MY Approach to Echocardiographic Assessment of Cardiotoxicity in Cancer Therapy

Como eu Faço a Avaliação Ecocardiográfica da Cardiotoxicidade na Terapia do Câncer

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Over the last three decades, we have seen a significant increase in cancer patients' survival and, as a result, the emergence of cardiovascular complications with the potential to offset the benefits obtained.[1,2]

Early diagnosis of cardiovascular impairment related to cancer treatment provides the opportunity for prevention and treatment, especially in myocardial dysfunction and, consequently, in the development of heart failure. [1,2]

Defining Cardiotoxicity

Several definitions of cardiotoxicity (CTX) regarding different therapeutic regimens and diagnostic criteria make it difficult to standardize it in the literature. We chose to follow the consensus of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI), defining CTX as left ventricular ejection fraction (LVEF) drop >10% (compared to pretreatment levels) to less than 53% or lower limit of normality.[3]

The role of echocardiography

echocardiography has established itself as the basis for CTX diagnosis and monitoring because it is a widely available, cost-effective and harmless method (free of risk, contrast and ionizing radiation), which makes it possible to repeat it numerous times. Whenever possible, the report should include: time interval from chemotherapy (CT) performed (how many days after the QT cycle, for example), which drugs were used, vital signs, and the data mentioned below.[2]

Simpson's method should be routinely used to calculate LVEF. However, its intra and interobserver variability can be as high as 10% (absolute value). Findings outside the expected parameters should be repeated and confirmed after 2–3 weeks of the initial finding.[4]

In the population of cancer patients, the 3D technique is preferable over 2D because it has shown greater reproducibility and accuracy in the recognition of borderline or slightly reduced LVEF. In patients undergoing chemotherapy, it presented the lowest intra and interobserver time variability (5.6%, absolute value).[5]

LVEF drop reflects a marker of late myocardial damage, accompanied by worse prognosis. Cardiac dysfunction only becomes evident when myocardial damage is significant. Therefore, its absence does not exclude cardiotoxicity.[5–7]

The application of strain by speckle tracking to analyze ventricular mechanics enables the detection of subclinical lesions with good reproducibility and accuracy. Multiple studies have demonstrated the value of global longitudinal strain (GLS) in the detection of subclinical myocardial dysfunction in patients during and after cancer treatment.[8–10] Its role seems to be more relevant in the association with borderline normal or slightly reduced LVEF (LVEF 50–59%).[3] Overall, although early detection of changes is conceptually important, the value of these actual abnormalities should be demonstrably correlated with clinical outcomes.[8]

In order to increase the accuracy of 2D echocardiography in detecting CTX signals, it is recommended to perform a combined LVEF analysis (Simpson's method), LV wall motion score calculation and longitudinal systolic function studies, especially where advanced methodologies are unavailable (3D echocardiography and myocardial strain study). Although there are no diagnostic reference values, the progressive decline in peak mitral annular systolic velocity using tissue Doppler (s'

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wave) and mitral annular plane systolic excursion (MAPSE) should be valued.[11–12]

Abnormalities in parameters related to diastolic function, such as E and A waves, E/A ratio, isovolumetric relaxation time and myocardial performance index, were described early after CT. However, longitudinal studies have not been able to reproduce the prognostic value of these findings and there is insufficient evidence to use this analysis in the diagnosis of CT-induced CTX.[12,13]

The prevalence of right ventricular involvement (assessed by anterior tricuspid annular excursion, s' wave and fractional area variation) and its prognostic value have not been properly studied yet. Data regarding the influence of CT on remodeling, ventricular function and mechanics are scarce and sometimes conflicting. Interestingly, the difference in RV longitudinal strain is more pronounced when the septal region is disregarded, suggesting greater RV myocardial sensitivity. [14]

Which patients are at high risk for cardiotoxicity?

Before starting cancer treatment, all patients should be evaluated for the risk of CTX. Factors related to the treatment proposed (which drugs are used and association with radiotherapy) and the presence of comorbidities, cardiovascular risk factors, age and gender should be considered. The presence of basal LVEF of 50–55% increases the risk of cardiac complications, especially when anthracycline is involved.[1-3,15]

Echocardiographic evaluation before therapy

The ASE/EACVI recommends evaluation of LVEF and SLG in all patients expected to undergo any therapy associated with the risk of CTX in order to assess any potentially underlying heart disease.[12] In the presence of structural abnormalities, systolic dysfunction (LVEF <50–55%) with or without SLG <16%, cardiac evaluation and control of associated cardiovascular risk factors is recommended.[3,12,15] (Figure 1)

Echocardiographic evaluation during therapy

Echocardiographic monitoring in asymptomatic patients during cancer treatment is recommended for all patients considered at high risk. The ASE/EACVI and the American Society of Clinical Oncology have different guidelines on how often it should be performed, reflecting the lack of literature data to support either of those guidelines.[1,2]

Monitoring during anthracyclic therapy should be performed after cumulative dose of 240 mg/m² and thereafter, at every 50 mg/m². During therapy with trastuzumab, the US FDA's recommendation is to repeat the echocardiography every 3 months, although asymptomatic LVEF drop in asymptomatic patients should not necessarily determine discontinuation of therapy, as found in the SAFE-HEARt study.[16] An evaluation at every 3 months is also recommended while tyrosine kinase inhibitors are used.[1–3,15]

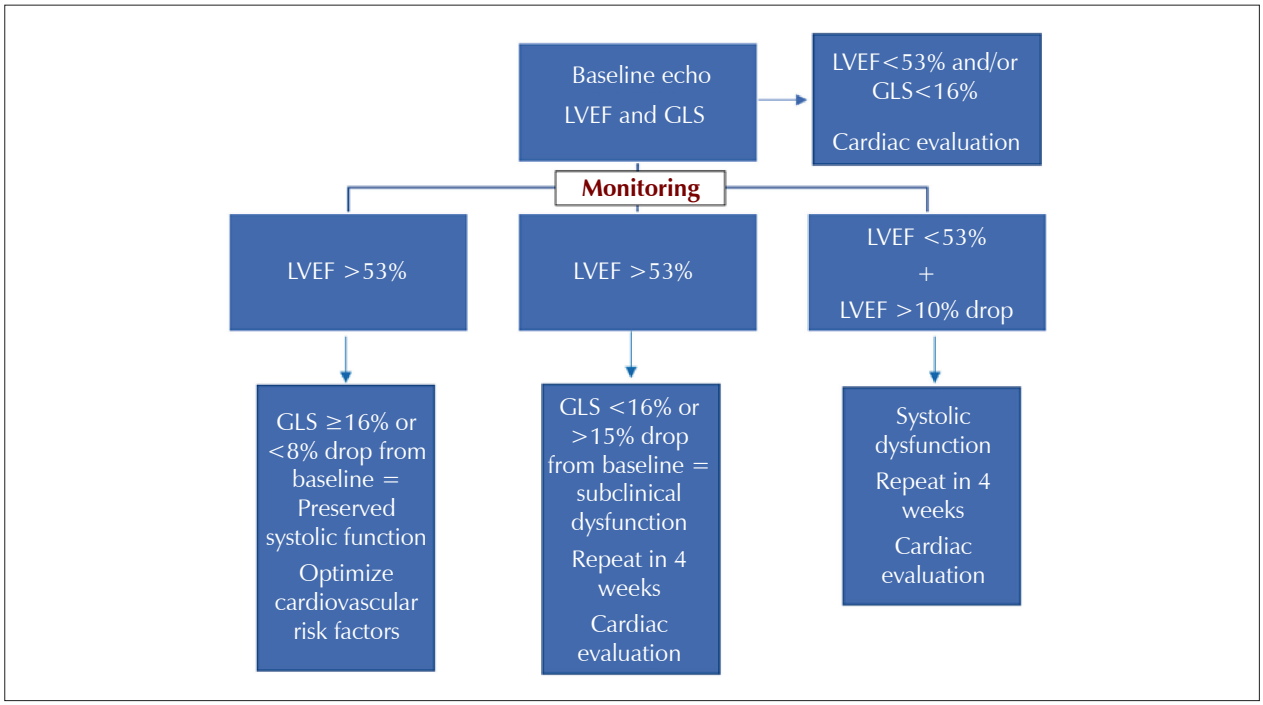

Figure 1 – *Flowchart for prior evaluation and monitoring during cancer treatment. LVEF (left ventricular ejection fraction), GLS (global longitudinal strain). In addition to echocardiographic evaluation, we suggest ECG (electrocardiogram) and biomarkers (natriuretic peptide and troponin). Monitoring depends on the associated risk factors and the drug used.*[3,15]

The presence of symptoms suggestive of CHF and alterations in biomarkers, such as natriuretic peptides and troponin, help in risk stratification and in determining the need for echocardiographic reassessment, including for other drugs, such as cyclophosphamide and carfilzomib.[1–3,15,17–18] (Figure 1)

Echocardiographic evaluation after therapy

Again, we have observed a lack of consensus regarding late follow-up.[1,2] We recommend echocardiography in the first 6 to 12 months after completion of anthracyclic treatment, since the study by Cardinale et al. demonstrated the prognostic value of LVEF after completion of CT and the prevalence of myocardial dysfunction (98% of cases) in the first 12 months.[1-3,15,19]

Radiotherapy

Radiotherapy, especially when the total dose exceeds 30 Gy (or more than 2 Gy per day) is related to various cardiovascular complications. Pericardial disease is described as the most common manifestation, usually occurring a few weeks after treatment. Acute pericarditis is usually self-limited. However, 10% to 20% of patients develop chronic or constrictive pericarditis after 5 to 10 years. Late-onset conditions occurring years or decades after exposure include: chronic pericarditis, mitral and aortic valve diseases, large and medium vessel vasculopathy (porcelain aorta and carotid stenosis), cardiomyopathies (dilated and restrictive forms), conduction disorders and coronary atherosclerotic disease (acute and chronic coronary insufficiency). Patients should be reevaluated after 5 years in high-risk cases and, thereafter, at every 5 years, including provocative tests for ischemia such as stress echocardiography.[15–20]

Conflict of interest

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

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