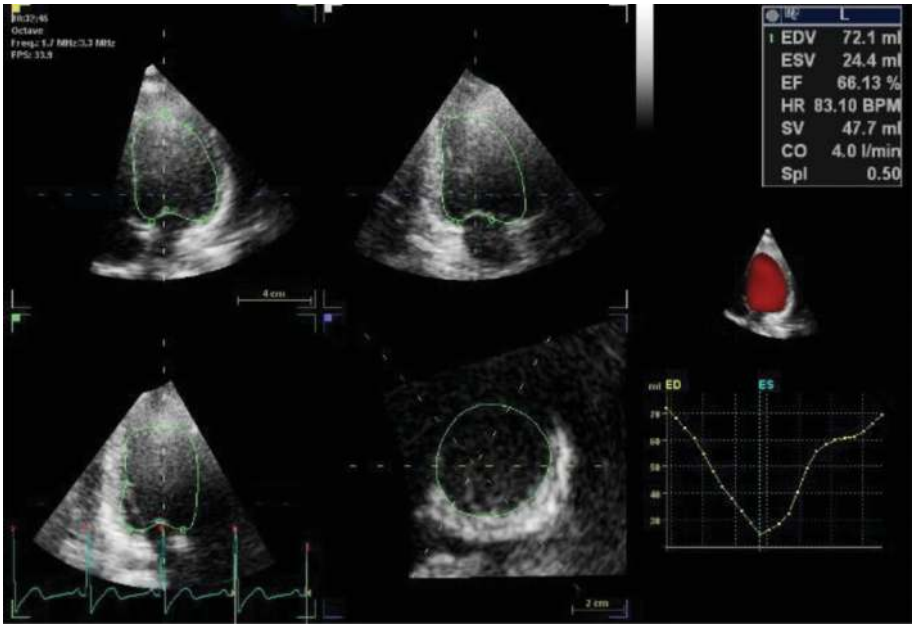

Figure 3. A three-dimensional reconstruction of the left ventricle in a patient receiving anthracyclines. Care is taken to show accurate contouring of the endocardial border in multiple imaging planes. Output includes end-diastolic volume, end-systolic volume and ejection fraction.

4.3. Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (CMRI) is increasingly playing a larger role in the imaging of paediatric cancer survivors. It allows for tissue characterization, identification of areas of fibrosis or oedema as well as a more precise and reproducible measurement of cardiac function than echocardiography. There is no need in CMRI for the geometrical assumptions to inherent in 2D echo, which can lead to imprecise echocardiographic measurements, and there is no need for optimal acoustic windows [21]. In paediatric cancer patients, minimal decreases in systolic function may lead to a change in management; thus, a sensitive method such as CMRI is useful for monitoring.

Chemotherapy, as expected, can produce myocardial changes such as tissue fibrosis, oedema and even necrosis. Other imaging modalities are not as sensitive as CMRI in detecting these changes, and CMRI may help in determining a nidus for an arrhythmia or differentiating potentially reversible vs. irreversible causes of myocardial depression. T2-weighted sequences are useful for determining oedema as these areas reveal a hyperintense signal. There is evidence that myocardial oedema is related to subsequent decreased RV function. T2 mapping can also be used to follow the course of a patient over time. The clinical benefit of this is being investigated and with time it is likely that there will be a more useful correlation with clinical outcomes [21]. Late gadolinium enhancement is useful in detecting areas of fibrosis or ischemia and can help determine prognosis in cardiomyopathies [22]. **Figure 4** shows an example of how CMRI can be used to detect scar and fibrosis by late gadolinium enhancement. This technique uses a T1 inversion sequence about 10 minutes after injection of a gadolinium-based contrast. CMRI can also quantify myocardial perfusion, helpful for the diagnosis of coronary artery disease [23].

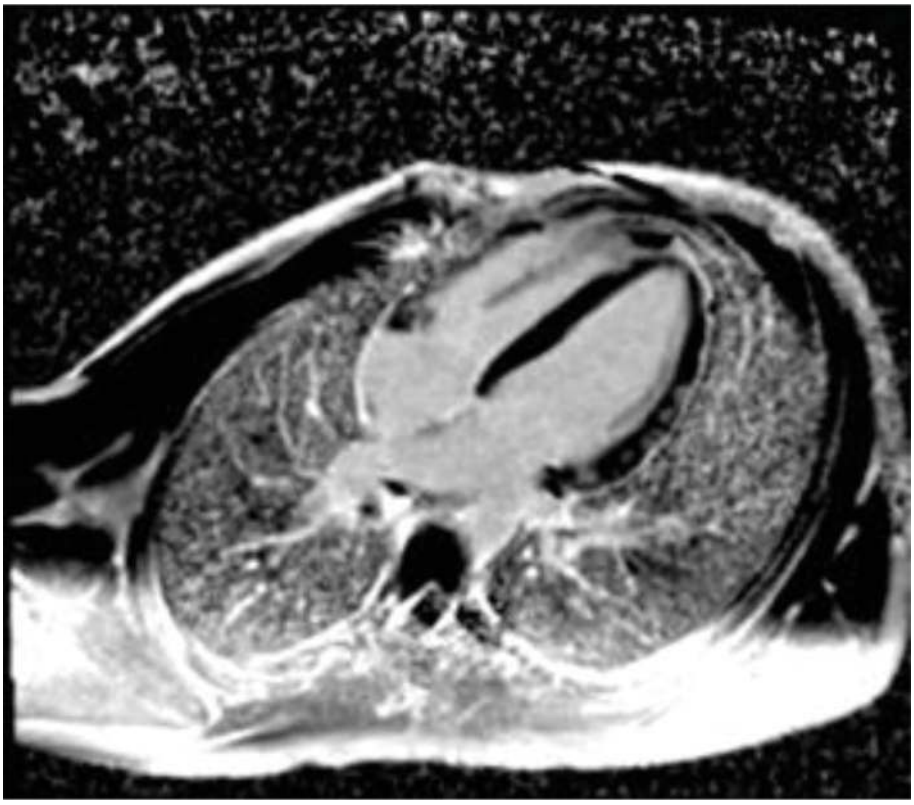

Figure 4. Cardiac MRI demonstrating scar and fibrosis using a late gadolinium enhancement technique.

While 3D echocardiography is emerging, CMRI has a higher sensitivity of detecting a left ventricular ejection fraction <50% [24]. CMRI is also useful in characterization of the right

http://dx.doi.org/10.5772/67043

ventricle because of its irregular shape that is not amenable to geometrical formulas. Although right ventricular dysfunction is not as common as left ventricular dysfunction in paediatric heart transplant survivors, its consequences can be just as severe.

CMRI can have its downside, especially in children, as it requires the patient to lie still, which may be difficult for young children. Anaesthesia is often necessary for an optimal exam of a child. Also, because most CMRI images require ECG gating CMRI and be difficult or impossible in the setting of arrhythmias. Metallic implants are often contraindicated with CMRI, or if placed in the thorax, they may produce significant artefact, which obscures images.

5. Biomarkers

Biomarkers can be used in conjunction with history, physical examination and imaging modalities to gather information on a patient's clinical status. Unfortunately, there is no single biomarker that can predict the cardiac prognosis of a patient.

Cardiac troponins are a widely used biomarker in the field of cardiology and have been found to be useful in evaluating anthracycline-induced cardiomyopathies [25]. Troponin I and troponin T are both sensitive and specific to cardiac damage. The troponin complex is on the thin filament of the contraction mechanism and is important in excitation-contraction coupling in the heart [26]. Cardiac troponin I increases with anthracycline exposure and appears to be dose related. Increased cardiac troponin T levels in the first 90 days of therapy have been shown to correlate with cardiotoxicity at 4 years of follow-up [25].

B-Natriuretic peptide (BNP) and NT-pro-B-natriuretic peptide (proBNP) are closely related cardiac biomarkers that can aid clinical management of heart failure. Impaired ventricular function leads to greater wall stress, which triggers the synthesis of pre-pro-B-type natriuretic; this is then broken down to proBNP and then cleaved to BNP. The purpose of these peptides is to protect the body from volume overload. BNP and proBNP are related but cannot be used interchangeably as their reference values are different. Also, the half-life of BNP is about 20 min where proBNP is about 1–2 h. The result of the release of BNP is smooth muscle and myocardial relaxation and diuresis and natriuresis [27]. BNP is elevated in children with anthracycline-induced clinical or subclinical heart failure and can be used along with imaging to trend the degree of heart failure [28].

Highly sensitive C-reactive protein (hsCRP) has been shown to predict cardiac events in adults; however, this was not found to be true in the paediatric population with heart failure, so it is not recommended for routine monitoring [29].

6. Management of cardiomyopathy

The best way to manage heart failure secondary to chemotherapy is to have a robust monitoring programme to prevent its occurrence in the first place. Aggressive medical management should begin in the asymptomatic patient once early signs of ventricular dysfunction are

detected [30]. Cardiotoxic medications should be avoided or minimized if possible to attempt to halt further progression.

There are few large multicentre studies in the paediatric literature to guide heart failure management so we extrapolate data from adults and apply many of the same principles to paediatric heart failure. The common classes of drugs to treat chemotherapy-induced cardiomyopathy include beta-blockers and angiotensin-converting enzyme inhibitors (ACEis).

6.1. Beta-blockers

Beta-blockers are the most effective when used shortly after anthracycline-induced cardiac injury [6]. Beta-blockers have been found to improve cardiac recovery when used as monotherapy or in combination with ACEi. Beta-blockers blunt heart rate responses so immunocompromised patients on beta-blockers should be monitored closely as their compensatory heart rate response may be blunted in times of stress. Adult trials of metoprolol and bisoprolol found that those drugs improve symptoms and survival in mild-to-moderate heart failure [31, 32]. Beta-blockers can be titrated based on heart rate response, and effective doses vary depending on the patient. The mechanism of beta-blockers in heart failure management is not completely clear but is thought to have reversed remodelling effects secondary to myocyte damage from prolonged adrenergic activation.

6.2. Angiotensin-converting enzyme inhibitors

ACEis are also commonly used in the management of heart failure secondary to chemotherapeutic cardiotoxicity. ACEis have the ability to decrease cardiac work by decreasing preload, afterload and wall stress [33]. They are also felt to improve cardiac remodelling. They should be used with caution in patients with renal insufficiency or concurrent treatment with nephrotoxic medications. Renal function should be monitored regularly, especially when titrating dose. There are several adult studies that showed benefit with ACEi in regard to mortality. One in particular suggests that a combination of enalapril and carvedilol (a beta-blocker) may increase left ventricular EF when started at the earliest signs of cardiac dysfunction [34]. In children, however, enalapril did not reveal an improvement in cardiac function [35].

6.3. Statins

Statins are not as widely used in the paediatric population but have antioxidative and anti-inflammatory effects and may play a role in prevention of cardiotoxicity. In adults, a retrospective case-control study revealed that patients who received statins at the time of anthracycline treatment had a lower incidence of HF at 2.5 years follow-up [36]. Statins are safe in children with the proper monitoring; however, their effects on chemotherapy-induced cardiomyopathy are unknown.

6.4. Ventricular assist devices

Ventricular assist devices (VADs) can now be considered in children with inotropic-dependent heart failure. The miniaturization of VAD is allowing for more children to be potential candidates with newer devices supporting lower body surface areas and weights. Most often,

http://dx.doi.org/10.5772/67043

chemotherapy-induced cardiomyopathies are slow to recover function if at all so VAD can be used as a bridge to transplant or in some cases, recovery [23]. VAD can allow patients to be discharged from the hospital, while they are awaiting a heart transplant or recovery. These devices are not without risks, however. Complications such as bleeding, thromboemboli or infection are not uncommon and require close monitoring. The proximity to the hospital as well as the social support system should also be considered when deciding to implant a VAD in a patient.

6.5. Heart transplantation

The definitive treatment for heart failure not responsive to medical therapy is transplantation. Some centres consider transplantation if a patient has been cancer-free for 5 years and are not requiring ongoing cardiotoxic medications. There may be exceptions based on the clinical picture. Unfortunately, immunosuppressive medications required for heart transplants decrease the body's ability to detect and destroy cancer cells so it is not uncommon for secondary malignancies to occur. While transplantation can be life-saving, the cardiac graft has a limited lifespan so the decision to proceed with transplantation should be carefully weighed.

7. Conclusion

Cardiac dysfunctions secondary to cancer treatments are not uncommon. Unfortunately, there have been few breakthrough treatment modalities to treat childhood cancer survivors with heart failure; thus, it is important that these patients are having routine cardiac surveillance to detect cardiac dysfunction before it is severe or the patient is symptomatic. This would allow for altering the treatment plan as well as starting on supportive therapy earlier, which may be beneficial allowing for full cardiac recovery. Institutions should develop robust protocols and have close collaboration with oncologists and cardiologists to ensure that these patients are receiving optimal care.

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