



## EDITORIAL COMMENT

**Cardiotoxicity: Will we ever unravel it?****Cardiotoxicidade: algum dia a desvendaremos?**

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Cardio-oncology (CO) is an emerging field, which has experienced an exponential growth both in awareness and research. Worldwide, CO units have been created and Portugal is no exception. A survey conducted by the CO Study Group of the Portuguese Society of Cardiology has shown that the number of centers providing CO care has already risen to a total of seventeen.

Cardio-oncology is clearly not a passing trend, as the reasons behind its rapid growth stem from multiple likely irreversible factors: better survival rates for cancer patients mean that there is more time for the development of meaningful late cardiac side effects, alongside the possibility of new cancers emerging; the accumulation of cancer therapies will increase the risk of cardiotoxicity; cardiology treatments also improve the survival rates of cardiac patients, making more patients eligible for further cancer treatments; lastly, the impressive number of new cancer drugs, especially targeted therapy and immunotherapy, seem to have more diverse cardiac effects, with an earlier presentation. Thus, a specific approach for these patients is essential.

Cardiotoxicity encompasses a spectrum of manifestations ranging from left ventricle (LV) dysfunction/heart failure to arrhythmias, coronary artery disease, hypertension, venous thromboembolic disease or pulmonary hypertension.<sup>1</sup> The most studied is cancer therapy-related cardiac dysfunction.

International recommendations both from Cardiology and Oncology societies<sup>1–3</sup> state that patients should be stratified before therapy, with close follow-up to detect and treat cardiotoxicity earlier. In this regard, LV strain assessed by speckle tracking has garnered interest, as some studies have shown that a reduction in global longitudinal strain (especially if >15%) is a predictor of subsequent reduction in LV ejection fraction (EF).<sup>4</sup> It should be pointed out that these studies included mainly patients treated with anthracyclines and/or trastuzumab.

In this issue of the Journal, Kanar et al.<sup>5</sup> sought to assess the cardiotoxicity of two established chemotherapy regimens for non-small cell lung cancer (NSCLC), with a special focus on the potential impact on LV strain. They included 71 NSCLC patients, 39 of whom were treated with paclitaxel plus carboplatin (PC) and 32 with vinorelbine plus cisplatin (VC), as well as 34 controls. All patients underwent an echocardiographic evaluation at baseline and at the end of treatment. In a median follow-up of 162 days, there were no cardiac adverse events and no differences in LVEF between the groups. However, there was a significant reduction in LV strain only in patients treated with PC regime. The authors thus concluded that this treatment regime may cause subclinical cardiotoxicity.

Carboplatin and paclitaxel are not new drugs. Carboplatin, a platinum-based antineoplastic, was approved in 1989 and is used in the treatment of a multitude of cancers such as ovarian, lung, head and neck or neuroblastoma. This class of drugs is associated with myocardial ischemia

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and arrhythmias, but that is especially true for cisplatin and much less frequent with carboplatin.<sup>1</sup>

Paclitaxel is an antimicrotubular agent approved in 1992 and plays an important role in the treatment of ovarian, breast and NSCLC, usually in combination therapy. Paclitaxel has been shown to increase the risk of sinus bradycardia, atrio-ventricular block and less frequently premature ventricular contractions and ventricular tachycardia.<sup>1</sup>

Regarding LV dysfunction, paclitaxel is considered by cardiology and oncology guidelines as a low-risk agent.<sup>1,2</sup> In fact, even in the most recent position statement concerning baseline cardiovascular risk assessment, paclitaxel was not included in the eight drug classes that require a stricter risk stratification and follow-up.<sup>3</sup>

Left ventricular dysfunction and heart failure have been reported when this agent is used simultaneously with anthracyclines, as it enhances anthracyclines cardiotoxicity by reducing its elimination and promoting its metabolism into more toxic metabolites.<sup>1</sup> As a result, they are currently administered separately.

There are no prospective large studies investigating the cardiotoxic effects of paclitaxel, but the clinical trials with hundreds of patients treated in monotherapy and in combination therapy did not reveal any major warning signs.<sup>6-8</sup> Furthermore, early-stage breast cancer trials with non-anthracycline therapy using a taxane had a good cardiac safety profile and it can be an option in high risk-patients.<sup>9</sup>

One may argue, however, that most of these studies were not performed using a specific cardiovascular protocol and none used myocardial deformation assessment.

Kanar et al.,<sup>5</sup> therefore, deserve merit for conducting a prospective study with a control group in a population naïve of potential cardiotoxic treatment, while exploring its effect with more sensitive and sophisticated measures of myocardial function. They are not entirely alone, as Altin et al.<sup>10</sup> published a similar study assessing the cardiotoxicity of PC regimen in gynecological diseases. Both studies showed a slight reduction in LV strain, without changes in LVEF or cardiovascular symptoms or events. However, the reduced number of patients included, and the short follow-up are important limitations of both studies, warranting caution in the generalization of their results.

From a clinical perspective, the key question is whether this reduction in LV strain should impact our practice. The answer is not clear. A drop in global longitudinal strain in patients treated with anthracyclines, a drug that is known to cause severe myocardial pathology, should be valued. But this is not the case in these two studies. Should cancer treatment be halted/changed and/or cardioprotective drugs be initiated? Should we increase the level of cardiac surveillance, adding to the strain of a growing number of cancer patients in echo labs and CO clinics, while potentially inducing further stress in cancer patients?

I do not believe so for now. But while the findings of Kanar et al.<sup>5</sup> will probably not lead to a major change in practice,

they are nonetheless relevant, highlighting the importance of further research with a broader scale, while making us more aware of a possibly greater risk of cardiotoxicity in this subset of patients.

## Conflicts of interest

The author has no conflicts of interest to declare.

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