

## EDITORIAL

# CARDIOVASCULAR CARE IN CANCER PATIENTS

## SEGUIMENTO CARDIOVASCULAR NO DOENTE COM CANCRO

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With improvements in cancer therapy and early diagnosis, pediatric cancer survival rates have significantly increased over the two last decades, with estimates indicating that around 80% of children will survive at five years after diagnosis. However, childhood cancer survivors (CCS) are at risk of developing cardiovascular (CV) disease, currently the second cause of late mortality and morbidity following recurrence of the original cancer. Indeed, mortality related to CV events is approximately eight-fold higher compared with age matched general population.<sup>1-3</sup> Risk of coronary artery disease (CAD), cerebrovascular accidents, and congestive heart failure in these patients is respectively 10, 9, and 15 times greater than in siblings.<sup>3</sup>

The pathogenesis of this increased cardiovascular risk is multifactorial and complex, mediated by modalities of treatment such as radiation exposure, anthracyclines and other chemotherapeutic agents and stem cell therapy.<sup>1-6</sup>

Possible complications of chemotherapy and/or radiation include myocardial dysfunction and heart failure, CAD, valvular heart disease, arrhythmias (acquired long QT syndrome, atrial fibrillation and atrioventricular block), arterial hypertension, thromboembolic disease, pulmonary hypertension and pericarditis.<sup>1-6</sup>

Strategies to prevent cardiotoxicity range from improvement of radiotherapy techniques that minimize irradiation to the heart, minimizing exposure to the chemotherapy, use of medications thought to prevent myocardial damage (e.g. dexrazoxane), and initiating cardioprotective drugs at the right time.<sup>3-7</sup>

CV disease related to radiation exposure is dependent of dose, volume and technique of irradiation. Cardiovascular toxicity appears to be progressive, risk is life long, and manifestations include congestive heart failure, CAD, pericardial disease, cardiomyopathy, valvular abnormalities and conduction abnormalities. Radiation exposure is also associated with traditional CV risk factors, namely hypertension, dyslipidemia, and type 2 diabetes mellitus (T2DM).<sup>1,4-7</sup>

Anthracycline treatment may induce dilated cardiomyopathy, subclinical left ventricle dysfunction, congestive heart failure and arrhythmia. Cardiomyopathy may develop in one of three forms: 1) an acute/subacute form, immediately after anthracycline administration, manifesting as transient arrhythmia, pericarditis/myocarditis syndrome, or left ventricular failure and generally reversible; 2) a chronic form, presenting within one year of treatment, and 3) a late onset, with ventricular dysfunction and arrhythmia developing years after treatment. The two last forms are dose-dependent.<sup>2</sup> CCS present clinical and subclinical toxicity at lower levels than adults. Younger age at diagnosis (particularly inferior to five years), female gender, combination therapy with other agents, mediastinal radiation, previous pre-morbid/co-morbid medical conditions (obesity, congenital heart disease, cardiac disease: coronary, valvular or myocardial, hypertension, diabetes mellitus, dyslipidemia) are associated with increased risk of anthracycline-related cardiomyopathy.<sup>2-8</sup>

Hematopoietic stem cell transplantation is associated with increased risk for CVD mortality and morbidity related to cardiomyopathy, congestive heart failure, cerebrovascular accident, CAD, rhythm disorders, hypertension, T2DM, and dyslipidemia.<sup>3</sup>

Additionally, CCS have higher rates of impaired glucose tolerance, T2DM, insulin resistance, and dyslipidemia, as well as increased risk of renal insufficiency and hypertension due to nephrotoxic medications, radiation to the abdomen, and graft-versus-host disease.<sup>3-10</sup>

Recommendations for CV assessment in pediatric cancer patients at diagnosis and follow-up state that initial evaluation should include clinical

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evaluation with identification of CV risk factors, electrocardiogram (ECG) and echocardiogram (ECHO), or cardiac magnetic resonance imaging if necessary. Periodic follow-up is required during treatment, according to clinical situation. After treatment patients should be monitored regularly and a complete history and physical examination is mandatory, with control of CV risk factors (e.g. diet, physical activity, smoking habits, drug use, physical activity).<sup>1,2,4,7-10</sup>

ECHO screening or comparable imaging assessment of cardiac function and ECG (with QTc interval evaluation) is recommended,

according to **Table 1**.<sup>4,11</sup>

Biomarkers, as cardiac troponin I and troponin T, B-natriuretic peptide (BNP), and T-pro-B-natriuretic peptide (proBNP), are also useful, combined with history, physical examination and cardiac imaging to monitor patient’s clinical status.<sup>1,2,4,6-10,12</sup>

Cardiology consultation is necessary in patients with subclinical abnormalities on screening evaluation, left ventricular dysfunction, valvular disease, dysrhythmia, or prolonged QTc interval.<sup>4</sup>

**Table 1** - Follow-up screening

Recommended ECHO frequency		
Anthracycline dose *	Radiation dose**	Recommended frequency
None	<15 Gy or none	No screening
	≥15 - <35 Gy	Every 5 years
	≥35 Gy	Every 2 years
<250 mg/m2	<15 Gy or none	Every 5 years
	≥15 Gy	Every 2 years
>250 mg/m2	Any or none	Every 2 years
*Based on doxorubicin isotoxic equivalent dose		
** Based on radiation dose with potential heart impact (radiation to chest, abdomen, spine, total body irradiation)		
ECG (including QTc interval evaluation)		
Baseline at start of long-term follow-up and repeated as clinically indicated		

Adapted from COG LTFU Guidelines<sup>4</sup>

ECG, electrocardiogram; ECHO, echocardiogram

Medical societies and other organizations have produced guidelines, consensus statements and position papers regarding cancer survivor surveillance and monitoring; the majority concerns the adult

population, but some are directed at the pediatric population and/or adult survivors of pediatric cancers (**Table 2**).

**Table 2** - Resources providing information and/or guidance for cardiovascular care of survivors of pediatric cancers

American Heart Association Scientific Statement on Pediatric, Adolescent, and Young Adult Long-Term Survivors <sup>6</sup>
Children’s Oncology Group (www.childrensoncologygroup.org) <sup>6</sup>
Dutch Childhood Oncology Group <sup>13</sup>
Scottish Intercollegiate Guidelines Network (www.sign.ac.uk)
UK Children’s Cancer and Leukemia Group (www.cclg.org.uk)
International Late Effects of Childhood Cancer Guideline Harmonization Group <sup>9</sup>
I Diretriz Brasileira de Cardio-Oncologia Pediátrica da Sociedade Brasileira de Cardiologia <sup>8</sup>

Modified from Ryan, *et al*<sup>7</sup>

In conclusion, CCS exposed to cardiotoxic therapy require long-term cardiac follow-up and monitoring. Nonpharmacological measures, such as exercise, healthy lifestyle, risk factor control, and treatment of comorbidities, are important in this population at high risk for premature CV disease. As manifestations can occur years to decades after exposure, this is a difficult issue: patients must be informed of the potential cardiotoxicity risks and consequences and provided with adequate follow-up in clinical practice. A coordinated effort among pediatric and adult oncologists and cardiologists is necessary to define best practices and improve outcomes for this patient population.

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