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Chemotherapy-induced cardiotoxicity

Rodolfo A. Morales Yera[1]✉, MD, MSc; Ludmila Sierra Pérez[1], MD, and Alexander Triana Díaz[2], MD

[1] Department of Clinical Oncology, Hospital Universitario Celestino Hernández Robau. Villa Clara, Cuba.
[2] Department of Cardiology, Hospital Universitario Celestino Hernández Robau. Villa Clara, Cuba.

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Acronyms
CT: chemotherapy
LVEF: left ventricular ejection fraction
RT: radiotherapy

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ABSTRACT
Cancer is a major public health problem in the world. Chemotherapy is indicated in several phases of the antineoplastic treatment, either as neoadjuvant, adjuvant or palliative therapy. One of the most worrisome side effects generated by chemotherapy is cardiotoxicity, and one of the main symptoms is heart failure, secondary to damage to the myocardium due to the direct and indirect toxicity of antineoplastic therapies. The objective of this article is to review the state of the art of the chemotherapy-induced cardiotoxicity, as well as to synthesize the different cardiotoxic effects, cardiotoxic mechanisms and methods that have been developed for its diagnosis and prevention.
Keywords: Cardiotoxicity, Chemotherapy, Heart Failure

Cardiotoxicidad inducida por quimioterapia

RESUMEN
El cáncer es un problema de salud pública de gran envergadura en el mundo. La quimioterapia está indicada en varias fases del tratamiento antineoplásico ya sea como terapia neoadyuvante, adyuvante o paliativa. Uno de los efectos secundarios más preocupantes generados por la quimioterapia es la cardiotoxicidad, y uno de los principales síntomas es el fallo cardíaco secundario a un daño a nivel del miocardio por la toxicidad directa e indirecta de las terapias antineoplásicas. El objetivo del presente artículo es realizar una revisión del estado del arte de la cardiotoxicidad inducida por quimioterapia, además de hacer una síntesis de los diferentes efectos cardiotóxicos, mecanismos de cardiotoxicidad y métodos que se han desarrollado para su diagnóstico y prevención.
Palabras clave: Cardiotoxicidad, Quimioterapia, Insuficiencia cardíaca

INTRODUCTION

Cancer is a major public health problem in the world. It is the second cause of mortality in the United States and is expected to surpass heart diseases as the leading cause of death in the coming 2025-2030[1].

In Latin America the incidence of cancer is lower (age-standardised rates of 163 per 100.000 inhabitants) compared to Europe (264 per 100.000) or the USA (300 per 100.000), but it causes high mortality. Cancer is consid-

✉ *RA Morales Yera*
Hospital Celestino Hernández Robau. Calle Cuba, e/ Barcelona y Hospital. Santa Clara 50200. Villa Clara, Cuba. E-mail address: rodolfomy@infomed.sld.cu

ered the third cause of death in this part of the continent. In Cuba, a total 24.646 and 24.462 cancer deaths were registered during 2015 and 2016, respectively; so it is the second leading cause of death in the country, preceded only by heart disease[2].

Although the age-adjusted incidence rate has declined over the past 10 years, the total number of patients with cancer continues to grow. This is associated with an aging population and improved survival, thanks to early detection and scientific-technological advances in treatment[3].

An up to 20% reduction in mortality and increased survival in patients with cancer have revealed cardiovascular toxicities neglected for years. Cancer and heart share multiple risk factors, but cancer treatment also behaves as a new risk factor and is associated with serious side effects as cancer treatment is also associated with cardiac complications[4,5].

Chemotherapy (CT) and radiotherapy (RT) have become basic pillars in the treatment of several types of cancer. They have provided increased survival rates in patients with cancer but usage frequency for clinical remission, dosage and mechanism of action may generate side effects in patients. Cardiotoxicity is among the most alarming. Despite having different manifestations, one of the main ones are heart failure symptoms, secondary to damage at the cardiac level as antineoplastic therapy has direct and indirect toxic effects[6,7]. This is why, cardiac function is one of the limiting dose variables during cancer treatment, since it contributes to the morbidity and mortality of the exposed population.

The term cardiotoxicity encompasses several pathological manifestations at the cardiac level resulting from cancer treatment. The most frequent is heart failure, which in some cases may be "advanced" and with high mortality, as it happens with the use of anthracyclines[8,9].

Reports show a 3.5 fold increased mortality compared to that of idiopathic cardiomyopathy[10].

The prospective cross-sectional study of Wise with 1853 adult survivors of childhood cancer reported that the prevalence of heart disease increased with age, ranging from 3-24% in survivors aged 30-39 years, and 10-37% in those aged 40 or older[11].

Cardiovascular assessment of CT-exposed patients, risk analysis, prevention and mitigation of cardiac injury, heart function monitoring during and after therapy, advancement in drug delivery, cardiotoxicity prevention and treatment, are measures to be taken in an interdisciplinary way to achieve an overall approach to the patient and facilitate a satisfactory outcome. This is why Cardio-Oncology arises as a basic discipline to comprehensively approach and treat these patients[12].

As a subspecialty, Cardio-Oncology aims to facilitate the treatment of cancer, so that patients can receive adequate treatment, with the least possible side effects or interruptions, which undoubtedly affect their vital prognosis[13].

CARDIOTOXICITY AND CHEMOTHERAPY

Cardiotoxicity is defined as a heart condition produced by exposure to chemotherapeutic agents[4]. The challenge is how to identify changes at the myocyte level[14].

The Cardiac Review and Evaluation Committee links the definition of cardiotoxicity in patients who have received CT, with the presence of one or more of the following criteria:

- Cardiomyopathy with compromised left ventricular function.
- Symptoms or signs of heart failure linked to a third heart sound, tachycardia or both.
- Decreased LV ejection fraction by at least 5% with values lower than 55% and presenting signs or symptoms or a 10% decrease when values are less than 55% in the ejection fraction with no signs or symptoms[12,13].

According to the American Society of Echocardiography (ASECHO) cardiotoxicity-related heart failure is a decrease in the left ventricular ejection fraction (LVEF) of >10% percentage points with respect to the baseline value or value <53% (normal reference value for two dimensional echocardiography)[14].

Chemotherapy is prescribed in several phases of antineoplastic treatment either as neoadjuvant, adjuvant or palliative therapy, for this reason, patients may present cardiotoxic events in any of these phases, early during treatment, or even 40 years after therapy is completed.

Classification of myocardial damage according to the time variable

Acute or subacute: when it develops from the initia-

tion of treatment up to two weeks after completion.

Chronic: when toxicity appears within one year after therapy completion. In turn, chronic cardiotoxicity has two forms: early, when symptoms occur within one year post-CT; and late, when symptoms occur one year after completion of therapy (**Figure 1**)[12,15].

Classification of antineoplastic drugs according to the rate of cardiotoxicity risk

- High risk: anthracyclines, cyclophosphamide and trastuzumab.
- Moderate risk: docetaxel, pertuzumab, sunitinib, sorafenib.
- Low risk: bevacizumab, dasatinib, imatinib, and lapatinib [16,17].

Among the toxic cardiovascular manifestations are: heart failure with ventricular systolic dysfunction (anthracyclines, trastuzumab, tyrosine kinase inhibitors, cyclophosphamide, bevacizumab), high blood pressure (bevacizumab), arrhythmias (anthracyclines and taxanes), hypotension (etoposide, alemtuzumab, cetuzumab, rituximab and interleukin 2), myocardial ischemia (5-fluorouracil, capecitabine, taxanes, alkaloids, bevacizumab), thromboembolism and pericarditis[12,17].

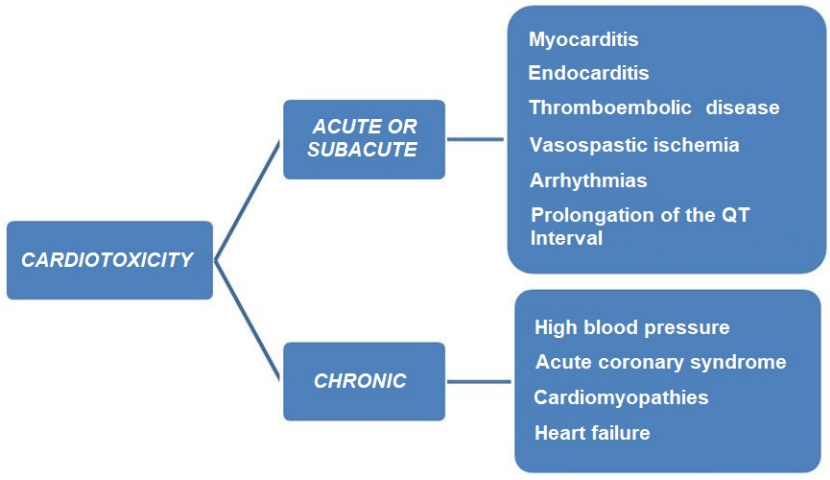

Figure 1. Clinical manifestations of antineoplastic-induced cardiotoxicity.

General and specific cardiotoxicity mechanisms

Chemotherapy-induced cardiotoxicity is mostly due to multifactorial mechanisms such as:

1. Formation of reactive oxygen species (ROS).
2. Impairment of mitochondrial structure and function.
3. Disruption of calcium and iron homeostasis.
4. Altered gene expression[18].

The ultimate consequence is cellular myocardial death, produced by the induction of apoptosis[17], associated with growth deprivation and angiogenesis suppression, leading to compromised repair capacity[12,18].

Types of potentially cardiotoxic antineoplastic agents

- Type I: cardiotoxicity with similar mechanism to anthracyclines "anthracycline effect". Its cardiac toxicity is dose-dependent and produces irreversible cardiac damage.
- Type II: cardiotoxicity with similar mechanism to trastuzumab "trastuzumab effect", related to a reversible cardiac damage that allows function recovery and treatment restart if indicated. This is achieved, because there are no ultrastructural changes in cardiac myocytes[13-17].

Type I cardiotoxicity: Anthracyclines

Its mechanism is related to the damage produced by free radicals in which the quinone group reduction in the Ring-B Modified Anthracyclines leads to the formation of a semiquinone radical, which is oxidized and generates free radicals such as superoxide forming hydrogen peroxide that interacts with the myocardium and produces an imbalance environment between the antioxidant mechanisms and proinflammatory substances, predisposing damage by the reduction of glutathione peroxidase, affected by the use of these drugs.

The formation of a ferric iron complex with doxorubicin catalyses this reaction and increases ROS, which contributes to the con-version of ferrous iron into ferric iron, and destroys the cell membranes and the endoplasmic reticulum, producing a decrease in iron intracellular calcium and a decrease in contractility. In turn, inflammatory cytokines induce the release of histamine, tumor necrosis factor alpha and interleukin 2, these cytokines induce dilated cardiomyopathy and beta adrenergic dysfunction. Apart from oxidative stress, topoisomerases have also been implicated in the toxicity associated with anthracyclines, the antitumor activity of doxorubicin is explained by the formation of a ternary complex with one of the isoenzymes known as Top2a -doxorubicin-DNA. These changes have been associated with an increase in apoptosis[12,19].

As a more important and practical concept, it is highlighted that this group generates myocyte damage that is dose-dependent (cumulative) and is therefore associated with early diastolic and late systolic dysfunction. Given the cardiotoxic effects described, the American National Heart Institute defines anthracycline cardiotoxicity as an absolute reduction of LVEF below 50% or a 10% fall of the LVEF in relation to the initial value, associated or not with the appearance of symptoms or signs of heart failure, a fact that motivated the formal indication of clinical-echocardiographic follow-up in a serial and scheduled manner, according to the risk stratification performed in each patient[4,6,9,12,15,17].

Type II cardiotoxicity: Trastuzumab

Trastuzumab inhibits human tumor cells proliferation that overexpress the HER2 protein; it binds HER2 extracellular subdomain. This epidermal growth factor is a transmembrane tyrosine kinase receptor that acts as a proto-oncogene and is related to the regulation of cell growth. It is overexpressed in 25% of breast cancers and is associated with poor prognosis. In the heart it is associated with neuregulin (peptide ligand of HER3 and HER4), which when bound with HER4 allows HER2–HER4 heterodimerization and subsequent phosphorylation and activation of several signaling pathways that increase: cell contact and mechanical coupling, and promote survival and contractile function, which are necessary for the development and survival of cardiac myocytes[12,19].

Trastuzumab exposure, through different molecular apoptosis-related mechanisms, may produce myocardial dysfunction[12,19]. It is important to point out that the cardiodepressant effect is transitory and reversible when the medication is stopped, with a recovery time of the LVEF of approximately one year, an important difference with type I. Its incidence is very variable, and depends on the associated risk factors, for example varies from 5 to 30% if used alone or associated with anthracyclines. This incidence also increases with age, previous cardiovascular disease, and prior history of RT or CT, or both, major risk factors associated with cardiotoxicity. In this sense, the cardiotoxicity in this group has actually decreased, simply with the best and strictest monitoring of risk factors and the intention to avoid the concomitant use of anthracyclines[4,6,9,12,15,17].

Other cytotoxic drugs that have been associated with cardiotoxicity

5-fluorouracil, busulfan, capecitabine, cyclophosphamide, cisplatin, dacarbamazine, fludarabine, mechlorethamine, melphalan, mitoxantrone, mitomycin, taxoids such as paclitaxel and docetaxel, as well as monoclonal antibodies such as: trastuzumab and rituximab, among others, they have been associated with cardiotoxicity [15] (**Figure 2**).

Taxoides

Taxoids, such as paclitaxel and docetaxel, also produce various cardiotoxic effects after administration. In the case of paclitaxel, combined or not with cisplatin, triggers cardiac disorders in some patients consisting of brady or tachyarrhythmias, atrio-ventricular and branch blocks, cardiac ischemia and hypotension, secondary to direct chronotropic effect in the Purkinje system, as it presents a 0.5% incidence[12].

The Paclitaxel formula that is clinically used is a mixture that contains the adjuvant Cremophor EL, which is also associated with cardiotoxicity, nephrotoxicity and hypersensitivity reactions[19]. The risk factors that predispose to cardiac toxicity include unstable angina, severe coronary diseases, congestive heart failure and atrial fibrillation[12,20].

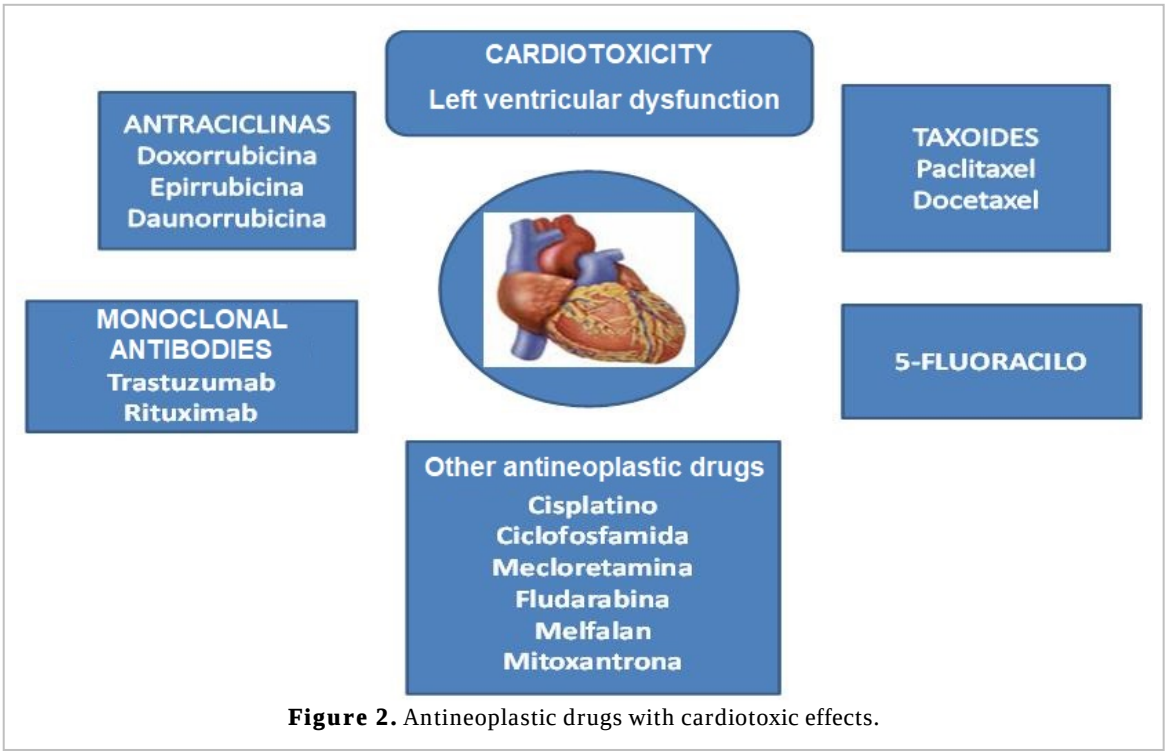

Figure 2. Antineoplastic drugs with cardiotoxic effects.

Fluorouracil

5-Fluorouracil is the second cardiotoxic drug in frequency, after anthracyclines[21]. It is estimated that 1 - 18% of patients treated with 5-FU, a uridine antimetabolite, have cardiotoxicity, which is more frequent when administered in continuous infusion. These patients show cardiac arrhythmias, myocardial ischemia, angina, congestive heart failure and sudden death. In the case of angina, it is the most frequent symptom during the first hours after starting therapy, secondary to coronary spasm [22].

Capecitabine, which is the oral form of 5-FU, also reports a high toxicity rate although the drug acts selectively on the tumor. The mortality rate of 2.2 to 13% during the follow-up of treatment with high 5-FU doses shows how dangerous these adverse effects can be[22].

Cyclophosphamide

Cyclophosphamide is an alkylating agent from the oxazoforin group, which is characterized by its capacity to damage DNA. It has been reported that at high doses produces acute effects such as: pericarditis, cardiac decompensation and cardiomyopathy in just 10 days after starting its administration, its effect is dose-dependent and is more common at amounts higher than 200 mg/kg.

Its fatal effects have been recorded in up to 11% of cases. Myocarditis, and less commonly heart failure, appear during the first weeks after treatment[12]. Some patients show decreased systolic function and, like the anthracyclines, Cyclophosphamide increases intracellular concentrations of free oxygen radicals[15].

Cisplatin

It has been reported that some patients treated with cisplatin develop acute myocardial infarction. Some studies suggest that these adverse effects are due to vascular damage, activation of platelet aggregation and the arachidonic acid pathway, and hypomagnesemia[15].

Bevacizumab

This inhibitor of vascular endothelial growth factor (VEGF) is associated with: myocardial dysfunction, hypertension and thromboembolic arterial events with an incidence of 1.6%, due to a decrease in the production of nitric oxide[12,19].

Sutinib y Sorafenib

Multikinase inhibitors, by inhibiting the VEGF receptor, are associated with: chest pain, decreased LVEF and contractile dysfunction, with electrocardiogram abnormalities in 18%, 12% and 16%, respectively[19].

Interferons alpha 2a and alpha 2b

May cause arrhythmias ranging from atrial to ventricular fibrillation in 20% of patients; and chronic use can lead to dilated cardiomyopathy [12,19].

Risk factors for developing chemotherapy-induced cardiotoxicity

In order to develop drug-related cardiotoxicity, some factors which are specific of the agent and the patient will interact. Regarding the drug, the type of agent, the dose applied during each session and the cumulative dose, as well as frequency, the route of administration and other combined agents, are factors that affect the form and time of toxicity presentation. Age (children and over 65 years), any previous cardiovascular disease, previous RT –mainly mediastinal–, metabolic alterations and hypersensitivity to different drugs are considered among the factors related to the patient[11,21,23].

Monitoring and diagnosis of cardiotoxicity

As a first step, a baseline cardiovascular examination should be performed to detect the cardiac risk factors of each patient. It is essential to treat (if present) high blood pressure and dyslipidemia before they start CT[23].

It is highly recommended to monitor cardiac function before, during and after CT, especially if anthracyclines are used to detect subclinical changes early, although at present there are no guidelines to establish the method or the range of choice to perform such monitoring[21,23].

Periodic evaluation of the cardiac function by means of transthoracic echocardiography is the bloodless diagnostic method most commonly used in oncological clinical practice to measure cardiotoxicity in CT patients, which is evidenced by a decrease in LVEF[23].

On the other hand, the 12-lead electrocardiogram presenting repolarization disorders, decrease of the QRS complex voltage (indicative of cardiomyopathy) and prolongation of the CT interval in those patients with extensive treatments with anthracyclines, has been referred to as an early marker of left ventricular dysfunction. However, these diagnostic methods underestimate cardiac damage, are dependent on the operator and suggestive changes due to cardiotoxicity only appear when significant myocardial dysfunction has already occurred, which limits early pharmacological intervention. Therefore, other methods and techniques have been proposed for accurate and timely detection of CT- induced cardiotoxicity[12,15,21,23].

The European Oncology Society recommends to assess LVEF at the beginning of antineoplastic therapy in patients older than 60 years or with cardiovascular risk factors, after the administration of half of the total cumulative dose of anthracyclines, before every subsequent dose and at 3, 6 and 12 months, respectively, after chemotherapy treatment cessation[15]. When there is a decline of LVEF by more than 10%, associated with an absolute LVEF less than 50%, suspending of anti-neoplastic therapy is recommended[15,23], since many studies have demonstrated that the presence of changes in LVEF is associated with chronic heart failure 3 years after the end of CT[23].

The biggest disadvantage of this technique is the inability to detect small changes. Fortunately, technological improvement allows new echocardiography tools, sufficiently developed to assess cardiac functioning and detect changes that are manifested long before LVEF deterioration, such as the myocardial tissue study, and specifically, the study of percentage change of the original myocardial length during the cardiac cycle, in a global form, called global longitudinal strain. This technique has been

shown to be useful in the subclinical diagnosis of several myocardiopathies, but in particular in the case of cardiotoxicity by antineoplastic agents[24].

Currently, advances in three-dimensional echocardiography, tissue Doppler, velocity and strain imaging and cardiac magnetic resonance appear also to be promising to detect subclinical changes [23,25].

Endomyocardial biopsy is described in the most recent publications of the AHA as the most sensitive and specific method for the diagnosis and monitoring of anthracycline cardiotoxicity, since it allows direct measurement of the presence and extension of cardiac fibrosis caused by CT, but its use it is limited because it is a bloody method[15, 21,23].

A controversial point regarding cardiac monitoring of patients who will receive CT is whether the LVEF should be determined at all before starting treatment. Many authors suggest that initial LVEF estimation is not performed if the patient does not have cardiovascular risk factors, if he or she will receive less than 300 mg/m^2 of doxorubicin, will not use trastuzumab concomitantly, or if she is a woman under 65 years of age without risk factors, but some authors do not accept these recommendations[23].

The measurement of specific serum biomarkers of myocardial injury has been proposed as an attractive, valid and novel strategy in the identification and monitoring of cardiotoxicity in patients treated with CT, due to its relative ease of use, predictability, precision and accuracy[15]. The main serum markers are troponin, BNP and NT-proBNP[17].

The use of biomarkers, especially troponin with its high negative predictive value, allows stratification of patients who do not require a strict cardiotoxicity follow-up, which reduces the use of unnecessary diagnostic methods and the costs for the health system and for patients[15].

Other forms of CT-induced cardiotoxicity, such as ischemia, arrhythmias and pericardial disease, can be identified using the same protocols and diagnostic methods used in patients with these manifestations who do not receive CT[23].

Although strategies to prevent cardiotoxicity have been emphasized, there is no consensus on the most effective way to approach these patients. This is why new prospective studies are required that include larger patient cohorts, and that use validated and commercially available methods for screening, with biomarkers that allow a better classification and stratification of the risk of cardiotoxicity; besides designing tools for its timely treatment[15].

Treatment and prevention of CT-induced cardiotoxicity

In March 2017, the American Society of Clinical Oncology (ASCO) published the guide for Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers. The purpose of this guide is to develop recommendations for the prevention and monitoring of cardiac function in such patients.

The guideline was based on the results of a systematic review that compiled 104 useful clinical studies published between 1996-2016, which were evaluated by the ASCO guidelines committee for the issuance of recommendations[26]. It is based on five elements:

1. Identify patients who are at risk of developing cardiac dysfunction: assess exposure to anthracyclines and RT, the use of tyrosine kinase inhibitors and possible cardiovascular risk factors (smoking, high blood pressure, diabetes, dyslipidemia and obesity).
2. Strategies to prevent or minimize the risk before initiating therapy: when performing the patient, a thorough clinical evaluation; discard the possible cardiovascular risk factors, and avoid or minimize the use of cardiotoxic therapies.
3. Measures to minimize the risk during therapy: modify and treat cardiovascular risk factors (smoking, high blood pressure, diabetes, dyslipidemia, obesity); incorporate cardioprotectors to the treatment (dexrazoxane), when administering a continuous or liposomal anthracyclines infusion; assess dosage, fields to be treated and technology to be used in patients receiving mediastinal RT.
4. Supervision of patients during treatment: through clinical follow-up, imaging studies (cardiac ultrasound, nuclear medicine, magnetic resonance), measurement of serum biomarkers (troponins, natriuretic peptide) and their referral to the cardiologist.
5. Supervision of patients with risk of cardiac dysfunction after treatment. This evaluation requires a careful clinical history and physical examination, as well as early identification of signs and symptoms related to cardiotoxicity.

These aspects must be taken into account to prevent myocardial damage without reducing the therapeutic efficacy in cancer treatment: the independent risk factors for developing cardiotoxicity, the cumulative dose of anthracyclines, African-

American race, extreme ages, diabetes, hypertension, overweight or low weight and serious comorbidities as they indicate the risk of cardiovascular events. This way, preventive measures can be applied[12,21,23]:

- Changes in the therapeutic schemes; favoring prolonged infusion application rather than boluses, with schemes ranging from 6 to 96 hours, since there is a 4.13-fold higher risk of developing cardiotoxicity with bolus application.
- The use of liposomal-coated anthracyclines, which prevent from entry into the myocardium without affecting tumor penetrance with a decrease in cardiotoxicity by up to 80%, compared with conventional forms.
- The use of anthracyclines analogues, such as epirubicin and mitoxantrone, which despite their decrease in therapeutic efficacy, exude lower cardiotoxicity.
- The use of the iron chelating agent, dexrazoxane, which inhibits peroxidation of lipid membranes with decreased cardiotoxicity in anthracyclines. Iron chelating agent is used at the same time as these medications, or the first dose at the beginning and the second dose when arriving at a cumulative 300 mg/m^2 dose.
- The individual use of each cardiotoxic agent and the reduction of therapeutic sessions with drugs such as trastuzumab.
- The OVERCOME study recommends the use of inhibitors of neurohormonal activity, such as: angiotensin-converting enzyme inhibitors and carvedilol, which provide protection against cardiotoxic effects when used during cancer therapy, due to their antioxidant effects.

When in spite of using preventive therapy, cardiotoxicity is detected under the established parameters already reviewed by echocardiography or other diagnostic methods, the aggressor drug must be suspended and establish an adequate treatment, even in asymptomatic patients with left ventricular dysfunction[22].

The treatment of choice is based on angiotensin-converting enzyme inhibitors and beta-blockers, when symptoms and actual heart failure appear, an adequate treatment integrating: diuretics, aldosterone antagonists, nitrates and though controversial, digoxin in very symptomatic cases or in the presence of rhythm disorders, should be established. According to the evolution and clinical response, the pertinence of restarting or changing the chemotherapeutic regimen will be considered[9,12,21,23].

CONCLUSIONS

CT remains one of the fundamental pillars in the treatment for several types of cancer, this is the first line of treatment for multiple locations, either used as exclusive treatment or combined with other therapeutic procedures. Chemotherapy has allowed an increased survival of patients with cancer; However, CT frequency to achieve remission, dosage and mechanism of action has generated side effects in patients. One of the most worrisome is generated by cardiotoxicity. Although emphasis has been placed on strategies to prevent it, there is no consensus on the most effective way to treat these patients. Its prevention and treatment are measures that must be taken in an interdisciplinary way to achieve a global approach to the patient and facilitate satisfactory outcomes, so that patients receive an adequate treatment, with the least number of side effects or interruptions, that undoubtedly affect their vital prognosis.

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