Study and cardiovascular follow-up of children and adolescents undergoing oncohematological treatments: Why, how, and when?

Estudio y seguimiento cardiovascular de niños y adolescentes sometidos a tratamientos oncohematológicos. ¿Por qué, cómo y cuándo?

María G. Jiménez-Carbajal*

Pediatric Interventional Cardiology/Pediatric Echocardiography, Centro Médico ABC, Mexico City, Mexico

Abstract

Review of several international publications in the medical literature related to cardiovascular evaluation in pediatric patients undergoing some type of oncohematological treatment, providing risk factors that together with chemo and/or radiotherapy impair adequate cardiovascular function in a particular way.

Key words: Cardiotoxicity. Oncohematological treatments. Children and adolescents.

Resumen

Estudio de revisión de diversas publicaciones internacionales en la literatura médica relacionados con la evaluación cardiovascular en pacientes en edad pediátrica sometidos a algún tipo de tratamiento oncohematológico, previendo factores de riesgo que en conjunto con la quimioterapia y/o radioterapia merman el adecuado funcionamiento cardiovascular de forma particular.

Palabras clave: Cardiotoxicidad. Tratamientos oncohematológicos. Niños y adolescentes.

Introduction

Given the significant increase in the diagnosis and treatment of oncohematological diseases in pediatric patients, based on chemotherapy and radiotherapy, and knowing that cardiovascular complications are the second cause of morbidity and mortality in surviving patients, it is necessary to know and disseminate the theoretical foundations of the effects of the therapeutics used for this purpose, as well as the bases for early detection and management of the adverse events that are related to them.

Method

This is an international review study of published data motivated by the observation of the complications occurring in patients with oncohematological conditions,
both during the administration of drugs and in those who are already at survival stage, with the increase in cardiovascular risk inherent to by all known modifiable and non-modifiable population factors.

**Results**

**Epidemiology**

At present, there is an estimated cure rate higher than 80% of children with oncohematological conditions, which increases disease-free life expectancy, but increases multiorgan toxicity, including cardiac toxicity, which generates the need for early detection and management of complications to improve patient quality of life\(^1\)-\(^3\). Nearly 60% of pediatric patients with oncohematological diseases receive anthracyclines\(^3\). It has been estimated that up to 65% of childhood cancer survivors treated with anthracyclines could experience subclinical myocardial dysfunction\(^4\); in this group of patients, cardiovascular disease is the main cause of cardiotoxicity-related morbidity and mortality, after cancer recurrence and secondary malignancies\(^1\),\(^5\)\(-\)^\(^7\). The incidence of clinical heart failure has been reported to be as high as 16%, 0.9-4.8 years after chemotherapy\(^1\),\(^5\).

**Cardiotoxicity**

Cardiotoxicity refers to cardiovascular alterations derived from oncohematological treatments\(^8\). It can be defined based on the left ventricular ejection fraction (LVEF) deterioration as Grade I: LVEF reduction of 10-20% with regard to baseline; Grade II: >20% reduction or drop below normal; and Grade III: appearance of symptoms of congestive heart failure\(^9\),\(^10\). The American Society of Echocardiography and the European Association of Cardiovascular Imaging use 53% as LVEF normal limit\(^8\),\(^11\).

**Risk factors**

**MODIFIABLE**

- Therapy-related factors such as anthracyclines cumulative dose, total doses administered in a day or cycle, and concomitant administration with other cardiotoxic agents. There are reports of the left ventricular (LV) dysfunction at doses as low as 240 mg/m\(^2\), which is why some authors consider that there is no “safe dose” of the drug\(^1\),\(^2\),\(^12\),\(^13\). Mediastinal irradiation with or without anthracycline treatment is another risk factor for cardiotoxicity, which occurs in cases of radiation to the heart even with low doses\(^14\)-\(^16\). Cranial irradiation is also a risk factor for cardiovascular diseases and abnormalities, probably mediated by growth hormone deficiency and related to lower LV mass\(^17\)-\(^19\).

- Individual factors include sedentary lifestyle, electrolyte abnormalities (mainly hypokalemia and hypomagnesemia), hypertension, dyslipidemia, endocrinopathies, obesity, diabetes, drug or alcohol use, and smoking\(^1\),\(^12\).

**NON-MODIFIABLE**

Pediatric age tumors can have lower latency periods, grow faster, and become highly invasive; most of them exhibit histological types that resemble fetal tissues at different stages of development and are considered to be of embryonic type, which generates large morphological diversity with varying degrees of cell differentiation\(^1\). Age <5 years at the time of treatment initiation represents an important risk factor for cardiotoxicity with an increase in afterload and a decrease in LV mass and walls thickness\(^1\),\(^12\),\(^20\),\(^21\). Female patients have a higher percentage of body fat, and doxorubicin is poorly soluble in fat; therefore, the higher risk among girls may be related to lower doxorubicin concentrations\(^22\),\(^23\). Children with preexisting cardiovascular conditions, children with cancer and elevated pretreatment troponin concentrations, some tumor genetic types (HFE C282Y mutation), as well as patients with chromosomal diseases such as trisomy 21 have a higher risk of anthracycline-related cardiotoxicity\(^13\),\(^24\)-\(^26\).

**Classification**

Cardiotoxicity can occur during treatment and up to 40 years after the conclusion of therapy, and it is classified as acute or subacute when it develops from the start of treatment to up to 2 weeks after completion\(^27\),\(^28\), and chronic when toxicity appears after 1 year of therapy completion. The latter, in turn, is divided into early when it occurs within the 1\(^{st}\) year after therapy and late if it occurs years after completion\(^10\),\(^29\)-\(^31\).

**Cardiotoxicity mechanism**

The goal of chemotherapy is to inhibit cell division; however, its clinical effect is not selective, it affects non-cancerous cells of the body and generates toxicity\(^27\),\(^32\). Antineoplastic drugs that entail the risk of producing cardiotoxicity are classified into two types\(^27\):
Type I: anthracycline-induced cardiotoxicity. Anthracycline cardiac toxicity is dose dependent and causes irreversible cardiac damage. No patient receiving anthracyclines is exempt from cardiac damage, even if it is minimal. Its presentation can be acute (dose independent and transient, related to type 1 hypersensitivity) or chronic (cumulative dose dependent, associated with an increase in apoptosis). Dilated cardiomyopathy might progress to restrictive cardiomyopathy, due to a decrease in the number of functional cardiomyocytes and stem cells able to regenerate cardiac tissue.

Type II: trastuzumab cardiotoxicity. It causes reversible cardiac harm that allows functionality recovery and restart of the regimen if indicated.

Combination therapy with type I and II agents is associated with a higher incidence of cardiotoxicity (27%).

There are other cardiotoxic drugs. Table 1 describes some of the drugs most widely used in pediatric oncology and hematology, referring their cardiovascular effects.

Mechanism of radiation damage

Radiation therapy can cause cardiotoxic side effects such as myocardial fibrosis, cardiomyopathy, early coronary disease, and valve and electrophysiological dysfunction. This cardiotoxicity is dose dependent and is correlated with the exposed area of the heart, the radiological technique, and patient age, with a higher incidence in younger patients. It is caused by acute damage and inflammation. Patients who receive more than 1500-3500 cGy show a 2- to 6-fold increased risk of heart disease, with high doses being related to myocardial ischemia from 12 years after treatment.

Diagnosis

All patients who will be treated with potentially cardiotoxic anticancer drugs should have a thorough clinical examination where the presence of a history of cardiovascular conditions such as congenital heart disease, heart valve disease, cardiomyopathy, history of

<table>
<thead>
<tr>
<th>Drug</th>
<th>Uses in pediatric oncohematology</th>
<th>Cardiovascular effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines (doxorubicin, daunorubicin, idarubicin, and/or epirubicin)</td>
<td>ALL, various solid tumors such as osteosarcoma</td>
<td>DCM, RCM, arrhythmias, QT interval prolongation, sinus node dysfunction, HF</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>HL, germ cell tumors, carcinomas</td>
<td>Ischemia, pericarditis, pulmonary fibrosis</td>
</tr>
<tr>
<td>Cyclophosphamide, ifosfamide (in combination)</td>
<td>NHL, leukemia, HL, Burkitt lymphoma</td>
<td>Acute cardiotoxicity, from subtle arrhythmias to fatal DCM. Myocarditis, HF</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>Hepatoblastoma, rhinopharyngeal carcinoma, germ cell tumors</td>
<td>Arrhythmias, ischemia, HF, and sudden death</td>
</tr>
<tr>
<td>Multikinase inhibitors, sunitinib and sorafenib</td>
<td>CML</td>
<td>Angor pectoris, HF, electrocardiographic alterations</td>
</tr>
<tr>
<td>Vincristine, vinblastine</td>
<td>LLA, lymphoma, Wilms’ tumor, Ewing’s sarcoma, neuroblastoma, and rhabdomyosarcoma</td>
<td>HBP, myocardial ischemia, veno-occlusive complications</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Some types of leukemia</td>
<td>Pericarditis pericardial effusion, cardiac tamponade</td>
</tr>
<tr>
<td>Cisplatin, carboplatin</td>
<td>Brain tumors, osteosarcoma</td>
<td>AF, SVT, left bundle branch block, and myocardial infarction</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Lung, ovarian, fallopian tube, primary peritoneal cancer</td>
<td>HBP, ATE, HF, ischemia, SVT</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>Medulloblastoma, primitive neuroectodermal tumors, rhabdomyosarcoma, and neuroblastoma</td>
<td>Bradycardia, hypotension</td>
</tr>
<tr>
<td>Steroids</td>
<td>ALL</td>
<td>HBP, QT interval prolongation</td>
</tr>
</tbody>
</table>

LV dysfunction, even asymptomatic, previous treatment with antineoplastic drugs, or previous chest irradiation should be evaluated. Vital signs frequent monitoring is recommended during chemotherapeutic agents infusion.

**Electrocardiogram**

It is recommended in all patients before and during treatment. Any electrocardiographic sign of cardiac toxicity such as resting tachycardia, ST interval changes, conduction disorders, QT interval prolongation, or arrhythmias should be detected. These alterations are non-specific, can be transient, and may not be related to the development of chronic cardiomyopathy.

**Echocardiogram**

LVEF baseline assessment should be obtained at treatment initiation for comparison with subsequent studies. A LVEF <53% is a risk factor for the development of heart failure, if it is ≤50%, starting a treatment regimen with drugs with high cardiotoxic potential is not recommended, and the possibility of an alternative regimen should be evaluated together with the oncologist. Although LVEF is the universally used parameter for decision-making, it is not sensitive for subclinical cardiac compromise early detection and depends on the preload and afterload changes that lead to transitory changes in it. Myocardial velocities determination with tissue Doppler at the level of the mitral annulus has been found to possibly be more sensitive for the detection of incipient ventricular dysfunction. Pulsed Doppler of the LV inflow tract allows assessing for the presence of a restrictive pattern: an increased E/E’ ratio (>15) is a specific parameter of end-diastolic pressure increase and is associated with the development of heart failure. Strain and strain rate determination currently play a preponderant role in ventricular dysfunction early detection. At baseline conditions, global longitudinal strain (GLS) improves cardiotoxicity-related ventricular dysfunction risk stratification versus 2D-LVEF. During antitumor treatment, GLS detects myocardial damage earlier and with less variability than LVEF. The combined use of GLS and troponin I improves the negative predictive value for ventricular dysfunction. At present, the preferred method for estimating LVEF is by three-dimensional echocardiography, which has less variability with regard to the two-dimensional method. It should be performed every time this resource is available.

**Magnetic resonance imaging**

It is the method of choice for cardiac mass, volumes, and ejection fraction evaluation. It is mainly used when echocardiography images are suboptimal or when there is discrepancy in LVEF measurement.

**Nuclear medicine**

It has high reproducibility in LVEF calculation with low interobserver variability. Disadvantages include exposure to ionizing radiation and impossibility for the valves and pericardium to be evaluated.

**Biomarkers**

Specific plasma biomarkers of myocardial injury are a useful tool for cardiotoxicity early detection and evaluation.

**Troponins**

Troponins are myocardial injury markers par excellence. Elevated levels of both troponin T and troponin I have been detected in patients receiving various chemotherapeutic agents when early determined with regard to the time, the antineoplastic treatment is received. This is correlated with a higher incidence and severity of LV dysfunction at follow-up. In patients who receive trastuzumab and show troponin I elevations, there is a higher possibility for them to develop ventricular dysfunction and to have a lower probability of recovery in comparison with those patients with troponin normal levels.

**Natriuretic peptides**

Brain natriuretic peptide (BNP) and the amino-terminal fraction of pro-BNP (NT-pro-BNP) are biomarkers with prognostic value and a possible guidance for the treatment of patients in this context. In the setting of the LV dysfunction and heart failure associated with chemotherapy-induced cardiotoxicity, there is sufficient evidence that persistent elevations of these markers are associated with higher risk for developing ventricular dysfunction (both systolic and diastolic).

**Endomyocardial biopsy**

It is the most reliable method for assessing myocardial injury; however, given that it is an invasive
procedure that obtains small myocardial samples and does not provide functional information, its use has been restricted to the monitoring and diagnosis of cardiotoxicity.$^{27}$

**Cardiotoxicity prevention**

It is mandatory to promote a heart-healthy lifestyle with regular physical exercise programs for all patients, regardless of the planned treatment.$^6$ Not exceeding a dose equivalent to 375 mg/m$^2$ of doxorubicin is recommended in children, and this threshold should be reduced to 300 mg/m$^2$ in case of associated radiation to the cardiac area.$^{60}$ Anthracycline prolonged infusions (>6 and up to 48 h) have been proposed instead of boluses; however, some authors propose that prolonged exposure of cardiomyocytes to anthracyclines could cause greater cardiac damage. This approach has the disadvantage that it compromises the possibilities of cure and, in addition, doses below the proposed ceiling dose have been shown to produce subclinical cardiac damage.$^3$ Administration of anthracycline analogues, such as epirubicin, has also been proposed, although Grades 1 and 2 cardiotoxicity has been observed.$^{3,31}$ or liposomal doxorubicin administration, which is associated with free doxorubicin low concentrations, with limited distribution in the myocardium.$^3$ The use of dexrazoxane, an iron chelating agent that inhibits lipid membranes peroxidation with a decrease in anthracycline secondary cardiotoxicity,$^{27}$ should be considered. Limiting the radiation dose to the cardiac area is also essential to reduce long-term sequelae and complications of chest irradiation. At present, the recommended dose in children and adolescents treated for Hodgkin’s disease after two cycles of chemotherapy is 20 Gy (vs. 30 Gy in previous protocols)$^{60}$.

**Treatment**

The drugs that are commonly studied and used to treat cardiotoxicity are angiotensin-converting enzyme inhibitors (ACEIs); however, the beneficial effects of these drugs and their ability to reduce the morbidity and mortality associated with anthracycline in childhood cancer survivors appear to be transitory.$^{26}$ Carvedilol provides cardioprotection by inhibiting reactive oxygen species, scavenging free radicals, preventing lipid peroxidation, and increasing Vitamin E concentrations.$^{42}$ Acute and chronic heart failure should be treated according to the time of presentation.

**Recommendations for cardiovascular evaluation and follow-up**

There is no current international consensus on the follow-up of pediatric patients undergoing oncohematological treatments. Some guidelines developed by expert groups recommend pediatric patients evaluation before chemotherapy by assessing LV systolic and diastolic function (initial permissible LVEF >50%). Another evaluation is recommended after half of the total cumulative dose prescribed in the treatment protocol or on reaching 200 mg/m$^2$ of doxorubicin, then every 100 mg/m$^2$ thereafter. In the case of patients with an initial LVEF <30%, the risk–benefit ratio with regard to antitumor treatment should be studied, discouraging the use of cardiotoxic drugs, especially anthracyclines. In patients with a baseline LVEF between 30 and 50%, echocardiographic evaluation should be performed before each chemotherapy cycle.$^{22}$ Patients receiving higher doses of anthracyclines and those receiving combination therapies should have more frequent systolic function assessment. In patients with echocardiographic evidence of valve disease and with a history of central catheters, evaluation and prophylaxis for bacterial endocarditis should be carried out.$^{61}$ Carotid and subclavian artery stenosis (10 years after having received radiation therapy) should be ruled out in patients treated with radiation fields that included these vessels at a dose of 40 Gy.$^{61}$

In the consensus and recommendations document published in 2017 by López Fernández et al. in Spain, some guidelines are established for initial and long-term follow-up of patients undergoing antitumor therapies during treatment, in cases of decreased LVEF, and in those undergoing radiotherapy$^8$ (Figs. 1-3). Although they are not specifically aimed at pediatric patients, they can be considered as a reference in clinical practice, always individually considering patient clinical status for assessments.

**Multidisciplinary teams in cardio-onco-hematology**

Cardio-onco-hematology teams bring together the professionals involved in the care of patients with cancer, with the purpose to facilitate treatment and minimize cardiovascular toxicity. The development of protocols for the prevention and early treatment of cardiotoxicity will avoid early discontinuation of antitumor drugs and will allow optimizing health outcomes and reducing costs.$^8$


**Figure 1.** Algorithm for evaluating the treatment of patients receiving antitumor drugs. TTE: transthoracic echocardiogram; LVEF: left ventricular ejection fraction; GLS: global longitudinal strain; NT-pro-BNP: aminoterminal fraction of pro-brain natriuretic peptide; LVD: left ventricular dysfunction.

**Figure 2.** Algorithm for evaluation and treatment of patients with decreased LVEF receiving antitumor drugs. LVEF: left ventricular ejection fraction; BB: beta-blockers; HF: heart failure; HBP: high blood pressure; ACEI: angiotensin-converting enzyme inhibitors.

**Discussion**

Cancer early diagnosis and efficacy of its treatment have currently led to a decrease in mortality; however, this has also brought reversible and irreversible cardiovascular complications; in some cases, the risk of death even exceeds the risk associated with tumor relapses\(^2\), which is why it is important to identify risk factors, as
well as close follow-up by the cardiologist, oncologist, or hematologist through the interaction between each one of them, for adequate monitoring of each patient to be carried out. Although there are some recommendations from expert groups for children and several more for adults, it is possible to build on those that best adapt to patient characteristics and those of the multidisciplinary team. Thus, in addition to the aforementioned follow-up strategies, the one published by Plana et al. in 2014 can be cited, where in the case of treatment with anthracyclines, a baseline echocardiographic evaluation is recommended, with a new evaluation at treatment completion and after 6 months. If the used dose is >240 mg/m², evaluation is recommended at each additional treatment cycle\(^1\). It should be remembered that the main strategy to minimize cardiotoxicity is early detection, for ventricular dysfunction preventive treatment to be early implemented\(^5\).

**Conclusions**

There are a significant number of oncohematological diseases in children with various antitumor therapies, which due to their nature affect the cardiovascular system as a whole, and it is, therefore, necessary for pediatric cardiologists, oncologists, and hematologists to be aware of the potential effects of the drugs and risk factors, as well as of cardiotoxicity primary and secondary prevention. The formation of multidisciplinary work teams with the necessary human and material resources is essential.
resources (cardio-onco-hematology clinics) is recommended, which in the long term will be reflected in hospital costs and in a positive physical and emotional impact on the patient and his/her family, as well as in an improvement in the comprehensive quality of care.

**Funding**

This research has not received any specific grant from agencies of the public, commercial, or non-profit sectors.

**Conflicts of interest**

The author declares that she has no conflicts of interest.

**Ethical disclosures**

Protection of human and animal subjects. The author declares that no experiments have been performed on humans or animals for this research.

Confidentiality of data. The author declares that she has followed the protocols of her work center on the publication of patient data.

Right to privacy and informed consent. The author declares that no patient data appear in this article.

**References**