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REVIEW

# Educational Paper: Decreasing the burden of cardiovascular disease in childhood cancer survivors: An update for the pediatrician

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**Abstract** The cardiovascular impact of cancer therapies on the heart is one of the major concerns in the long-term follow-up of childhood cancer survivors (CCSs). Long-term cardiovascular effects include the development of left ventricular dysfunction resulting in congestive heart failure and ischemic heart disease, as well as valvular and pericardial disease. This is mainly ascribed to the cardiotoxic side effects of chemotherapeutic agents (especially anthracyclines) and radiotherapy, but other factors such as radiation and inflammation play a role in the effect of childhood cancer on the cardiovascular health. The most concerning effect is the high incidence of symptomatic heart failure in CCS patients treated with anthracyclines. More than 50 % of CCSs treated with anthracyclines develop asymptomatic left ventricular dysfunction after cancer therapy, with approximately 5 % developing clinical signs of heart failure during long-term follow-up. Once CCS patients develop congestive heart failure, prognosis is poor and is not influenced by current medical treatment strategies. To reduce the long-term burden of cardiovascular disease in pediatric cancer patients, a diversified approach will be necessary. In the acute phase, prevention of cardiac damage through the use of cardioprotective agents (e.g., dexrazoxane) or by administering less cardiotoxic chemotherapeutic agents is to be considered. A recent randomized trial suggested that the use of dexrazoxane reduced cardiac toxicity without affecting cancer outcomes. Especially patients requiring high doses of chemotherapeutic agents could benefit from this approach. Recent data suggest that genetic testing might identify patients at higher risk for cardiotoxicity. This seems mainly related to genes involved in drug metabolism. This would allow personalized approach adjusting chemotherapy based on cardiovascular risk profiling. This could be combined with newer monitoring strategies in the acute phase using newer echocardiographic techniques and biomarker screening to identify patients with early damage to the myocardium. For the long-term CCS cohort, early detection and treatment of early dysfunction prior to the development of congestive heart failure could potentially improve long-term outcomes. Promoting healthy lifestyles and controlling additional cardiovascular risk factors (e.g., obesity, diabetes, arterial hypertension) is an important task for every physician involved in the care of this growing cohort.

**Keywords** Chemotherapy · Childhood cancer survivor · Cardiotoxicity

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## Introduction

Significant progress has been made over the past 4 decades in improving survival of childhood cancer. Currently around 80 % of all children diagnosed with cancer survive, resulting in a large cohort of childhood cancer survivors (CCSs) [5, 25]. There are over 325,000 childhood cancer survivors

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alive in the USA, with the CCS population in Canada likely in excess of 30,000 [26, 59]. CCSs are at significant risk of serious morbidity and premature mortality as a result of their cancer therapy [9]. Apart from cancer recurrence and secondary cancers, cardiovascular disease is the most important risk factor influencing long-term survival. Direct cardiotoxicity, mainly caused by anthracyclines (e.g., doxorubicin, daunorubicin) which are administered to more than 50 % of children with cancer [52], is a major cause of cardiomyopathy, but other factors such as radiotherapy and inflammation play a role in the increased incidence of cardiovascular disease in CCSs. Congestive heart failure is the most common problem after cancer treatment, but other problems such as ischemic heart disease, valve disease, and pericardial disease are more commonly observed in CCSs [62]. This review summarizes the current data on cardiovascular outcomes in CCSs, the insights into the mechanisms, and overviews current management and prevention strategies. We decided to mainly focus on the long-term effects in the surviving population and less on the acute effects. The review is based on a comprehensive literature search using two different electronic databases (PubMed and Web Of Science) for the keywords chemotherapy, anthracycline, radiotherapy, children, childhood cancer survivor, cardiotoxicity, heart failure, left ventricular (LV) dysfunction, cardiac ischemia, valvular disease, pericardial disease, autonomic, electrocardiogram, and long QT.

## Epidemiology of cardiovascular disease in childhood cancer survivors

Although observed frequencies vary between studies, up to 60 % of patients treated with an anthracycline will develop echocardiographic abnormalities during long-term follow-up [46]. These abnormalities are progressive in a proportion of patients [34, 45, 54]. The risk of congestive heart failure (CHF) in children exposed to a cumulative anthracycline dose greater than 300 mg/m$^2$ approaches 10 % by 20 years after their cancer therapy [95], but even children exposed to lower doses of anthracyclines are at increased risk for CHF [46, 68]. Different large cohort studies have collected data on the long-term cardiovascular impact of childhood cancer. The Childhood Cancer Survivor Study is a large retrospective cohort study looking at the incidence and severity of chronic health conditions in adult CCSs [70]. Interesting in this study is that the health data were compared with information from CCS siblings. The cardiac outcome data were obtained by a health questionnaire filled out by 14,358 5-year survivors of cancer diagnosed under the age of 21 [68]. Compared to their siblings, CCSs reported a higher risk for congestive heart failure (hazard ratio (HR) 5.9), myocardial infarction (HR 5.0), pericardial disease (HR 6.3), and valvular abnormalities (HR 4.8). The risks for congestive heart failure, valve disease, and pericardial disease were two to five times higher in patients who were exposed to anthracyclines. This study also suggests that the cumulative risk continues to increase up to 30 years after the cancer diagnosis. The high mortality associated with some of the cardiac abnormalities probably explains why cardiac disease is the third cause of late death in CCSs, after primary cancer recurrence and second malignancy, and the leading cause of non-cancerous late death [7–9]. Children who survive their primary cancer are affected by higher mortality rates from cardiovascular complications in the range of 10 to 20 times above the general population [51, 82]. A more recent large retrospective cohort [96], including 1,362 patients clinically evaluated by a cardiologist, identified 50 cardiac events in 42 patients who survived at least 5 years after cancer diagnosis. Congestive heart failure was the most common cardiac complication (54 %), followed by cardiac arrhythmia (18 %), ischemia/myocardial infarction (12 %), valvular disease (12 %), and pericarditis (4 %). Apart from cardiotoxic chemotherapeutic agents, radiotherapy is an important contributor to long-term cardiac disease [42, 68]. Chest radiation increases the risk of congestive heart failure, pericardial disease, valve disease, and ischemic heart disease by two- to sixfold [68]. In Hodgkin's lymphoma survivors treated with radiation involving the chest, 42/415 patients (10.4 %) developed coronary artery disease at median time of approximately 9 years after treatment, and another 7 % developed carotid/subclavian artery disease at a median of 17 years after treatment [42]. Of the same groups, 6 % developed valvular dysfunction about 25 years after radiotherapy. This mainly affected the aortic valve with a higher than expected frequency of cardiac interventions for aortic valve disease [42].

## Risk factors

Different risk factors for the development of long-term cardiotoxicity have been well characterized for the patients treated with anthracyclines mainly based on multivariate analysis from different retrospective cohort studies (Table 1) [46, 55]. Risk factors include young age at chemotherapy, female gender, high cumulative dose (250–300 mg/m$^2$ or above), and development of acute cardiotoxicity during the treatment [99]. Although there is a well-known positive association between higher cumulative doses of anthracyclines and the risk of cardiotoxicity, it is also well established that lower doses can also cause cardiotoxicity [6, 41, 47, 54–56, 75, 86]. As cardiotoxicity is a progressive disease, length of follow-up is a risk factor. Concomitant exposure to radiation, trisomy 21, and African–American descent are additional risk factors [35]. Combination chemotherapy using anthracyclines with other drugs such as cyclophosphamide, trastuzumab, cisplatinum, and methotrexate can also increase the risk of cardiovascular toxicity [16].

**Table 1** Risk factors for cardiotoxicity

| Risk factor | References |
|---|---|
| Higher anthracycline dose >300 mg/m$^2$ | Krisher 1997, Silber 1993, Lipshultz 1991, 2005, Hudson 2007, Rathe 2010, Amigoni 2010 |
| Combination chemotherapy | Chen 2009, Watts 1991, Gottdiener 1981, Simbre 2005 |
| Female gender | Lipshultz 1995, Kremer 2002 |
| Concomitant exposure to mediastinal radiotherapy | Chen 2009, Heidenreich 2003 |
| Young age at diagnosis | Grenier 1998 |
| Length of follow-up | Grenier 1998 |
| Trisomy 21 | O'Brien 2008 |
| African–American race | Grenier 1998 |

Most relevant for the pediatric population is combination treatment with cyclophosphamide which seems to increase the risk for acute cardiotoxicity [48, 49, 89]: high doses of cyclophosphamide (>60 mg/kg/day) may cause acute heart failure and bolus doses of up to 180 mg/kg have been reported to cause pericardial effusion [33, 64, 100]. The effect of combination treatments on long-term outcomes is less well studied.

Apart from these traditional risk factors, recent genetic studies have identified potential genetic risk factors related to genomic variants between individuals. A pharmacogenomic study [98] showed that risk stratification for anthracycline toxicity could be based on certain polymorphisms in genes involved in anthracycline metabolism influencing drug pharmacokinetics. Gene polymorphisms in carbonyl reductases may be implicated in increased risk of cardiotoxicity in patients homozygous for the CBR3 G allele [12], who developed cardiomyopathy after low to moderate doses of anthracyclines. This potentially introduces the concept of genetic risk stratification and personalized medicine into the care of childhood cancer. Children treated with anthracyclines could be genetically profiled, and their treatment strategy could be tailored based on their genetic risk profile (lower dosage, use of cardioprotective agents, and different monitoring strategy, as discussed below). These preliminary

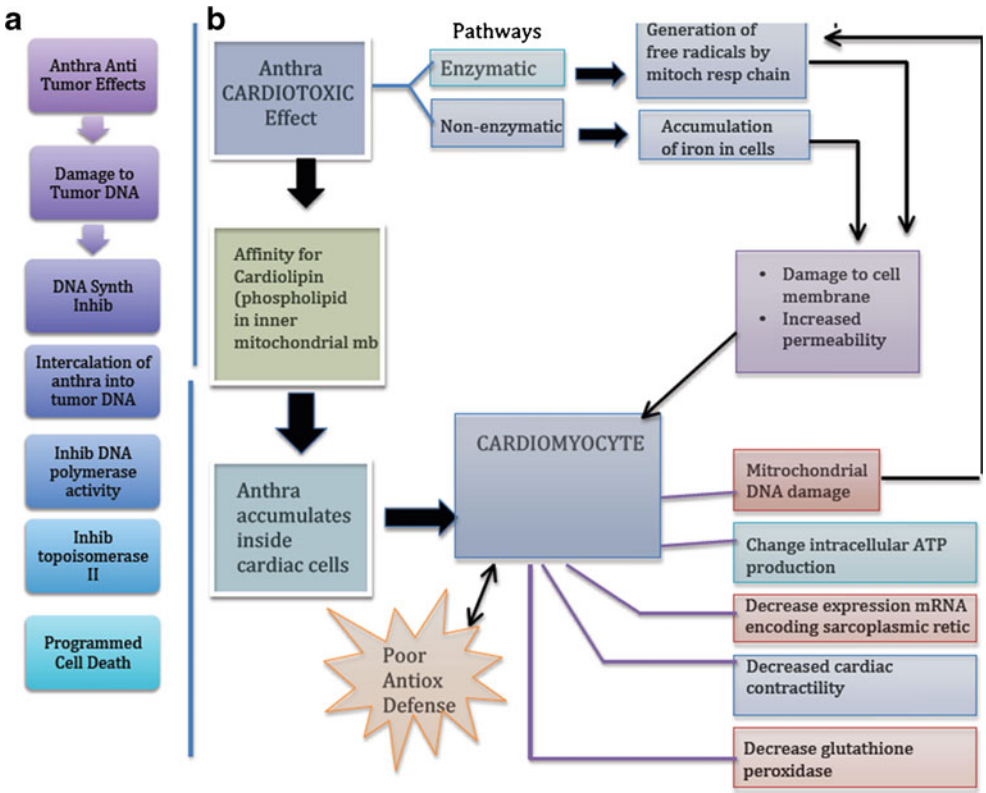


**Fig. 1** Anthracycline cardiotoxicity. **a** Mechanism of anthracycline antitumor effect and **b** mechanism of cardiotoxicity. *Anthra* anthracycline, *DNA Synth Inhib* DNA Synthase Inhibition, *Mitoch resp chain* mitochondrial respiratory chain, *Mb* membrane, *Retic* reticulum, *Antiox* antioxidant

data need to be further explored but could potentially significantly impact cancer treatment strategies.

Radiotherapy exposure is associated with increased risks for coronary artery disease, valve disease, and pericardial disease [42, 68]. The radiation dose is an important risk factor with any dosage involving the heart exceeding 1,500–3,500 cGy increasing the risk for cardiac disease during long-term follow-up (more than 20 years) [4]. Higher doses can cause myocardial ischemia as early as 12 years post-exposure, as shown in shorter-term follow-up studies [37, 43, 76]. As with chemotherapy, the cardiac effects of radiotherapy seem life-long and appear to be progressive [71, 91]. This seems to suggest that any hit to the heart either by drugs or radiation seems to cause irreversible damage resulting in progressive dysfunction, which brings us to the mechanisms of disease.

## Mechanisms of cardiotoxicity

Understanding the mechanisms of cardiotoxicity is important for comprehending the strategies that might be used to prevent cardiac damage during chemotherapy and radiotherapy. Multiple mechanisms of acute cardiac injury have been proposed, largely based on animal studies and cell culture work (Fig. 1). One of the most important mechanisms by which anthracyclines cause cardiac injury is by formation of reactive oxygen species, which induce oxidative cell membrane damage [29]. Myocardial cells seem more vulnerable probably related due to the more limited antioxidant capacity of cardiac myocytes compared to other tissues and organs. Anthracyclines also affect mitochondrial metabolism due to iron accumulation and changes in mitochondrial gene expression [29]. This causes further oxidative damage and affects myocardial energy metabolism. Cell membrane changes and other mechanisms influence calcium metabolism resulting in increased intracellular calcium levels. This activates the pathways resulting in apoptosis and cardiac cell death in certain more vulnerable cells. In the surviving cells, anthracyclines influence transcriptional mechanisms resulting in decreased expression of cardiac specific genes including sarcomeric proteins [74]. While normal myocardium has some regenerative capacity, recent studies showed that anthracyclines influence cardiac repair mechanisms by reducing the pool of cardiac stem cells and possibly through inhibiting other regenerative pathways such as the ErbB1 pathway [18]. It is believed that the synergistic effect of trastuzumab treatment together with anthracycline treatment is related to the inhibition on the cardioprotective effect of the ErbB pathway. The specific effects of chemotherapeutic agents on the pediatric myocardial substrate have not been well studied. A reduction of the number of cells in a growing heart with an inhibition of regenerative pathways and damage to the remaining cells, probably explains why there is a long-term effect of a hit earlier in life.

Apart from the direct effect of anthracyclines on the myocardial cells, chemotherapeutic agents may damage the heart through indirect mechanisms. Histological findings in patients who died from toxicity caused by combination treatments of cyclophosphamide and anthracyclines have shown coronary endothelial damage with microvascular thrombi causing ischemic areas in the myocardium [87]. High-dose treatment with cyclophosphamide used in children may result in cardiac damage caused by endothelial injury, extravasation of toxic metabolites with myocyte damage, interstitial hemorrhage, and cell edema [32, 33, 65]. Intracapillary myocardial thrombi resulting in microvascular myocardial ischemia have been described [72]. Data regarding the impact of chemotherapy on the endothelium and vascular structures in children are limited, but damage to these structures may be involved in an increased risk for ischemic heart disease later on in life. Radiotherapy involving the chest can cause damage to all structures of the heart, including myocardium, valves, pericardium, coronary arteries, and the conduction system [2, 3, 71, 91]. Studies in mice have demonstrated that radiation causes acute injury with inflammation leading to apoptosis and myocardial fibrosis [63]. Chemotherapy associated with mediastinal radiotherapy increases the risk of cardiovascular toxicity [46, 53]. Radiotherapy-induced fibrosis of the myocardium and thickening of the pericardium can lead to myopericarditis and endocardial fibrosis, with resulting valvular disease [58]. More recently, advanced and updated radiation therapy techniques have attempted to minimize the exposure of cardiac tissue to the radiation field; however, the risk of subsequent heart disease is not eliminated [78].

Independent of the mechanism, the loss of myocytes causes thinning of the myocardium with a resulting increase in wall stress. Due to defective regenerative and adaptive pathways in the remaining myocardial cells, the usual physiological adaptive responses to increased wall stress seem deficient. This results in a pathological remodeling process with progression of reduced contractility, cardiac remodeling, and progressive ventricular fibrosis. This ultimately results in symptoms of congestive heart failure in a subgroup of patients. Table 2 summarizes the supposed mechanisms of cardiovascular effect and their clinical effects for the different chemotherapeutic drugs.

## Approach to diagnosis and management

Comprehensive guidelines for surveillance of late toxicity from cancer therapies have been published by different groups [1, 17,

**Table 2** Mechanism of cardiotoxicity by clinical presentation and chemotherapeutic agent

| Presentation | Mechanism | References |
|---|---|---|
| Heart failure | | |
| Cyclophosphamide | Endothelial and myocyte injury | Kupari 1990 |
| Mitomycin | Semiquinone radical produced under aerobic condition and generation of superoxides | Tomasz 1974 |
| Trastuzumab | Effect on Her2/Her4 signaling and cardiac protective pathways | Liu 2006 |
| Chest pain (ischemic) | | |
| Cisplatin | Infusion can cause chest pain with increased cardiac enzymes | Berliner 1990, Schimmel 2004 |
| Fluorouracil, 5-FU | Ischemic syndrome, angina to acute myocardial infarction, coronary spasm | Gradishar 1990 |
| Capecitabine | Angina, myocardial infarction, Possibly less toxic than 5-FU | Pai 2000, Schimmel 2004 |
| Hypertension | | |
| Bevacizumab | Common side effect reported in clinical trials 4–35 % | Miller 2005, 2007, Pande 2007 |
| Sorafenib | Major side effect, reported in 17–43 % | Procopio 2007, Ratain 2009 |
| Bradycardia | | |
| Paclitaxel | Variable incidence (0.1–31 %), usually reversible and asymptomatic | Rowinsky 1993, McGuire 1993 |
| QT prolongation | | |
| Arsenic trioxide | Incidence from 26–93 %, with QTc >500 milliseconds in 40 % of patients in one trial, returning to baseline 8 weeks after therapy | Soignet 2003, Barbey 2001 |

40], including the Children's Oncology Group's, a consortium of over 200 pediatric cancer services in North America (guidelines available at www.survivorshipguidelines.org). All guidelines recommend a similar clinical approach, which includes history and physical examination for cardiovascular symptoms and signs of congestive heart failure, ECG (not for anthracycline alone), and cardiac imaging. Echocardiography or radionuclide angiography is recommended for the evaluation of systolic function at baseline and then periodically during long-term follow-up. In most centers, echocardiography has replaced radionuclide angiography as it is less invasive and does not involve radiation exposure. The frequency of imaging studies is based on the risk profile including the age at treatment, cumulative anthracycline dose, and radiation treatment. Follow-up intervals range between once a year and every 5 years. ECG is recommended for evaluation of the QTc interval at baseline and is repeated at regular intervals. Currently, an international group of pediatric oncologists and cardiologists is working on more detailed international guidelines. Waiting for clinical symptoms to occur has proven to be an ineffective strategy: once heart failure occurs, the outcome is poor despite medical treatment. Early detection and treatment of subclinical cardiomyopathy might improve long-term outcomes, although this has not yet been substantiated by prospective research studies. In the meantime, prospective monitoring of cardiac function is recommended and a decrease in cardiac function should be closely monitored and may prove to be a rationale to start early treatment. One of the main problems for this strategy is the poor definition of early cardiac dysfunction. Currently, decision making in the different surveillance protocols is based on changes in LV ejection fraction (EF). However, the intrinsic variability of the echocardiographic EF measurements reduces the sensitivity for detecting changes in myocardial function. Generally, a decrease in EF by 15 % within normal range, or a decrease of 10 % if the value is below the lower limit, is considered clinically relevant [21]. In most pediatric oncology surveillance protocols, an absolute EF value of 60 % is considered the lower theshold of normal. Better standardization of measurements and modern echocardiographic equipment certainly improves the reliablity of the measurements. In borderline patients with an EF between 50–59 %, cardiac magnetic ressonance imaging is a potential additonal imaging modality [9]. Apart from the measurement problem, a decrease in LVEF is considered a late change that reflects the presence of significant myocardial damage [56]. This is related to cardiac compensatory mechanisms that become active when cardiac dysfunction is present in an attempt to maintain cardiac output and ejection fraction. Early myocardial damage and remodeling precede a decrease in ejection fraction. LV remodeling can be detected by echocardiogram by routine measurements done in most laboratories, such as LV wall thickness, LV diastolic dimension-to-thickness ratio, and calculated LV wall stress. Also, newer echocardiographic techniques looking directly into the cardiac muscle, such as tissue Doppler velocities and myocardial deformation parameters (strain), may be

helpful for the early detection of myocardial dysfunction. Recent studies in adults and children undergoing chemotherapy have demostrated that changes in tissue Doppler velocities and systolic strain parameters precede and predict changes in LV ejection fraction [22, 73, 80]. Stress echocardiography, either using IV dobutamine or exercise, could potentially be helpful in detecting subclinincal disease by identifying patients with decreased systolic or diastolic reserve [77, 84], although the prognostic value of the subclinical findings has not yet been demonstrated.

Apart from imaging parameters, serum biomarkers can be used to detect myocardial damage. These include biomarkers reflecting acute damage such as troponin and high-sensitive troponin as well as parameters reflecting chronic damage such as BNP and NT-pro-BNP [19, 27, 28, 38, 39, 44, 60, 61, 88]. The use of these biomarkers is still controversial, and there are no recommendations in the guidelines regarding their use, despite a significant amount of literature addressing their potential usefulness in detecting early myocardial damage. A number of systematic reviews have been published, and they highlight the paucity of good-quality and well-designed prospective studies, the absence of standardization for monitoring and reporting of echocardiographic parameters, cardiac outcomes, and event-free survival with appropriate statistical analysis [14, 85].

## Clinical manifestations

Late cardiotoxicity is defined as the occurrence of significant left ventricular dysfunction resulting in symptoms of congestive heart failure more than 1 year after starting chemotherapy. It is a progressive disease that is generally irreversible. Apart from systolic dysfunction, changes in diastolic function can be very prominent, probably related to progressive myocardial fibrosis associated with the disease. Medical treatment is identical to any other patient with congestive heart failure. This includes the use of diuretics, afterload reduction (angiotensin converting enzyme inhibitors), and beta-blockers. When medical management fails, mechanical support and cardiac transplantation are the only treatment options. There is still uncertainty on the utility of early treatment. Currently, the professional guidelines recommend starting treatment in asymptomatic patients if there is a decrease in left ventricular ejection fraction as documented by echocardiography. Once patients are symptomatic, heart failure treatment does not significantly influence the outcomes [52, 53, 57, 86]. At present, there are no good evidence-based data to support early treatment of asymptomatic patients with cardiovascular medications, but several ongoing studies are currently further examining this strategy.

## Electrocardiographic abnormalities and arrhythmias

Most of the data available [10, 11, 23, 24, 30, 36, 67, 79, 94, 97], long-term cardiac electrical abnormalities in CCSs are based on retrospective studies and case series. Most studies describe acute changes during treatment. These include cardiac arrhythmias that generally are an acute manifestation of cardiovascular toxicity [31]. In acute cardiotoxicity, the presence of other comorbidities (such as renal and hepatic disease, anemia, and concomitant infection) and the use of medications prolonging the QT interval (antifungals, antiemetics, quinolones) are common. Electrolyte disturbances caused by vomiting, diarrhea, and decreased appetite further increase the risk of QTc prolongation and arrhythmias. Prolongation of the QTc interval appears to be a dose-related and transient phenomenon [23]. During long-term follow-up, supraventricular tachycardia (SVT) was reported as occurring in 1.8 % of children in a large series of 168 patients diagnosed with different cancers at a mean age of 8.1 (5.3) years, followed up for a mean of 5.6 years (3.2–8 years) [16]. Sudden death, presumably due to arrhythmia, was reported in 3/15 patients in a retrospective case series. These 15 patients were described as presenting with clinical diagnosis of cardiotoxicity from anthracycline and were a subset of 300 patients evaluated after 4 years of receiving anthracycline. Fourteen of 15 had conduction abnormalities and arrhythmias. Two other patients had syncope, and one required an implantable defibrillator related to CHF [90]. Overall, this corresponds to increased susceptibility to arrhythmia as seen in patients with cardiomyopathy. In a retrospective descriptive study of 134 patients (mean age of 15±4 years) who underwent chemotherapy at median time of 5±4 years prior to the 12-lead ECG or 24-h ambulatory ECG monitor, 44 % had documented abnormalities. Children treated with anthracyclines developed atrial ectopic rhythm in 6 %, prolongation of the QTc in 14 %, flat or inverted T waves in 2 %, and deep Q waves in inferior leads in 3 %. Patients who received radiation therapy were noted to have pathologic Q waves in 10 % of cases. As the patients were asymptomatic, these changes were considered minor and did not require treatment, but the authors recommended periodic monitoring with ECG including Holter monitors [50]. QT dispersion or QTc dispersion is the difference between the longest and the shortest QT or QTc intervals on a 12-lead ECG, and it has been suggested as a noninvasive predictor of development of heart failure after hematopoietic stem cell transplant in children [67] and adults [69], but further study is needed to validate these findings.

It is reasonable to conclude that several electrical abnormalities may be detected in patients exposed to cancer therapies. Abnormalities diagnosed in the ECG and Holter in childhood cancer survivors cannot be attributed exclusively to the cancer therapy in the acute phase, as other comorbidities may contribute in variable degree. In the long term, ECG and Holter have not been considered highly sensitive or specific for early detection of chronic cardiotoxicity.

## Vascular abnormalities, endothelial and autonomic dysfunction, hypertension, and persistent sinus tachycardia

Post-chemotherapy patients have an increased risk for early atherosclerosis and coronary artery disease compared to a normal population, particularly in patients who underwent mediastinal irradiation [13, 20, 63, 101]. The vascular effects of chemotherapy have not been well studied. Endothelial dysfunction has been reported in young Hodgkin's patients (age range between 12–30 years) at least 2 years post-mediastinal radiation as opposed to those who did not receive radiotherapy and controls [101]. Further research on the direct vascular toxicity and the long-term effects on early atherosclerosis is warranted. This could have important implication for preventive strategies including more rigorous monitoring of lipid abnormalities. Apart from the direct vascular effects, cancer treatment also seems to affect the autonomic nervous system. Autonomic dysfunction [13] as assessed using baroreflex sensitivity (BRS) was shown to be more prevalent in CCSs compared to normal controls. In the same study, abnormal BRS was associated with diastolic but not systolic cardiac abnormalities. This association requires further study. Symptomatic autonomic dysfunction requires further diagnostic testing and sometimes treatment. Some patients may benefit from autonomic testing, and in the presence of persistent sinus tachycardia, other causes, such as thyroid dysfunction, anemia, hypovolemia, and physical deconditioning, need to be ruled out, and treatment may be required [66, 92]. The presence of vascular abnormalities and autonomic dysfunction could result in blood pressure abnormalities. Few studies evaluated the prevalence of systemic hypertension in childhood cancer survivors. A recently published study following a large cohort of 277 adult survivors of childhood cancer with a median age of 28 years (18–48 years) reported arterial hypertension in 13/92 (14.1 %) of the patients with LV systolic dysfunction (low fractional shortening), in 5/33 (15.2 %) of patients with regional wall motion abnormalities, and in 17/29 (58.6 %) of patients with abnormal diastolic function [13]. These data again suggest a possible relationship between vascular and cardiac abnormalities that requires further study. Because of the higher risk of heart failure and ischemic heart disease in this population, primary prevention of atherosclerotic disease seems rational. This involves prevention and early treatment of arterial hypertension, obesity, lipid disorders, diabetes, and, generally, advocacy for a healthy lifestyle. This is an important role for all healthcare providers involved in the care of this growing patient population. All health care providers should be aware that being a CCS should consider a significant cardiovascular risk factor.

## Specific preventive strategies

The primary goal in terms of prevention involves minimizing cardiotoxicity while optimizing cancer treatment efficacy. Several strategies have been used, as shown in Table 3. Only a few of the strategies have been evaluated in the context of randomized controlled trials.

### Different drug infusion protocols

Apart from trying to reduce the cumulative dosage of anthracyclines, different infusion protocols including prolonged and slower infusion rates have been tried to reduce the acute toxicity. In adults, anthracycline infusion duration of 6 h or longer seems to reduce the risk of clinical heart failure and subclinical cardiac damage. There are, however, no good data in children, and this should be further evaluated in well-designed randomized controlled studies [95].

### Use of cardioprotective agents: dexrazoxane

Initially designed as a chemotherapeutic agent and found to lack efficacy, dexrazoxane has been administered with anthracyclines or trastuzumab in adults and children, aiming to reduce cardiotoxicity. Dexrazoxane is an iron chelator that protects the myocardium from oxidative damage. A consensus paper [93] highlights the advantages of its use in pediatric patients, but despite well-documented evidence that dexrazoxane offers cardioprotection in children, it is still not widely used by oncologists. Wexler compared children receiving anthracyclines with and without dexrazoxane and showed that the children who received dexrazoxane had a 22 % risk of subclinical cardiotoxicity while the controls had 67 %. A randomized controlled trial in children undergoing chemotherapy for acute lymphoblastic leukemia showed that in the acute phase [56], troponin T levels in children receiving dexrazoxane were lower compared to the group not receiving the cardioprotective agent. A long-term follow-up study looking at the same cohort 5 years later showed that patients who received dexrazoxane had a less reduced left ventricular wall thickness and thickness-to-dimension ratio. This finding was only significant in boys,

**Table 3** Prevention strategies proposed by current practice guidelines

| GOAL | REFERENCE |
|---|---|
| Strategy: limiting dose of anthracycline | |
| Limitation of cumulative dose of doxo at 300 mg/m$^2$ | Schuchter 2002 |
| Strategy: infusion versus bolus | |
| Adults: continuous infusion had less cardiotoxicity | Legha 1982, Hortobagyi 1989, Shapira 1990 |
| Children: no benefit from continuous infusion | Lipshultz 2002, Levitt 2004 |
| Strategy: use of anthracycline analogues | |
| Epirubicin produces equivalent toxicity to doxo and does not improve response rate and survival, in females with advanced breast cancer | Perez 1991 |
| Idarubicin has similar cardiotoxicity as doxo, better efficacy than daunorubicin | Creutzig 2001 |
| Mitoxantrone in dose-equivalent administration has less cardiotoxicity than doxo | Herman 1997, Alderton 1992 |
| Strategy: use of liposomal anthracyclines | |
| Liposomal doxorubicin in adult randomized controlled trials, same efficacy as regular doxorubicin but less cardiotoxicity | Batist 2001, Harris 2002, Safra 2003 |
| Liposomal daunorubicin in adults, high cumulative doses (600–900 mg/m$^2$) are cardiotoxic | O'Byrne 2002, Fassas 2002 |
| Pegylated liposomal doxorubicin in adult RCT, same survival, but less cardiotoxicity with pegylated liposomal doxorubicin, HR 3.1 (95 % CI 1.58–6.31) | O'Brien 2004 |
| Strategy: cardioprotectants | |
| Dexrazoxane In children, there is no sufficient evidence to make a recommendation for routine use of dexrazoxane; it might be justified if the risk of cardiac toxicity is high in individual children | Van Dalen 2011, Schwartz 2009 Lipshultz 2010, Choi 2010 |
| Other agents: Human studies—L-carnitine, coenzyme Q10, vitamin E and C, N-acetylcysteine, phenethylamines, carvedilol, and amifostine Animal studies—probucol, vitamin A, carotenoids, selenium, and glutathione | Van Dalen 2011 |

indicating that girls are more sensitive to the cardiotoxic effects of anthracyclines. At 5-year follow-up, there was no survival difference between both groups, suggesting that the cardioprotective agent did not affect the antineoplastic effect of the drug. The authors suggested that in children with a high risk of cardiotoxicity, there may be some benefit in considering the use of dexrazoxane. Recommendations by the Clinical Practice Guidelines of the American Society of Clinical Oncology, endorsed by the Children's Oncology Group, consider doses of 300 mg/m$^2$ or higher in patients under 18 years of age at the time of treatment or any dose in infants as significant risk factors for cardiotoxicity. In these patients, the use of dexrazoxane should be considered [81].

### Liposomal anthracyclines

Encapsulation of anthracyclines into liposomes allows the drug to travel inside a protective capsule and be delivered more safely to the target tumor cells, where it can penetrate more easily, as tumor cells are usually not connected by tight capillary junctions. The myocardium is characterized by tight capillary junctions, which prevent liposome-encapsulated anthracyclines from crossing the capillaries into the myocardial tissue [15, 83]. Several randomized controlled trials have been performed in adults, and a recent meta-analysis of the different trials suggests that the use of liposomal anthracyclines reduces the risk for clinical and subclinical heart failure. There are, however, no pediatric data available.

## Conclusion

Childhood cancer survivors are at increased risk of premature cardiovascular disease and early mortality. At each stage of the treatment and follow-up specific measures should be put in place for trying to prevent the cardiac side effects of cancer treatment. Based on current available data, we propose the following preventive strategies.

In the acute treatment phase:

- lowering the dosage of cardiotoxic agents as much as safely possible;
- use of cardioprotective agents when higher doses of anthracyclines are administered;
- serial echocardiographic monitoring during the acute phase with early medical treatment if significant changes

in ejection fraction are detected. Current data suggest that tissue Doppler imaging and strain data are capable of detecting early changes prior to changes in EF, but this will need further validation in larger pediatric populations;
– the use of routine follow-up using cardiac biomarkers and genetic risk profiling, needs further investigation.

After acute treatment, all patients who have been exposed to cardiotoxic agents or chest irradiation should be followed by a cardiology service on a regular interval. The interval can vary according to the patient's risk profile. For the chronic patient group, we propose the following preventive strategies:

– promotion of healthy lifestyle and control of other cardiovascular risk factors such as hypertension, obesity, diabetes, and lipid disorders;
– early cardiac medical treatment if changes in ejection fraction are noted. The use of biomarkers and newer imaging modalities such as tissue Doppler and strain imaging in the decision for early treatment should be further explored.

Reducing the cardiovascular burden in this patient population will require close collaboration between all health care providers involved in the care of this growing population of CCSs. It is an important area of research, and hopefully, newer strategies will allow us to better identify patients at risk, reduce cardiotoxic exposure, and provide early detection methods and better treatments. This will significantly impact the long-term survival and quality of life of this patient group.

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