Contemporaneous Screening Options of Cardiotoxicity Related to Oncological Treatment

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Opções Contemporâneas de Rastreio da Cardiotoxicidade Relacionada a Tratamentos Oncológicos

Opciones Contemporáneas para el Rastreo de Cardiotoxicidad Relacionada con el Tratamiento del Cancer

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INTRODUCTION

The recent advances of oncologic therapies ensured the individualization of the treatment and are associated to additional survival[1]. In line with this setting, the incidence of cardiac toxicity side effects has grown as well as the appearance of new etiologies of cardiovascular injury[2].

Cardiotoxicity screening extrapolated from the regimens utilized in pivotal studies is classically achieved through the mensuration of pre-treatment risk with physical exam preceded by anamneses associated to electrocardiogram and measurement of the left ventricular ejection fraction (LVEF) by echocardiogram or by *Multigated Acquisition Scan* (MUGA Scan)[3].

Nevertheless, recent studies reported more sensitiveness of new options with screening potential as the dosage of ultrasensitive troponin and serum brain natriuretic peptide, cardiac magnetic resonance and echocardiogram with evaluation of the myocardial deformation (echocardiogram *strain)*[4].

Regardless of more sensitiveness of detection of cardiac injury in the classic methods, the contemporaneous have fragilities and limitations that hamper the consensus of its utilization in the clinical practice[4]. The paucity of clinical trials that demonstrate the actual benefit of adopting more expensive cardiac evaluations when decision to initiate or interrupt an oncologic therapy is to be taken, appears to play a key role for decision making[5].

This article will discuss classical and contemporaneous diagnostic methods of cardiotoxicity screening and management related to oncologic treatment.

CARDIOTOXICITY

The general incidence of cardiotoxicity is influenced by a combination individual factors (comorbidities) and the characteristics of the oncologic treatment (agents, schema of administration, area included in the field of radiotherapy)[6].

The antineoplastic therapies can elevate the risk of development of congestive cardiac insufficiency 15-fold, of cardiovascular diseases, 10-fold and brain strokes, 9-fold with growth of late mortality as described by Armstrong et al.[7], who evaluated a population of children and adolescents after 15-25 years of oncologic treatment, revealing a risk 8.2 times bigger of cardiac death when compared to a population paired by gender, not exposed and of the same age-range, in addition to considerable morbidity[7].

Broadly, the cardiac dysfunction can be classified as acute, sub-acute and chronic when based in the type of histological alteration and clinical evolution related to oncologic treatments types I and II (Plan 1), with impact in the modification of conduct in relation to antineoplastic therapy [8].

The most severe cardiotoxicity-related clinical manifestations are both cardiac dysfunction and insufficiency. Seldom, myocardial ischemia, ventricular and supraventricular arrhythmia, arterial hypertension, pericarditis and thromboembolic events can evolve unfavorably[9] (Table 1).

The new drugs for oncologic treatment deserve differentiated attention, mainly because of the distinguished

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Plan 1. Classification of cardiomyopathy associated to the use of chemotherapics

Cardiotoxicity	Oncologic Agent	Relation with cumulative dose	Findings of the endomyocardiac biopsy	Reversibility of the injury
Type I	Anthracyclines Alkylating	Yes	Vacuoles, destruction of sarcomeres Necrosis	No
Type II	Monoclonal antibodies Inhibitors of tyrosine kinase	No	No apparent cellular destruction	Yes (majority of the cases)

Table 1. Cardiovascular toxicity of the main antineoplastic agents utilized

Antineoplastic Agents	Cardiovascular effects	Main physiopathology	Incidence
Anthracyclines[10] (doxorubicin, epirubicin, Idarubicin)	Left and right ventricular dysfunction	Lipidic peroxidation, oxidative stress	7%-26%
Fluoropyrimidine[11] (capecitabine, 5-fluourouracil)	Cardiomiopatia isquêmica e arritmias ventriculares	Endothelial dysfunction and coronary vasospasm	1%-19%
Alkylating[12] (cyclophosphamide in high doses, ifosfamide, platinum agents)	Hemorrhagic myocarditis, lethal acute pericarditis	Direct oxidative cardiac injury	7%-28%
Taxanes[13] (paclitaxel, docetaxel)	Sinus brachycardia, atrial fibrillation, ventricular arrhythmia and myocardial ischemia	Polymerization of tubulins leading to dysfunction of microtubules with disorders of the cellular division and massive liberation of histamine	<0.1%-31%
Blocker of receptor of HER-2[14] (trastuzumab)	Left ventricular insufficiency	Alteration of the mitochondrial integrity leading to dysfunction of contractility without deep alterations in the ultrastructure of cardiomyocytes	1%-27%
Inhibitor of angiogenesis[15] (bevacizumab)	Arterial hypertension and thromboembolic phenomena	Adrenergic or renovascular etiology. Increase of the dysfunction of endothelial cells and reduction of the nitric oxide and prostaglandins	1.7%-3.0%
Inhibitors of tyrosine kinase[16] (sorafenib, sunitinib)	Arterial hypertension, myocardial ischemia, cardiac insufficiency and myocardial dysfunction	Arterial hypertension relates with the inhibitor of vascular endothelial growth factor receptor	8%-28%
Immune checkpoint inhibitors[17] (nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab)	Pericarditis and myocarditis	Increase of the immune system response	1%-2%
Cyclin-dependent kinase 4/6 inhibitors[18] (ribociclib)	Bradycardia and prolongation of interval QTc	*	<2%

Note: *Still insufficient data.

pattern of injury. The checkpoint inhibitors can cause a spectrum of autoimmune toxicities as myocarditis and pericarditis[17]. The cyclin-dependent kinase 4/6 can induce the cardiac arrhythmia by prolonging the interval QTc[18]. In these two groups of drugs, the incidence seems to be low, but ongoing studies will attempt to understand the causal mechanism, the ideal screening and management of cardiotoxicity, either preventive and/or therapeutic.

CLASSICAL METHODS

It is crucial the initial evaluation of the risk of development of cardiac complication before administering the oncologic therapy[19].

During anamnesis, it is attempted to encounter risk factors for the development of cardiac dysfunctions as diabetes, renal disease, heart valve disease, arterial hypertension, cardiac insufficiency and/or previous arrhythmias[20].

The classification of the *New York Heart Association* (NYHA) of 1994 serves as comparative parameter during treatment, being an indirect way to clinically evaluate the level of cardiac dysfunction developed[21]. It is uncommon for patients to evolve to NYHA III or IV during oncologic treatment and the deterioration of the left ventricular function can be evaluated in the asymptomatic phase through echocardiogram[22].

The electrocardiogram is useful for the evaluation of arrhythmias and previous vascular events, but limited for cardiovascular function. Regardless of its worldwide availability, is frequently underutilized. It is important to monitor previous alterations since new changes may suggest acute and/or subacute cardiovascular injury[23]. The main variations include alteration of ventricular repolarization, interval QT, acute coronary syndromes, supraventricular and ventricular arrhythmias, possibly to suggesting pericarditis and myocarditis[24].

Currently, systolic function and LVEF measurement are crucial for the optimal screening of cardiotoxicity[4]. They can be measured either by bi-dimensional echocardiogram or by MUGA, imaging tests conducted routinely in clinical practice[25].

Both methods have limitations. While the sensitiveness of detection of ventricular dysfunctions can be reduced in the bi-dimensional echocardiogram in patients with obesity and pulmonary disease, in MUGA, failure may occur in the mensuration of LVEF in patients with arrhythmias[26]. Additionally, the transthoracic echocardiogram presents favorable cost-benefit and is innocuous to the patient. Moreover it is occasionally utilized as alternative method to confirm some mensuration when MUGA is limited and requires exposure to radiation[27].

CONTEMPORANEOUS METHODS

Ultrasensitive troponin

It is a biomarker formed by several subunits, whose elevation is highly sensitive for myocardial injury, without, however, identifying the clinical cause of the cellular injury[28]. Witteles[29], evaluated the validity of troponin I as biomarker of early detection of cardiac toxicity to several antineoplastic drugs and concluded in its review that troponin I can serve as a marker of susceptibility to cardiac toxicity only for some patients sub-populations[29]. Positive results were documented as well with troponin T where the increase of the serum concentration soon after the administration of some chemotherapies associated to the subsequent risk of abnormalities of the left ventricle as, for instance, reduction of the wall thickness and dilation. In addition, the serum levels of troponin T increase according to the accumulated dose and severity of the injury.

Although not used routinely, the dosage of plasmatic troponin can be utilized as early marker of cardiotoxicity and it is anticipated that in the future, it can guide modifications of the therapeutic regimens[30].

Brain natriuretic peptide

The atrial natriuretic factor, the brain natriuretic peptide and the brain natriuretic type C form the family of the natriuretic peptides that play a key role in the cardiovascular homeostasis and modulation of cellular growth. The plasmatic concentrations of the atrial natriuretic factor and of the natriuretic peptide type B increase in response to the distention of the atrial tissue and appear to be antagonists to effects of angiotensin II in the vascular tonus, frequently involved in the physiopathology of the cardiopathies[31].

Dores et al.[32] conducted a prospective study for early detection of trastuzumab induced-cardiotoxicity, utilizing the plasmatic concentration of the natriuretic peptide type B and LVEF. There was no significant difference between LVEF pre-treatment and three months after and in the concentration of the natriuretic peptide type B, but due to the reduced sample size, new studies are awaited for a definitive conclusion[32].

Echocardiogram with evaluation of myocardial deformity (strain)

The speckle tracking, now available in several echocardiograph systems allows the evaluation of different components of the myocardial deformation – longitudinal, radial and circumferential strain[33].

Global longitudinal strain is sensitive to detect early alterations of the ventricular function before the clinical

manifestations and alteration of LVEF. However, there is no standardization of its use and cut-off as predictor of cardiotoxicity[34].

Cardiac magnetic nuclear resonance

The golden standard for the evaluation of the volumes, mass and LVEF, it is the procedure of choice to detect inflammation, necrosis and myocardial fibrosis with high resolution[35,36].

It has high sensitivity to early detection cardiac function deterioration and myocardial alterations, even subclinical. Further to being highly reproducible, it ensures the functional evaluation and myocardial perfusion and it is useful still in patients with limited echocardiographic window[37].

However, the elevated cost, the necessity of repeated exams and limited availability impair the routine clinical follow up. Additionally, there is no consensus about the recommendations when identification of subclinical alterations diagnosed occurs in oncologic patients[38].

Current scenario and future perspectives

Despite consolidated, clinical practice is still in need of evidence-based cardiotoxicity screening. Either for complementary methods or clinical evaluation, the current guidelines only mimic the screening regimens utilized in pivotal studies.

The possible damage generated with temporary interruptions of oncologic therapeutic regimens potentially curative based in the result of a complementary exam revealing minor cardiac injury in asymptomatic patients must be considered as it is frequently observed in breast cancer patients in adjuvant treatment with trastuzumab[39,40].

The incoming of contemporaneous methods brought in sensitivity to detect incipient cardiac alterations, but still these results cannot be used to modify the oncologic treatment regimen, unlike the conventional radiologic methods[5]. The incorporation of these new technologies contributed crucially to distinguish cardiotoxicity related to antineoplastic or to other causes that eventually can be curable and/or reversible[30].

Consequently, cardiotoxicity screening continues sustained in the classical approach. The contemporaneous methods appear to be exception in clinical practice, requiring individualization of the patient by a multi-disciplinary team[41].

Published studies and others ongoing are meant to the sphere of prevention based in the use of medications, which possibly would reduce the cardiac damage (inhibitors of the enzyme conversion of angiotensin, beta blockers)[42]. Other lines of research explore the better management of patients with preexisting myocardial disease[43].

Evidences about the sensitivity, specificity and cost analysis to adopt screening classic methods combined or not with contemporaneous are awaited and then to provide data on prevention, monitoring and conduct about oncologic patients who are prolonging their survival, much in part because of new drugs and changes of life habits.

CONCLUSION

The contemporaneous methods are more sensitive than the classics to detect cardiotoxicity. The elevated cost, difficult access and scarce consensus about the approach of the subclinical alterations are the major limiting factors for its incorporation into clinical practice. The definition of the screening regimen, considering the access, the cost and clinical applicability is yet to be concluded after completion of prospective studies.

CONTRIBUTIONS

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There are no conflict of interests to declare.

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