Progress in Pediatric Cardiology 36 (2014) 11–18

Contents lists available at ScienceDirect

Progress in Pediatric Cardiology

journal homepage: www.elsevier.com/locate/ppedcard

Review

Anthracycline cardiotoxicity in survivors of childhood cancer: Clinical course, protection, and treatment

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ARTICLE INFO

Available online 2 October 2014

Keywords:
Anthracyclines
Dexrazoxane
Childhood cancer survivors
Cardiac late effects
Cardiotoxicity
Childhood cancer

ABSTRACT

Childhood cancer survivors are now living longer as a result of advancements in cancer treatment, but not without consequences. Cardiovascular disease is the leading non-cancer-related cause of morbidity and mortality in long-term survivors of childhood cancer. Cardiotoxicity associated with cancer treatment in children can be pervasive, persistent, and progressive. Serum cardiac biomarker concentrations during therapy can predict late cardiotoxicity; although there is still a need for validated cardiac monitoring guidelines. The cardioprotective strategy of continuous infusion of doxorubicin, while showing short-term benefit in adults, provides no long-term cardioprotection or improvement in event-free survival over bolus-infusion in children with a diagnosis of acute lymphoblastic leukemia. However, dexrazoxane protects the heart from the cardiotoxic effects of anthracycline treatment and does not interfere with oncologic efficacy or increase the risk of second malignancies. The emerging field of cardio-oncology emphasizes the need for collaborations between cardiologists and oncologists to find a balance between oncologic efficacy and the risks of cardiotoxicity to maximize the quality of life and survival for long-term survivors of childhood cancer.

1. Introduction

Many survivors of childhood cancer are now living longer and into adulthood as a result of advancements in cancer treatment: in the past 30 years, 5-year survival has increased from about 60% to 83% [1]. However, the same treatments that cured cancer can also increase the risk of treatment-related complications that reduce quality of life. About 75% of childhood cancer survivors will experience a chronic health condition within 30 years after diagnosis [2].

Cardiovascular disease is the leading non-cancer-related cause of morbidity and mortality in long-term survivors of childhood cancer [2–5]. Survivors are 8 times more likely than the general population to die from cardiovascular disease, 15 times as likely to suffer from heart failure, more than 10 times as likely to have coronary artery disease, and more than 9 times as likely to have had a cerebrovascular accident during the first 30 years after cancer diagnosis [2].

Here, we review the course, risk factors, prevention, and treatment strategies of anthracycline-induced cardiotoxicity in childhood cancer survivors, as well as areas of research that could increase our understanding of the disease and establish evidence-based monitoring guidelines and therapies that will hopefully improve quality of life.

2. Course of cardiotoxicity

Anthracycline-induced cardiotoxicity can present as early as a few days after the first exposure to decades after treatment has ended [6]. Acute cardiotoxicity manifests within a week of treatment; early-onset cardiotoxicity, within a year of treatment; and late-onset cardiotoxicity, a year or more after therapy [7–13]. Late-onset symptoms can also present in patients who had neither acute nor early-onset cardiotoxicity [14].

Acute cardiotoxicity occurs in less than 1% of patients [7,8,10]. It often manifests as arrhythmias, electrocardiographic abnormalities, heart failure, or as a myocarditis–pericarditis syndrome [7,8,10,15]. Acute cardiotoxicity may resolve when treatment is stopped but patients with acute toxicity are at higher risk for developing late cardiotoxicity [7,15].

Early-onset cardiotoxicity may present as left ventricular (LV) dysfunction, electrocardiographic changes, and heart failure [7–11,13,16]. We found that anthracycline-treated survivors of childhood leukemia initially experienced a dilated cardiomyopathy with reduced LV fractional shortening and LV contractility along with LV dilation. Slowly, these signs changed to a restrictive-like cardiomyopathy with normal-

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http://dx.doi.org/10.1016/j.ppedcard.2014.09.012
1058-9813/

to-reduced LV dimensions and markedly reduced LV wall thickness for body-surface area, reduced LV fractional shortening, and reduced LV contractility [14] (Fig. 1). The restrictive phase seems to manifest as a relative decrease in LV dimension for body-surface area with a geometrically consequent rise in LV wall thickness for body-surface area, leading to a normal LV thickness-to-dimension ratio, a marker of LV remodeling. Left ventricular mass and cavity size become progressively smaller and become inadequate for body size. This cardiomyopathy is marked by a shrinking myocardial and cavity size ("Grinch" syndrome) and appears to be a long-term risk for premature symptomatic cardiovascular disease in childhood cancer survivors [17].

In late-onset cardiomyopathy, LV function deteriorates and is often accompanied by the loss of cardiomyocytes, LV wall thinning, and sometimes LV dilation [18–20]. Echocardiographic findings may include reduced LV fractional shortening, decreased LV mass, depressed LV contractility, and lower LV end-diastolic posterior wall thickness, along with increased LV afterload [7].

3. Risk factors

Treatment-related risk factors, modifiable and non-modifiable risk factors, and potential genetic predisposition all impact the degree and progression of anthracycline-related toxicity in children [7].

Higher cumulative anthracycline doses are associated with a greater risk of late cardiac compromise. The risk of cardiotoxicity is 11 times as high in children who receive cumulative anthracycline doses of more than 300 mg/m^2 compared to those who receive less [21]. However, since studies have proven that cardiac damage can occur even at doses less than 240 mg/m^2 [14], and they often progress, there is no "safe" dose of anthracyclines over a lifespan that is free of measurable cardiotoxicity.

In adults, continuous infusions of anthracycline may reduce peak serum anthracycline levels and may decrease the risk of early cardiotoxicity [22], but pediatric studies have supported this finding or found continuous infusion to be cardioprotective for late cardiotoxicity

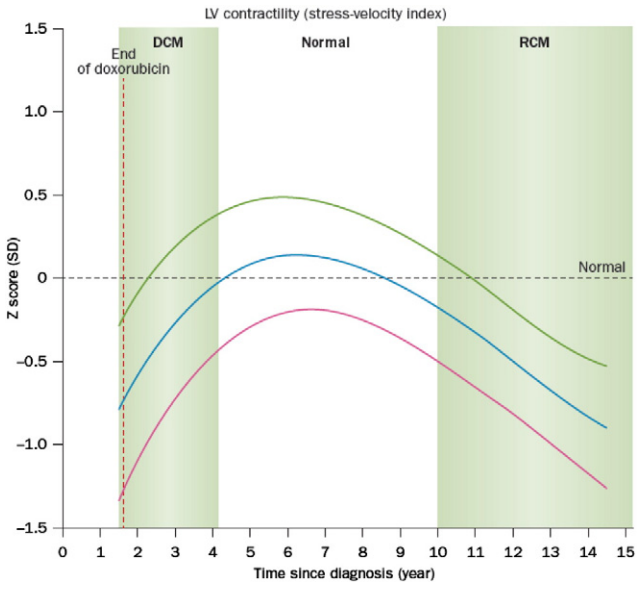

Fig. 1. Progressive cardiac dysfunction after doxorubicin therapy in children treated for acute lymphoblastic leukemia. Dilated cardiomyopathy (DCM) was characterized by echocardiographic signs of reduced left ventricular (LV) fractional shortening and contractility with LV dilation. In time, the pattern changed, and children showed signs consistent with a restrictive cardiomyopathy (RCM): normal to reduced LV dimension with significantly reduced LV thickness, fractional shortening and contractility. Blue line indicates the overall group mean in this model. Green and red lines are the upper and lower 95% CI from the predicted mean.
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[23]. In a multicenter, randomized trial of children with high-risk ALL, 8 years after diagnosis, neither cardioprotection nor event-free survival was better in patients who received doxorubicin as a continuous or as a bolus infusion [23]. Both treatment groups had similar values of LV function and structure with lower LV fractional shortening, LV end-diastolic posterior wall thickness, and LV mass and increased LV end-systolic dimension. Also, 10-year event-free survival was not significantly different (83% and 78% for continuous and bolus doxorubicin infusions, respectively), suggesting no effect on cancer treatment [23]. Other studies with a 5–7 year follow-up further strengthen these findings [24,25]. Continuous infusions have been found to increase hospital stay, costs, and the risks of thromboembolic events and mucositis [26], and while some clinicians do not recommend it in view of lacking evidence, it is still incorporated into pediatric treatment protocols for cardioprotection.

Long-term cardiac morbidity due to chest-directed radiotherapy is well established. In a 5-year multicenter study consisting of 4122 French-British childhood cancer survivors, a linear relation between the average radiation dose and the risk of cardiac mortality was established (the estimated relative risk at 1 Gy was 60%) [27]. Other similar studies have demonstrated the significantly extra risk of cardiac mortality when high cumulative anthracycline doses were combined with radiotherapy [5,8,13].

Cranial irradiation is a standard of treatment for childhood leukemia, brain cancers and to prevent brain metastases. Decreased LV mass and LV dimensions over a 10-year follow-up were found in patients exposed to cranial irradiation compared to those without this exposure [28]. These decreases were associated with decreased insulin-like growth factor 1 concentrations that were likely related to growth hormone deficiency. Thus, cranial irradiation is an additional risk factor in cardiotoxicity.

There are various non-modifiable and modifiable risk factors like female sex, trisomy 21, younger age at treatment, longer follow-up after treatment, and the presence of pre-existing cardiovascular disease and co-morbidities (high blood pressure, and obesity) [7]. Girls are more susceptible to anthracycline-induced cardiotoxicity than boys, possibly due to their higher body fat percentage [29]. Doxorubicin intracellular cardiomyocyte concentrations may be increased during treatment for childhood cancer in patients with a larger percent of body fat, since dosage is often calculated based on body-surface area but doxorubicin is poorly absorbed by fat that comprises part of the body-surface area [18]. Hormone-induced alterations of mast cells, and other immune effector cells are associated with sex-related differences in doxorubicin toxicity in animal studies [30]. Follow-up studies reveal that survivors diagnosed at a younger age are more likely to experience LV wall thinning relative to body-surface area [18]. Additionally, there is a higher prevalence of LV dysfunction in patients with longer follow-up and thus, the length of follow-up is an important risk factor [31].

Childhood cancer survivors are more likely to lead a more inactive lifestyle [32] and report watching more television than their siblings [33,34], and thus are less likely to meet physical activity guidelines. Physical inactivity is possibly the most important risk factor associated with cardiovascular disease and other risk factors of atherosclerosis, such as metabolic syndrome, which can be behaviorally modified. Maximal myocardial oxygen consumption is lower in cancer survivors than in sibling controls, particularly in females (possibly due to higher body fat concentration), those at an older age, those with methotrexate exposure, and those with high or low LV masses [35].

The prevalence of obesity and increased body fat is greater among subpopulations of childhood cancer survivors than in the healthy population [33,36]. The Childhood Cancer Survivor Study reported an increased prevalence of obesity, but only in girls treated for ALL [36]. In a study by Miller et al. the body composition measures did not differ between female survivors and siblings; the mean BMI of both groups was greater than 24 kg/m^2, while male survivors had a higher percentage of body fat and trunk fat than that of their siblings and were more likely to be overweight or obese [33]. These findings suggest that the overall