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Troponins and natriuretic peptides to detect cardiotoxicity: useful biomarkers or paradise lost?

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This article refers to 'Troponins and brain natriuretic peptides for the prediction of cardiotoxicity in cancer patients: a meta-analysis' by L. Michel et al., published in this issue on pages xxx.

In the past decades potent antineoplastic treatments brought hope to the millions of patients with cancer. As a result of increased survival rates and prolonged life expectancy, cardiotoxicity presents as a significant complication of several old therapies, including anthracyclines, but also newer antineoplastic treatments, such as immunotherapy. In turn, the number of cancer survivors being affected by cardiovascular (CV) disease is steadily increasing.[1–3] There is an intense scientific interest in cardiotoxicity, but the understanding, definition, and treatment of patients with CV disease prior or due to antineoplastic treatment is still largely opinion-based, in the absence of strict evidence-based guidelines. Likely, patients prone to cardiotoxic complications may benefit from pre-emptive CV treatments. However, the overall risk for cardiotoxicity is not very high in many patients and inter-individual responses to antineoplastic treatments vary significantly. Therefore, it remains challenging to identify patients who will benefit from such treatments. Several studies have explored if elevations in CV biomarkers, most notably natriuretic peptides (NPs) and cardiac troponins (cTn) could be used to guide CV treatments.[4–7] However, these studies had small sample size and heterogeneous populations. At current, there is no consensus on the use of biomarkers and CV treatments in patients with cancer. There is a pressing need for prospective data to prove (or disprove) if cardiac biomarkers could predict LV systolic dysfunction in patients receiving antineoplastic treatments.

In the current issue of the Journal, Michel et al.[8] recognized the importance of this and present a systematic analysis of the data available in an effort to find optimal diagnostic and prognostic cardiotoxicity biomarkers. The authors focused their meta-analysis on the most frequently used antineoplastic treatments, such as anthracyclines, with or without the combination with trastuzumab, regimens commonly used in patients with HER2-positive breast cancer. Further, they restricted themselves to the cardiac biomarkers with the strongest rationale, given that they are cardio-specific markers, that have been studied most extensively: NPs, including B-type natriuretic peptide (BNP) or the N-terminal pro-BNP (NT-proBNP), and cTn, both high-sensitivity (hs) and conventional cTn assays.[9] They included trials that measured circulating cardiac biomarkers before and after chemotherapy, and demanded that included trials also evaluated left ventricular (LV) function prior to and after antineoplastic treatment, either by echocardiography, magnetic resonance imaging or radionuclide ventriculography. This resulted in a meta-analysis of in total 5691 patients. In their analysis the authors focused on three major points: the general response of circulating biomarkers to antineoplastic treatment, their significance in predicting chemotherapy-induced cardiotoxicity and lastly, their response to preventive treatments. Michel et al. should be applauded for their efforts of going through a substantial amount of data in an attempt to answer some of these fiery questions.

They demonstrate that a substantial percentage of patients (22%) show an increase in circulating cardiac biomarkers above the established cutpoint, either conventional cTn or hs-cTn, or BNP/NT-proBNP, after antineoplastic treatment. This validates, once again, that stringent cardiologic monitoring in patients receiving antineoplastic treatment, especially ones with the high CV risk profile, yields a high suspicion of cardiac damage. In addition, LV dysfunction was observed in 17% of patients. Indeed, those patients had higher cTn levels compared to the patients without LV dysfunction. The highest risk was observed in the high-dose chemotherapy subgroup (20%; 178/907). In this subgroup, the likelihood for LV ejection fraction impairment was much higher in patients with elevated cTn compared to cTn-negative patients [odds ratio (OR) 12, even more pronounced under high-dose regimens; OR was 98 in

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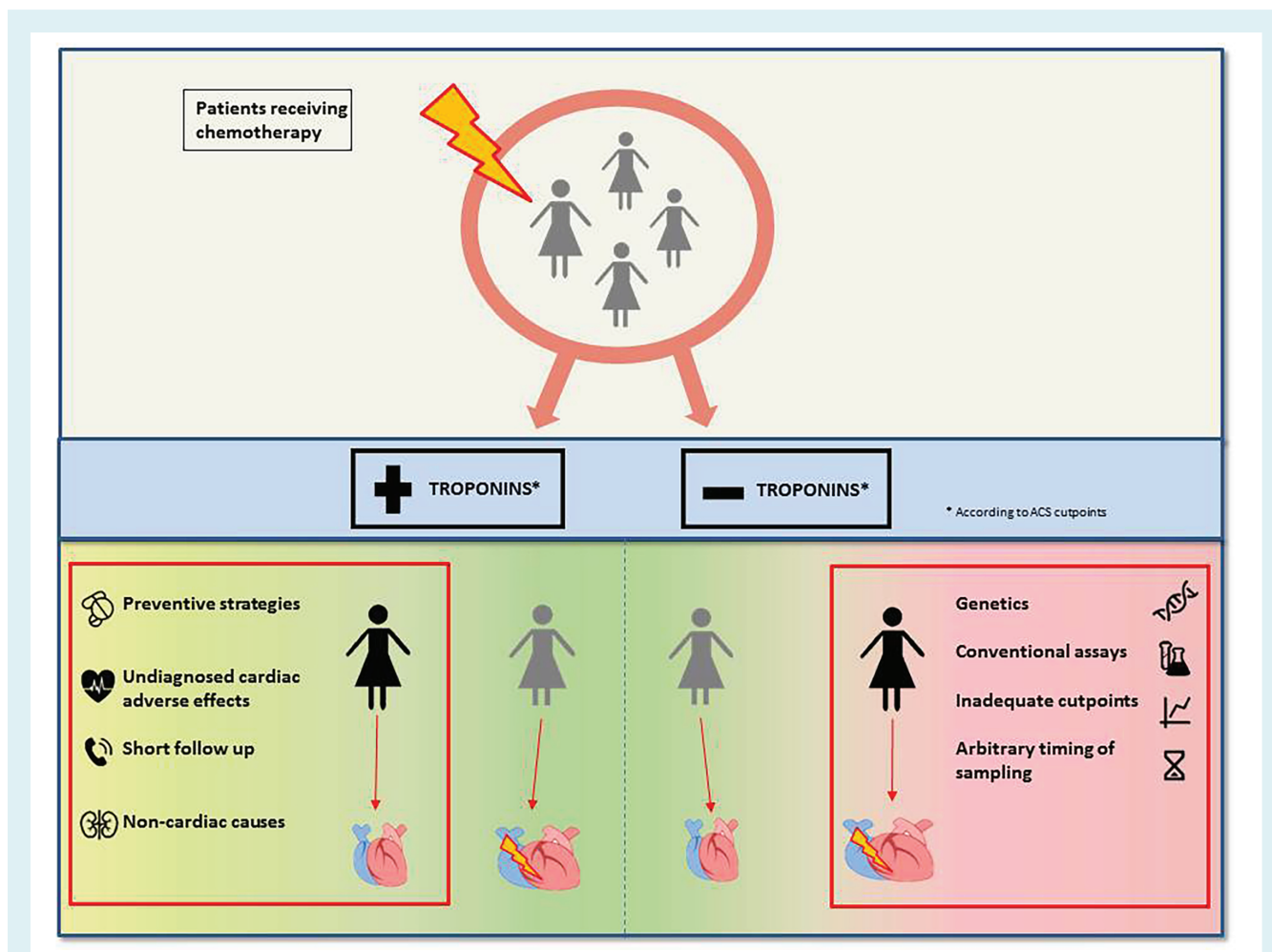
Figure 1 Illustration of different outcomes between troponin-negative and troponin-positive populations. The incidence of chemotherapy-induced cardiotoxicity is higher in the troponin-positive population [according to acute coronary syndrome (ACS) cutpoints], however some troponin-positive patients never develop left ventricular dysfunction (left side of the figure). On the other hand, some troponin-negative patients do develop left ventricular dysfunction (right side of the figure). Several factors may play a role in this apparent discrepancy, which have been described and include (but are not limited to) genetic factors, treatments, and methodological issues such as time of sampling and use of cutpoints.

this group!]. Clearly, cTn are powerful predictors of LV dysfunction, especially in high-risk patients. They are easy to measure, available in almost all automated platforms, and given frequent blood tests that oncology patients undergo, cTn could very easily be part of the standard blood draws.

Are the signals with cTn real and biologically meaningful? Notably, the studies included in the meta-analysis used without exemption the cutpoints as defined by the manufacturer. In other words, the employed cutpoints were optimized for ruling out acute coronary syndrome (ACS). Since cardiotoxicity and ACS have different pathophysiological mechanisms, optimal cutpoints for cardiotoxicity will likely differ. Furthermore, it has been demonstrated that cTn cutpoints are sex and age-specific, showing that women and younger patients generally exhibit lower levels. As a result, smaller but still significant deviations in cTn levels could have easily been missed.[10] In other words, it is likely that cardiac

injury in younger women will more often remain undiagnosed. This is not an academic discussion: 43% of the publications included in the meta-analysis studied only (female) patients with breast cancer, so that the true sensitivity and specificity of cTn in diagnosing early cardiac injury likely would significantly improve if sex and age-adjusted cutpoints would have been applied. Moreover, as also debated by the authors, conventional and hs-cTn assays may generate different results: hs-cTn could detect more patients at higher risk for developing cardiotoxicity than conventional assays,[11–13] although this meta-analysis could not validate this assumption. Compared to the conventional assays, the use of hs-cTn increases the sensitivity of diagnosing early myocardial injury due to ACS by detecting much lower values.[14] If we adopt the same logic in diagnosing myocardial damage due to cardiotoxicity, using hs-cTn should more accurately uncover young women with high CV risk for developing cardiotoxicity.

Finally, the most important aspect of biomarker response to antineoplastic treatments may be the timing of sampling. This is an hitherto relatively unexplored aspect of proper biomarker assessment. The sequel of events following chemotherapy and the exact timing of myocardial injury is still unclear. Distinct antineoplastic treatments and protocols, individual patient responses, and diverse preventive treatments may give rise to very heterogeneous dynamics of myocardial injury, and culminate in a very different timing of biomarker release. For the time being, we advocate that repetitive, standardized sampling, at fixed time points should be executed in future oncology trials, so that cardiotoxicity may be studied in the same vein as the efficacy of the oncolytic agents.

The signal for BNP/NT-proBNP was less clear. Elevated mean absolute BNP/NT-proBNP levels were more predominantly observed in patients with LV dysfunction treated with anthracyclines. We must take into account the much lower number of patients is being studied (far lower than for cTn), but other factors may also explain the differences. Troponins are immediately released after chemotherapy-induced damage to the cardiac muscle, whereas regulation of NPs is more complex and it is likely that NP levels start to increase over a longer time period. In our opinion, the current analysis does not rule out the usefulness of NPs in cardiotoxicity, but timing and cutpoints are not yet established. As for cTn, levels of BNP/NT-proBNP largely depend on sex and age, and co-morbidities importantly confound their levels.[15]

In addition to their main findings, the authors also present interesting data on specificity and response to treatment. Despite very robust OR for LV dysfunction for patients with elevated cTn (11.8, 95% confidence interval 4.3−32), and moderately robust OR for the patients with elevated BNP/NT-proBNP (1.7, 95% confidence interval 0.7−4.1) in this meta-analysis, no test is 100% specific. In other words, there were also patients with elevated cTn (48%) or BNP/NT-proBNP (71%) levels that did not develop LV systolic dysfunction. Clearly, the biomarker response is not linearly reflected by the cumulative dose of cardiotoxic therapies, but it is affected by a panel of factors, including genetics, environmental factors and diverse preventive treatments (*Figure 1*). In patients with cancer, this most likely weighs in even more, as e.g. infections, dehydration, kidney failure, and anaemia are more frequently observed.[16]

Lastly, with regard to preventive therapy, the authors show that treatment with beta-blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers significantly reduced cTn levels in patients treated with anthracyclines (OR 4.1). It has previously been suggested that preventive heart failure treatment diminishes the cardiotoxic effects of anthracycline and trastuzumab.[17,18] In a meta-analysis, where trials are pooled, it is inevitable that some granularity gets lost, e.g. it is possible that some of the trials included patients that are already receiving preventive treatment for any reason (hypertension, ACS primary coronary prevention).

The authors conclude that cTn and BNP/NT-proBNP should be recommended for monitoring patients receiving anthracyclines and anthracycline-combination chemotherapies. Although we agree that the signal elevated cTn and NT-proBNP levels sent is very strong, in the absence of adequate cutpoints and knowledge on the optimal timing of a sampling regimen, this recommendation remains vague at best. We believe that standard protocols for biomarker sampling will fill, to some extent, the knowledge gap we are faced with now. Generalized diagnostic protocols will improve and standardize the cardiotoxicity work-up, and help the cardio-oncology community to shape the terminology and diagnostic criteria. Only after this, treatment studies and algorithms may be designed, which will ultimately improve the outcomes of this complex and growing patient category.[19]

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