Towards pre-treatment imaging prediction of chemotherapy-related cardiotoxicity

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Although the significant advances in cancer therapy obtained during the last decades have prolonged the survival of many patients, this improvement has been achieved at the expense of an increase in cardiovascular complications secondary to chemotherapy and/or radiotherapy.[1] Consequently, cardiovascular (CV) disease is the first cause of death in patients who survive cancer.[2] The pathogenic basis of this repercussion would be a direct toxicity of chemotherapy agents on cardiac structure and function or an accelerated development of CV disease, especially in subjects with previous risk factors. This cardiotoxicity can manifest itself in a wide clinical spectrum, which includes uni or biventricular systolic dysfunction, myocardial ischemia, valvular heart disease, arrhythmias, arterial hypertension, thromboembolic disease, and peripheral, pulmonary vascular or pericardial involvement.[2] The most common manifestation is heart failure, a research endpoint that is usually a late phenomenon. However, the frequency and severity of this damage is a function of the drugs used, alone or in combination, and the dose administered in each patient.[1] Thus, some cytostatic agents mainly determine systolic dysfunction of variable degree, such as anthracyclines and trastuzumab, while others, such as 5-fluorouracil and its prodrug, capecitabine, are more frequently associated with the development of acute myocardial ischemia.[3]

Observational clinical studies that explored the relationship between CV risk and cardiotoxicity found that age, hypertension, diabetes, smoking, previous radiotherapy and pre-existing CV disease are associated with an increased risk of post-chemotherapy myocardial damage. However, the causal relationship between treatment with different cytostatic agents and cardiotoxicity still remains uncertain.[3] Although the detailed mechanisms underlying chemotherapy-related cardiotoxicity (CTRC) are unknown, a correct risk stratification prior to therapy represents a major clinical challenge, which can benefit from the contributions of various imaging techniques. It is then understood that, to optimize the therapy of cancer patients, a greater collaborative effort is required between multiple disciplines, a collective effort to prevent and manage CTRC without compromising the quality of cancer care or its clinical benefits. Nuclear cardiology imaging can contribute to the diagnosis and prognostic stratification of these patients from various perspectives. Thus, gated-SPECT, for example, can update the risk stratification in the presence or suspicion of underlying ischemic heart disease, and even suggest the possibility of endothelial dysfunction and plaque rupture as the main underlying mechanisms in selected cases.

Current evaluation of CTRC relays on serial measurements of left ventricular ejection fraction (LVEF)

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Table 1. Imaging methods for early prediction of CTRC

Pre-treatment		During treatment	
Process	**Technique**	**Process**	**Technique**
Myocardial deformation (strain)	Echocardiography	LVEF decline	Echocardiography, RNV, CMR
LV dyssynchrony	RNV	Myocardial deformation (strain)	Echocardiography, CMR
		Myocardial sympathetic denervation	^{123}I-MIBG scintigraphy, ^{11}C- hydroxyephedrine PET, ^{18}F-fluorobenzylguanidine PET.
		Cardiomyocyte apoptosis	^{99m}Tc-annexin V
		Cardiomyocyte necrosis	^{111}In-antimyosin
		Glucose metabolism	^{18}F-FDG PET
		Fatty acid metabolism	^{123}I-BMIPP SPECT
		Myocardial edema	T2-CMR

through 2-D echocardiography or planar radionuclide ventriculography (RNV). RNV has been used successfully for this purpose for more than 30 years, since Schwartz et al demonstrated its clinical impact in a cohort of 1487 cancer patients treated with doxorubicin monitored over a 7-year period.[4] It has been considered the gold standard method for evaluating LVEF changes over time because of its high sensitivity, specificity and reproducibility.[5,6] Despite wider availability, lower cost and lack of ionizing radiation, 2-D echocardiography has the disadvantage of depending on geometric assumptions (that can turn inaccurate when ventricular dimensions increase), acoustic window and operator skills, that ultimately determine a higher interobserver and intraindividual variability.[7] Although 3-D echocardiography overcomes the problem of geometric assumptions improving reproducibility, it still has to deal with inadequate acoustic windows for example in breast cancer patients treated with mastectomy.[8]

The most critical limitation of the traditional strategy of serial measurement of LVEF is that LVEF decline comes too late. By the moment a significant decrease (at least a 10% decrease to a final value lower than the normal limit according to guidelines) is detected, subclinical myocardial injury has been progressing for quite a long period to compromise enough tissue to outrange myocardial compensatory reserve. By this time, the optimal moment for therapeutic intervention may have been missed and LV dysfunction can be irreversible for a considerable number of patients, with up to 45% of patients failing to respond to standard heart failure therapy.[9] Thus, the ideal imaging biomarker for CTRC should be able to detect the early asymptomatic pathological processes leading to LVEF decline. Echocardiography measure of myocardial strain has recently emerged as an early marker, being able to detect changes at low doses of chemotherapy.[10] The first randomized controlled study using global longitudinal strain (GLS) as a predictor of ventricular dysfunction will soon be reporting valuable data.[11] Cardiac magnetic resonance (CMR) combines high reproducibility for LVEF assessment with information on LV structure and the ability to perform tissue characterization. Despite the high cost, it represents a promising tool for CTRC evaluation.[12]

Radionuclide molecular imaging techniques offer the possibility of visualizing different pathophysiologic processes at the tissue level that could elucidate early subclinical myocardial injury. The processes that have been evaluated comprise sympathetic innervation through ^{123}I-MIBG or PET tracers, myocardial cell injury and necrosis through ^{111}In-antimyosin, apoptosis and cell death through ^{99m}Tc-annexin V, glucose metabolism through ^{18}F-FDG and fatty acid metabolism through ^{123}I-BMIPP.[13,14] Despite promising preliminary results in many cases, large-scale clinical studies to translate these techniques to routine clinical use are still pending. Standardization of technical protocols and development of simple and reproducible methods for quantification will be previously needed, and availability and cost issues will also need consideration. In addition, certain tools derived from gated imaging techniques could contribute to detect contractile or metabolic abnormalities much earlier than systolic dysfunction and induced ischemia, which are difficult to detect and quantify by other techniques. This represents a double

clinical application to diagnosis (once cardiotoxicity is installed) and prevention (when it is not yet detected by other common techniques such as echocardiography or tissue Doppler). Imaging techniques that have been reported to be able to predict CTRC are summarized in Table 1.

Imaging methods for risk stratification before chemotherapy starts have been far less investigated. While baseline LVEF values over 50% have not been consistently related with the development of CTRC, other parameters such as LV volumes and GLS have been reported as possible predictive markers deserving more investigation.[15] Regarding conventional nuclear medicine techniques like RNV, this topic had not been addressed before until the work by Jones et al, presented in this issue of the Journal.[16] The authors included 177 patients evaluated with serial planar RVG at baseline and after cardiotoxic chemotherapy every 3 months for up to 2 years. Fourier phase analysis was applied to reprocessed RNV images and approximate entropy (ApEn) was estimated, plus other more classical parameters based on first order statistics. Phase analysis has demonstrated high sensitivity, specificity and reproducibility to quantify mechanical synchrony,[17] a measure of cardiac performance quite independent of ventricular function.[18] However, there are few studies aimed to characterize the ventricular contractile dynamics associated with other structural heart diseases that are not accompanied by altered ventricular conduction, that is, beyond its usefulness to predict response to cardiac resynchronization therapy.

The study of entropy and its surrogates as ApEn using nuclear imaging techniques refresh the interest in the subject of ventricular mechanical dyssynchrony in a high-risk population that has been not fully studied, such as cancer patients. The application of this concept in cardiology had been mostly limited to the autonomic CV evaluation through heart rate variability in selected populations. In nuclear cardiology, the theoretical background of entropy had provided only a collateral variable, of little independent practical value over the other parameters that characterize the phase histogram obtained by gated-SPECT, RVG or PET. Fortunately, some recent investigations in patients with left bundle branch block and chronic kidney disease with normal myocardial perfusion have promoted the study of this construct as a predictor of major CV events.[19,20]

Although this is a retrospective study that includes only a small number of events (11 cases in 177 breast cancer patients), its findings are auspicious (an AUC of 0.87 for the best predictive model, improving the discrimination power of ApEn when combined with baseline LVEF) and generate some hypotheses of great clinical relevance for subsequent studies: can the appearance of severe systolic dysfunction be accurately predicted before chemotherapy?, which variables (pre-test and/or intra-test in the case of analyzing post-stress phase changes) could play a predominant role in this predictive function?, and even, what are the underlying mechanisms? Even though large prospective studies are required to answer these questions, we believe that the results provided by the researchers represent a potential greater contribution of conventional nuclear cardiology to the investigation of new predictive algorithms for CV post-chemotherapy complications, complementing the interpretation of the results by the nuclear cardiology physician and improving the multidisciplinary decision making. Technical issues associated with the influence of other patient-specific variables (like age, sex, previous CV condition, therapy-related and tumor-related variables) or acquisition factors on ApEn, should also be quantified in larger series, with a careful clinical extrapolation of the results. Additionally, SPECT imaging has been reported to improve reproducibility of phase analysis in RVG and may contribute to better identify patients at risk.[21]

The findings by Jones et al are an important incentive to understand the pathogenesis of CTRC and the potential clinical application of imaging in the prevention of cardiotoxicity as it is currently conceived, better selecting the patients who can complete the oncological therapies, those who will need a careful follow-up, or even helping to modify the post-test therapeutic options. Finally, the results offer an opportunity to reformulate an important clinical reflection: an optimal risk-benefit balance of chemotherapy represents a great clinical challenge that must be individualized, acknowledging the contributions of various disciplines and imaging techniques. Without losing this horizon, a correct and timely risk stratification and a close clinical monitoring by the multidisciplinary oncology team is essential. Future prospective studies with a large number of patients aimed to explore several variables of mechanical behavior, alone or in combination with early markers of myocardial damage, may contribute to individualize this risk stratification, avoiding serious events in many cases, and defining the usefulness of specific therapeutic interventions in the prevention of serious CV events that may occur during or after chemotherapy. As more new agents are introduced for cancer therapy and more patients survive cancer, this field is bound to evolve accordingly, and nuclear cardiology has the means to regain prominence.

Disclosure

Rodolfo Ferrando Castagnetto and Federico Ferrando-Castagnetto declares that they have no conflict of interest.

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