Cardiotoxicity in Cancer Treatment: New Frontiers in the Multimodality Diagnostic Approach

Cardiotoxicidade no Tratamento Oncológico: Novas Fronteiras na Abordagem Diagnóstica Multimodalidade

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Continued improvements in the effectiveness of cancer treatment have led to the current existence of millions of survivors of different types of pediatric and adult cancer worldwide. However, a parallel increase in the incidence of toxicity-related morbidity and mortality of many of the drugs used has created a new epidemiological challenge in this population. With a wide spectrum of involvement, cardiovascular toxicity is one of the most aggressive side effects of cancer therapy and is currently one of the leading causes of mortality in cancer survivors worldwide.[1] Different mechanisms are associated with this, including: direct damage to cardiomyocytes, endothelial injuries, hemodynamic or metabolic disorders, conduction disorders and thrombotic events. This cascade of involvement is potentially associated with different cytotoxic and immunotherapeutic chemotherapies or radiation therapies, and may have an acute onset or take years to be consolidated.[2]

The recent discovery and increasing use of new molecular targeted drugs (targeted therapies) in cancer treatment, as well as multimodal and multi-drug treatment regimens, have created new challenges and increased the special interest of cardiologists and oncologists in the subject. The main focus of the professionals involved today is the early detection of myocardial involvement and the early prediction and treatment of associated cardiac dysfunction. The current American Society of Clinical Oncology guidelines recommend risk stratification for cardiac dysfunction prior to the initiation of any potentially cardiotoxic drug.[3]

Despite the growing interest of the scientific community, there is no universal definition of cardiotoxicity and multiple controversies still persist on the topic. Cardiotoxicity is a generic term that can range from coronary artery disease (CAD), peripheral vascular disease, systemic or pulmonary hypertension, arrhythmias and heart failure, to valvular or pericardial involvement. Regarding cardiac involvement, the most widely recognized diagnosis of cardiotoxicity is based on abnormalities in left ventricular systolic function (LV) measured by a single method, usually LV ejection fraction (LVEF), sometimes on a single occasion.[4] A significant absolute (below a certain level) or relative (relative to pretreatment values) change in LVEF should be considered for diagnosis, but thresholds considered relevant for clinical decision-making vary within the different guidelines available. According to the 1st Brazilian Guideline for Cardio-oncology of the Brazilian Society of Cardiology published in 2011, in line with the American National Institute of Health (NIH), cardiotoxicity is defined as the asymptomatic reduction of LVEF between 10% and 20% (grade I), reduction in LVEF below 20% or below normal (grade II) or the onset of symptomatic heart failure (grade III).[5] A number of more recent studies contest these criteria, especially because they select only patients with established dysfunction (late phase) and because they do not consider subclinical myocardial involvement, when other parameters (especially myocardial strain) are known to be more sensitive. Notwithstanding such controversies, the most widespread definition of cardiotoxicity currently considers an LVEF drop ≥10% to <53% (suggesting confirmation upon further examination after 2–3 weeks), according to the Consensus of the American Society of Echocardiography.[6] We also know that LVEF measurement is subject to considerable intra- and inter-observer variability, as well as frequent discrepancies between different imaging modalities.[4] Therefore, limiting cardiotoxicity detection to a single LVEF measurement underestimates the clinical significance of other manifestations associated. These shortcomings and controversies may contribute to the current understanding that cardiotoxicity may be an underdiagnosed clinical condition.

In this context, the use of serum biomarkers — especially troponins and natriuretic peptides — is a commonly adopted strategy for early identification of subclinical myocardial damage and intensive follow-up of these patients,[5] often requiring complementation of workup. Echocardiography is still the mainstay of cardiac toxicity imaging,[7] especially with advanced 3D, strain and tissue Doppler techniques. Other imaging modalities such as computed tomography (CT) and cardiac magnetic resonance imaging (MRI) may add important information in a multimodality approach, often for the purposes of complementing it and in specific clinical situations[8]. For example, the high sensitivity of cardiac CT to detect pericardial effusion and thickening is known to be superior to echocardiography.[8] However, the role of cardiac CT in cardio-oncology is mainly restricted to the evaluation of coronary or valvular calcium and obstructive CAD.[8]

The high precision in ventricular functional analysis, as well as in the characterization of myocardial edema, inflammation and fibrosis have made cardiac MRI (CMRI) a method of great versatility and potentiality in the assessment of cardiotoxicity. In cardio-oncology, CMRI had its first recommendations in the complementary evaluation of LVEF in patients with limited echocardiographic window or in the presence of borderline

Keywords

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functional parameters, especially when more reliable and accurate LVEF measurements were necessary to justify discontinuation of chemotherapy. In the age of targeted therapy, myocarditis became the most feared cardiac complication of cancer treatment (especially associated with a class of overwhelmingly successful immunotherapy known as immune checkpoint inhibitors) and CMRI was then raised to a new level due to its high sensitivity and specificity in this diagnosis through a combination of delayed enhancement techniques, and T1 and T2 mapping.[9] Advanced CMRI techniques (Figure 1) are still extremely valuable in the evaluation of fibrosis classically related to radiotherapy and some anthracyclics, as well as in the detection of myocardial deposits of amyloid material (causing increased extracellular volume on T1 mapping) or iron (with T2* time reduction) potentially associated with the use of some chemotherapeutic agents. In addition, CMRI plays a central role in the diagnosis of intracavitary thrombi, assessment of vascular complications (MR angiography) and may be an alternative in the evaluation of ischemia (stress CMRI) in patients receiving therapies potentially associated with vasospasm or accelerated atherosclerosis.[7] More recently, CMRI myocardial strain analysis in chemotherapy patients has demonstrated the ability of the method to detect important subclinical abnormalities.[9]

Although recent studies have shown a potential use of PET-CT in the early detection of cardiotoxicity,[10] the role of nuclear medicine in cardiotoxicity screening is limited by the high cost and limited availability of these methods. Scintigraphy techniques are currently in disuse in this context; however, the high precision in PET/SPECT myocardial perfusion analysis plays a role in the risk stratification of CAD in some patients. Recent evidence suggests that cardiac MRI may have an incremental value in the evaluation of myocarditis compared to PET-CT or CMRI alone.[11]

In the future, the role of imaging in cardio-oncology will depend on how we will be able to better and earlier predict subclinical cardiac involvement in an attempt to prevent or interfere in the progression of this process.[12] New tools with artificial intelligence are promising, especially in the identification and understanding of new parameters beyond conventional visual analysis.[13] It is known that the population of patients at risk for cardiotoxicity differs in many respects from those with primary cardiovascular risk, corroborating the need for collaboration among all members of the multidisciplinary team involved in developing individualized workup strategies and therapies. The correct indication and interpretation of the different diagnostic methods available - with their specific advantages and limitations (Chart 1), in a cost-efficient multimodality approach - is central in this process.

Conflict of interest

The authors declare that there is no conflict of interest regarding this manuscript.

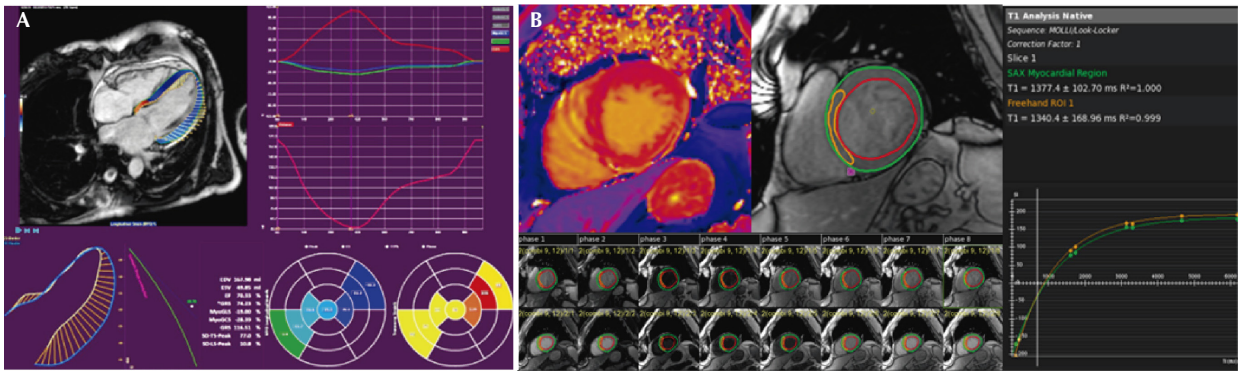

Figure 1 – *Advanced techniques in cardiac magnetic resonance imaging: (a) left ventricular myocardial strain by normal (global and segmental) strain; (b) abnormal left ventricular T1 mapping (high T1 values and increased extracellular volume in the septum of a patient with myocarditis).*

Chart 1 - Main aspects in the multimodality diagnostic approach of cardiotoxicity.

Diagnostic modality	Advantages	Disadvantages
Echocardiography	Low cost and wide availability (2D) Good time resolution (3D) Ability to detect subclinical strain	Operator-dependent Patients with limited acoustic window Variable spatial resolution
Cardiac computed tomography	Noninvasive Excellent sensitivity and specificity to confirm/rule out coronary artery disease	Radiation Limited role in myocardial tissue characterization
Cardiac magnetic resonance imaging	Gold standard in volumetric/functional evaluation and tissue characterization	High cost and limited availability in small centers
Nuclear Medicine	Functional and metabolic assessment with relative accuracy and reproducibility High precision in myocardial perfusion analysis (PET/SPECT)	Radiation High cost and limited availability in small centers (PET-CT)

PET/SPECT: Positron Emission Tomography/ Single Photon Emission Computed Tomography; PET-CT: Positron Emission Tomography-Computed Tomography.

References

1. Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin. 2016;66(4):271-89.

2. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, et al.; Task Force Members; ESC Committee for Practice Guidelines (CPG); Document Reviewers. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur J Heart Fail. 2017;19(1):9-42.

3. Armenian SH, Lacchetti C, Barac A, Carver J, Constine LS, Denduluri N, et al. Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2017;35(8):893-911.

4. Chung R, Ghosh AK, Banerjee A. Cardiotoxicity: precision medicine with imprecise definitions. Open Heart. 2018;5(2):e000774.

5. Kalil Filho R, Hajjar LA, Bacal F, Hoff PM, Diz Mdel P, Galas FR, et al. [I Brazilian Guideline for Cardio-Oncology from Sociedade Brasileira de Cardiologia]. Arq Bras Cardiol. 2011;96(2 Suppl 1):1-52.

7. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2014;27:911-39.

7. Plana JC, Thavendiranathan P, Bucciarelli-Ducci C, Lancellotti P. Multi-Modality Imaging in the Assessment of Cardiovascular Toxicity in the Cancer Patient. JACC Cardiovasc Imaging. 2018;11(8):1173-86.

8. Lancellotti P, Nkomo VT, Badano LP, Bergler-Klein J, Bogaert J, Davin L, et al.; EuropeanSociety of Cardiology Working Groups on Nuclear Cardiology and Cardiac Computed Tomography and Cardiovascular Magnetic Resonance; American Society of Nuclear Cardiology, Society for Cardiovascular Magnetic Resonance, and Society of Cardiovascular Computed Tomography. Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. J Am Soc Echocardiogr. 2013;26(9):1013-32. Erratum in: J Am Soc Echocardiogr. 2013;26(11):1305. Bergler, Jutta [corrected to Bergler-Klein, Jutta].

9. Jordan JH, Todd RM, Vasu S, Hundley WG. Cardiovascular Magnetic Resonance in the Oncology Patient. JACC Cardiovasc Imaging. 2018;11(8):1150-72.

10. Seraphim A, Westwood M, Bhuva AN, Crake T, Moon JC, Menezes LJ, et al. Advanced Imaging Modalities to Monitor for Cardiotoxicity. Current treatment options in oncology. Curr Treat Options Oncol. 2019;20(9):73.

11. Chen W, Jeudy J. Assessment of Myocarditis: Cardiac MR, PET/CT, or PET/MR? Curr Cardiol Rep. 2019;21(8):76.

12. Steingart RM, Chandrashekhar Y, Marwick TH. Imaging in Cardio-Oncology. Where Are We and Where Should We Be Going? JACC Cardiovasc Imaging. 2018;11(8):1209-11.

13. Araujo-Filho JAB, Nascimento-Jr A, Gutierrez MA, Nomura CH. Inteligência Artificial e Imagem Cardíaca: Precisamos Falar sobre Isso. Arq Bras Cardiol: Imagem Cardiovasc. 2019;32(3):154-6.