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EDITORIAL COMMENT

Subclinical cardiotoxicity in cancer therapy: The impact of early detection☆

Cardiotoxicidade subclínica em oncologia: o impacto da deteção precoce

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The cardiotoxic effects of cancer treatment are a major problem, even as the increasing efficacy of therapeutic agents has led to some cancers being transformed into chronic diseases with reduced risk of progression or recurrence, and even cured in certain cases. Nevertheless, increased survival, sometimes with life expectancy similar to that of the general population, has been overshadowed by the risk of long-term effects of cardiotoxic cancer therapies. Breast cancer has been the focus of particular attention since it frequently affects women of an age-group with a long life expectancy which may be reduced due to cardiotoxicity.[1]

Cardiotoxicity can manifest in different forms, ranging from arrhythmias to coronary, valvular or pericardial injury, but possibly the most feared effect is ventricular dysfunction ultimately resulting in heart failure,[2] which obviously has a direct impact on prognosis.

Ventricular dysfunction resulting from cardiotoxicity appears to be multifactorial, but it is still unclear which factors are involved. While type I cardiotoxicity (typically caused by anthracycline therapy, dose-dependent, and with early signs of apoptosis) is considered irreversible, not all patients develop irreversible damage. On the other hand, while dose-independent type II cardiotoxicity, as seen with trastuzumab, does not lead to apoptosis and the associated cardiac dysfunction usually reverses, this does not always occur.[3] Various studies have suggested age, female gender, hypertension, renal failure, pre-existing heart disease and genetic predisposition as risk factors for cardiotoxicity induced by anthracyclines, but it is not known to what extent these variables are associated with other types of chemotherapy-induced cardiotoxicity.[4]

Irrespective of the factors involved, the need for early detection of ventricular dysfunction is indisputable and is recognized by various medical societies.[3,4] Pre-treatment assessment is recommended, since the findings may influence the choice of chemotherapy drug, as is regular monitoring of ventricular function.

It is thus clear that cardiac imaging has an important role in functional assessment. At present, the recommended criterion to screen for cardiotoxicity is reduced ejection fraction (EF).[3,4] Although EF is influenced by multiple variables, particularly preload and afterload, it is certainly the best studied functional index and is the most widely used for prognostic studies in cardiology.

Among cardiac imaging modalities, echocardiography is considered the first-line method for evaluating these patients because of its wide availability, easy repeatability, versatility and lack of radiation exposure.[3] However, the variability associated with two-dimensional

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echocardiographic study of chamber volumes and EF can reach 11%; three-dimensional study is therefore recommended to reduce variability and improve diagnosis of cardiotoxicity.[5] While magnetic resonance imaging is the reference method to measure EF and is able to detect myocardial fibrosis, most centers have limited access to this technique, which is usually not available for routine clinical monitoring and at present is only indicated in cases of inconclusive findings or where medication may be discontinued based on EF by echocardiography.[3,6]

Speckle tracking echocardiography to assess myocardial strain has been shown to be able to detect early changes in ventricular function in various diseases, before any change in EF or the appearance of clinical manifestations. Changes in strain are a better predictor of risk than EF in heart failure patients.[7,8]

Various studies have suggested that in patients undergoing cancer treatment, particularly chemotherapy but also radiotherapy, speckle tracking echocardiography is useful for early detection of myocardial injury as a predictor of subsequent reduction in EF, which has limited sensitivity in the initial stages of ventricular dysfunction and heart failure, both of which are late events that adversely affect survival. In a systematic review of 21 studies including 1504 patients, changes in global longitudinal strain occurred early after beginning anthracycline therapy and preceded alterations in EF,[9] although not all studies reported these results or the same indices as predictors.[10] The small size of many studies and the heterogeneity of the study populations, particularly with regard to the chemotherapy agents used, may have contributed to the differences found.

The aim of the single-center study by Portugal et al.[11] published in this issue of the *Journal* was to prospectively analyze changes in myocardial contractility, as assessed by speckle tracking study of longitudinal strain, in a relatively large population of 158 breast cancer patients undergoing chemotherapy with anthracyclines and trastuzumab, and to determine their relationship with the development of cardiotoxicity defined in accordance with the guidelines. In a mean follow-up of 5.4 months, the authors observed an overall incidence of cardiotoxicity of 18.9%, rising to 38.1% in those treated with both drugs, similar to the figures reported in other series.[9,10] They also found decreased global longitudinal strain in 61.4% of the population, and this was an independent predictor of cardiotoxicity on multivariate analysis, with a 4.88-fold increased risk (odds ratio 4.88, confidence interval 1.32-18.0, p=0.017).

These findings, which are in line with those of other studies, albeit of smaller populations or retrospective in nature, lend support to the idea that the more subtle changes in ventricular function represented by alterations in myocardial deformation parameters enable earlier diagnosis of ventricular dysfunction and thus open up the possibility of early therapeutic intervention aimed at improving long-term prognosis. Supporting this view is the fact that in patients treated with anthracyclines and with evidence of cardiotoxicity, an inverse relationship has been observed between time to therapy with enalapril and bisoprolol or carvedilol and improvement in EF, resulting in complete or at least partial recovery from ventricular dysfunction.[12] Preliminary studies are being designed aimed at identifying more sensitive markers of the need to initiate secondary prevention therapy, but it is still early days and the results of multicenter, prospective and randomized trials are awaited in order to establish appropriate guidelines.[3,4]

There are still a number of controversial issues that need to be resolved, especially given the rapid developments in cancer drugs and treatments. The factors involved in triggering cardiotoxicity also need to be clearly identified so they can be promptly and appropriately corrected. Another area of debate concerns the most appropriate diagnostic strategies and follow-up in terms of evaluation methods, serial assessment and interpretation, as well as the best treatment algorithms to minimize long-term complications. The diagnostic techniques available are also evolving and offer new opportunities for the detection of early subclinical changes, particularly in myocardial structure and histopathology, and new biomarkers are being investigated,[13,14] opening up new possibilities for diagnosis and secondary prevention.

Conflicts of interest

The author has no conflicts of interest to declare.

References

1. Truong J, Yan AT, Cramarossa G, et al. Chemotherapy-induced cardiotoxicity: detection, prevention and management. Can J Cardiol. 2014;30:869–78.
2. Felker GM, Thompson RE, Hare JM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med. 2000;342:1077–84.
3. Plana JC, Galderisi M, Barac A, 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.
4. Zamorano JL, Lancellotti P, Munoz DR, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines. Eur Heart J. 2016.
5. Thavendiranathan P, Grant AD, Negishi T, et al. Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes: application to patients undergoing cancer chemotherapy. J Am Coll Cardiol. 2013;61:77–84.
6. Kongbundansuk S, Hundley WG. Noninvasive imaging of cardiovascular injury related to the treatment of cancer. J Am Coll Cardiol Imaging. 2014;7:824–38.
7. Rangel I, Gonçalves A, de Sousa C, et al. Global longitudinal strain as a potential prognostic marker in patients with chronic heart failure and systolic dysfunction. Rev Port Cardiol. 2014;33:403–9.
8. Cho GY, Marwick TH, Kim HS, et al. Global 2-dimensional strain as a new prognosticator in patients with heart failure. J Am Coll Cardiol. 2009;54:618–24.
9. Thavendiranathan P, Poulin F, Lim K, et al. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy. A systematic review. J Am Coll Cardiol. 2014;63:2751–68.
10. Negishi K, Negishi T, Hare JL, et al. Independent and incremental value of deformation indices for prediction of trastuzumab-induced cardiotoxicity. J Am Soc Echocardiogr. 2013;26:493–8.
11. Portugal G, Branco LM, Galrinho A, et al. Importância da deformação longitudinal na detecção da cardiotoxici-

dade induzida por quimioterapia e na identificação de padrões específicos de afectação segmentar. Rev Port Cardiol. 2017;36:9–15.
12. Cardinale D, Colombo A, Lamantia G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. J Am Coll Cardiol. 2010;55:213–20.
13. Jordan JH, Vasu S, Morgan TM, et al. Anthracycline-associated T1 mapping characteristics are elevated independent of the presence of cardiovascular comorbidities in cancer survivors. Circ Cardiovasc Imaging. 2016;8, pii:e004325.
14. Yu AF, Ky B. Roadmap for biomarkers of cancer therapy cardiotoxicity. Heart. 2016;102:425–30.