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Insights of CECCY Trial: Should Troponin be the Target for Anthracycline Cardiotoxicity Prevention?

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Advances in oncology such as better access to health care system, earlier cancer diagnosis and new chemotherapies have led to longer survival of oncologic patients over the last decades [1]. However, this population is vulnerable to cardiovascular drug-related adverse events like cardiomyopathy, which leads to heart failure and impairs survival and quality of life [2,3]. Among different classes of chemotherapeutic agents, anthracyclines (ANT) stand out as the most related to cardiomyopathy, and may affect cancer survivals in 9% of all cases [4].

The most widely recognized definition of cardiotoxicity is based on changes in left ventricular ejection fraction (LVEF) [5]. A drop in 10% to a value below 50% or associated with heart failure symptoms during or after cardiotoxic agent's use suggests cardiotoxicity [2]. Although largely used in different trials, this definition raises some concern, since LVEF reduction may represent a late stage of myocardial injury and therefore it only allows the diagnosis in a point where full recovery is less likely. In order to improve detection of cardiotoxicity, there is a growing body of evidence on the use of biomarkers elevation [6] and myocardial strain reduction [7] as subclinical cardiotoxicity markers, although so far there is no formal recommendation of treatment based on them.

Once chemotherapy-induced cardiomyopathy is present, prompt heart failure treatment should be started with neuro-hormonal antagonists such as angiotensin converter inhibitor (ACE), angiotensin receptor blockade (ARB) and betablockers. Despite contemporary heart failure treatment, up to 89% of patients with anthracycline-induced cardiotoxicity do not experience complete recovery [8,9]. In order to avoid decreasing LVEF and exposing the patient to the risk of irreversibility of cardiac dysfunction even with heart failure treatment, prevention of chemotherapy-induced cardiotoxicity has been the focus of research in the last years.

Non-pharmacological prevention as stopping smoking, consuming healthy diet and adopting moderate aerobic exercise should always be stimulated to reduce cardiovascular risk [10]. Regarding pharmacological therapy there are two approaches in primary prevention of anthracycline-induced cardiotoxicity: to reduce the cardiotoxic effects ANT and initiate a cardioprotective medication. The first approach is possible by decreasing cumulative dose of the agent, using continuous infusion and preferring liposomal forms of the drug [11]. In the second approach, so far, only dexrazoxane is FDA approved to avoid ANT cardiotoxicity in metastatic breast cancer patients who received >300mg/m² of doxorubicin [12]. Cardiovascular drugs such as beta-blockers, ACEIs and BRAs showed controversial results and are not recommended as a routine in patients under chemotherapy [13].

Earlier Small randomized studies suggested carvedilol [14] and nebivolol [15] were protective against LVEF changes. The PRADA (prevention of Cardiac Dysfunction During Adjuvant Breast Cancer therapy) trial [16] evaluated cardio-protection using metoprolol and candesartan in 130 patients and showed benefit of candesartan, but no difference between metoprolol and placebo.

The largest randomized trial evaluating carvedilol versus placebo in cardiotoxicity, the CECCY trial (Carvedilol Effect in Preventing Chemotherapy Induced Cardiotoxicity) [17], included 200 patients with breast cancer and use of anthracyclines and it showed no difference in LVEF between both groups. There was a slight decrease in left ventricle diastolic diameter in the carvedilol group.

However, the rate of events was lower than calculated (14.5% in the carvedilol group and 13.5% in the placebo group), which may have interfered on the results. Interestingly, in this study patients in the carvedilol arm had lower troponin values than the placebo arm, raising the possibility of subclinical cardiotoxicity protection.

Troponin (cTn) is a complex of three regulatory proteins (troponin C, troponin I, and troponin T) that are integral to muscle contraction in skeletal muscle and cardiac muscle. Prolonged ischemia, trauma, inflammation, or cardiotoxic agents may result in injury of cardiac cells. This injury is accompanied by the destruction of cell membranes and organelles and the release of cTn along with other proteins into the blood [18]. These proteins are the most studied biomarker in subclinical anthracycline-induced cardiotoxicity [6].

Cardiac troponin I (cTnI) elevation was described in one third of patients after high-dose anthracycline [7,19], and the degree of cTnI elevation was associated with the cumulative dose of anthracycline [20]. This biomarker is also associated with the degree of left ventricular dysfunction. In one cohort, patients achieving cTnI level over 0.5ng/mL presented significant and persistent LVEF reduction, while patients with transient LVEF decrease had cTnI levels below 0.5ng/mL [21]. In another study, cTnI values persisting >0.08ng/mL over a month after therapy was associated with 84% risk of cardiotoxicity, while cTnI below de reference range was associated with 1% risk [19].

Considering this correlation, Cardinale et al. studied cardioprotection using enalapril, an angiotensin converter inhibitor widely used in the management of heart failure, in 114 who developed positive troponin during anthracycline treatment compared to placebo [22]. The enalapril group had significantly lower incidence of heart failure and asymptomatic ventricular dysfunction. The same author studied 273 patients comparing enalapril in one arm in all patients before chemotherapy versus another arm using enalapril only in patients who developed positive troponin during chemotherapy [23]. There was no difference between groups, suggesting enalapril use could be triggered by troponin elevation.

Besides troponins, other biomarkers have been studied in subclinical cardiotoxicity. Natriuretic peptides have controversial correlation with cardiotoxicity in literature. Some evidence suggests association between NT-proBNP level and cumulative dose of anthracycline [24,25]. However, in two cohorts, while cTn predicted cardiac toxicity, natriuretic peptides did not [26,27]. Markers of inflammation and endothelial dysfunction are also target of research6, but they are less used in clinical practice.

Early identification of subclinical left ventricular dysfunction is also possible using global longitudinal strain (GLS), which is an evaluation of two-dimensional speckle-tracking allows for a study of global and regional myocardial deformation to detect subtle alterations in systolic function, particularly related to anthracyclines chemotherapy [28]. Evidence including a metanalysis of 21 studies and 1782 patients with cancer suggests GLS can identify subclinical myocardial dysfunction and also has prognostic implication regarding chemotherapy-induced cardiotoxicity or heart failure [7]. The use of GLS could identify patients with higher risk of cardiotoxicity and improve cardiac surveillance.

Using this rationale, the SUCCOUR study evaluated a GLS-based-approach to initiation of cardioprotection compared to standard care to reduce the risk of future LVEF decrement, interruption of cancer therapy or cancer therapy-related cardiac dysfunction (CTRCD) [29]. Anthracycline exposed-patients with another risk factor for heart failure were enrolled to start cardioprotection with ACEI and betablocker after LVEF reduction in 10% to less than 55% or 5% with symptoms of heart failure or after GLS relative reduction in 12%. Comparing both groups, there was no difference in final ejection fraction. However, at the final follow-up, 44 patients in the GLS-guided arm were treated with cardioprotective drugs versus only 20 patients had the same treatment. As a result, 21 patients (13.7%) in the ejection fraction-guided arm while only 9 patients (5.8%) in the GLS-guided arm met criteria for CTRCD (p=0.022), with a number needed to treat of 13. In a post-hoc analysis, the study also showed lower reduction in the ejection fraction among GLS-treated patients (2.9%) compared to ejection fraction-treated patients (9.1%).

Systematic cardiac surveillance with more sensitive technologies and a higher frequency of measurements will lead to a greater incidence of detected cardiotoxicity. In order to maintain a balance between the rational use of resources and maximal patient safety, new recommendation approaches take into account patient's baseline risk of cardiotoxicity [30]. Cancer patients scheduled to receive potentially cardiotoxic cancer therapies should be evaluated for cardiotoxicity risk according to the baseline cardiovascular profile and risk factors, pre-existing cardiovascular disease, type and dose of cancer therapy. This baseline cardiovascular risk will provide a personalized management plan for surveillance during cancer treatment.

Regarding cardioprotection, these evidences, especially from CECCY trial and SOCCOUR trial, suggest that cardiovascular medications in all patients without stratification do not translate in clinical benefit. However, they suggest that it is possible to identify patients with subclinical myocardial damage and therefore identify the subgroup that could benefit from intensive surveillance and cardioprotective medications. Current guidelines

recommend assessment of cardiac toxicity using LVEF measurement, but this approach needs to be changed. More sensitive and reproducible biomarkers such as troponin should be studied associated with GLS to precociously treat cancer therapy related therapy dysfunction and reduce morbimortality in this population.

Disclosure Statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the present manuscript.

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