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Review

Detection and monitoring of cardiotoxicity by using biomarkers: Pros and cons
Remarks on the international colloquium on cardioncology.

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ABSTRACT

Long-term survival of cancer patients can be worsened by cardiovascular morbidity and mortality due to anticancer treatments, based on both traditional and novel anticancer drug-based regimens. The current standard for monitoring cardiac function, based on periodic assessment of left ventricular ejection fraction by transthoracic echocardiography or multi-gated radionuclide angiography, detects cardiotoxicity only when a functional impairment has already occurred, precluding any chance of preventing its development. The limitations of this approach may be surmounted by the use of cardiac biomarkers. Many studies performed both in children and in adults have shown that slight increases in troponins are predictors of further development of cardiac dysfunction. However, other studies failed to find any usefulness in troponin determination. These discrepancies may be due to different times of sampling, lack of standardization, the use of different methods with different sensitivity, and finally not uniformly defined cardiac endpoints. Beyond troponins, the most studied biomarkers in cancer patients treated with potentially cardiotoxic drugs are natriuretic peptides. For them no definite conclusions can be drawn; however, as the findings available in literature show different results. Still, most of data indicate that the persistent increase of BNP or NT-proBNP is associated with the evidence of cardiac dysfunction. Troponin is the gold standard marker for evaluating chemotherapy-induced cardiac injury; BNP and NT-proBNP are hemodynamic indexes. Hence, if we are looking for early myocardial damage during chemotherapy the most useful marker may be troponin; conversely, if we are looking for cardiac dysfunction in asymptomatic long-term cancer survivors, BNP and NT-proBNP are probably the biomarkers of choice.

1. Introduction

The extraordinary advances in pharmacological cancer treatments have led, in recent years, to a meaningful improvement in the prognosis of oncologic patients, reducing mortality for many forms of cancer [1]. Their effectiveness, however, may be thwarted by the cardiovascular toxic effects that a variety of different anticancer treatments can exert. Indeed, not only traditional cytotoxic chemotherapeutic agents, such as anthracyclines, but also novel, so called "targeted" therapies, such as monoclonal antibodies and small molecule tyrosine-kinase inhibitors, may affect the cardiovascular system, decreasing both quality of life and survival of patients [1]. As a consequence, a cardiologic surveillance aimed to prevent cardiotoxicity in patients undergoing anticancer therapy is, at present, of paramount importance.

2. Cardiac monitoring

The main goals of cardiac surveillance in cancer patients are:

- to detect myocardial injury early,
- to identify patients more prone to develop cardiotoxicity early on, and
- to initiate a prophylactic or cardioprotective treatment in high risk patients.

The current standard for monitoring cardiac function, based on periodic assessment of left ventricular ejection fraction (LVEF) by transthoracic echocardiography or multi-gated radionuclide angiography, detects cardiotoxicity only when a functional impairment has already occurred, precluding any chance of preventing its development [2,3]. This approach, in fact, represents a relatively insensitive tool for identifying cardiotoxicity at an early stage, or for predicting late declines in function, mainly because no considerable change in LVEF occurs until a critical amount of myocardial damage has taken place, and the damage only comes to the forefront after compensatory mechanisms are

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exhausted. Moreover, the evidence of a normal LVEF does not exclude the possibility of later cardiac deterioration. In addition, the measurement of LVEF presents several challenges related to image quality, the assumption of left ventricular geometry, load dependency, and expertise [4].

3. Can a biomarker approach help us to reach these goals?

The limitations of the assessment of LVEF may be surmounted by the use of cardiac biomarkers. Indeed, a novel approach, mainly based on the use of troponins, has emerged in the last decade, resulting in a cost-effective diagnostic tool for early, real-time identification and assessment and monitoring of cancer drug–induced cardiotoxicity. This approach seems to overcome most of the limitations of the techniques described above as it has proven to be more sensitive and more specific, cheaper, repeatable without damage to the patients, readily available even in small hospitals, and without inter-observer variability [4,5].

4. What characteristics does a biomarker have to have?

The characteristics of an ideal cardiac biomarker are high sensitivity, high specificity, it has to be measurable with a standardized and reproducible system, it has to be a cost-effective assay. Additionally, it has to have the following clinical characteristics: the ability to influence therapy and to improve patient outcome (Table 1) [6]. Troponins address all these points. Troponins are probably the best characterized marker for evaluating chemotherapy induced cardiac injury, being the most cardiac-specific biochemical markers among those currently available for the diagnosis of myocardial injury [5,6]. In addition to the nearly absolute cardiac tissue specificity, troponins have a high sensitivity for detecting very small necrosis that would not have been discovered in an earlier era using less sensitive biomarkers such as creatine kinase, and its MB iso-enzyme. The usefulness of troponins in the identification of drug-induced cardiac injury has been highlighted in a report by The Expert Working Group on Biomarkers of Drug-Induced Cardiac Toxicity of the Nonclinical Subcommittee of the Advisory Committee for Pharmaceutical Science, which is one of the foremost panels of the Food and Drug Administration [7]. From a clinical point of view, one of the most important indications for using cardiac troponins in the evaluation of drug-induced cardiotoxicity seems simply to be the monitoring of therapy employing anticancer drugs, mainly anthracyclines alone or in combination with other cytostatic agents [8]. The approach using troponins is minimally invasive, it costs less than echocardiogram and, particularly, it is less expensive than a nuclear LVEF assessment. Moreover, the interpretation of the results doesn't depend on the experience of the operator, thus avoiding the possibility of inter-observer variability.

The role of cardiac troponins as indicators of early anthracycline-induced cardiotoxicity and their ability to predict subsequent myocardial dysfunction has first been studied in animal models [9,10]. Troponin elevations have been shown to increase proportionally with escalating anthracycline doses administered; and correlated with the degree of cardiac damage noted on histology [10,11]. The clinical significance of these findings is supported by data showing that troponin elevations present during chemotherapy are associated with a significantly elevated risk of left ventricular dysfunction. The elevation of troponin levels during chemotherapy has been demonstrated in a number of populations, including hematological malignancies and breast cancer patients [12–21]. In these studies, the elevation of the marker preceded deterioration in echocardiographic cardiac function indexes. In addition to the evaluation of the risk based solely on absolute troponin levels, evidence that the magnitude and kinetics of troponin I and troponin T elevations appear to correlate with the degree of left ventricular dysfunction present in subsequent echocardiography checks [22]. Data from our group demonstrated these findings in high-dose chemotherapy treated patients [23–25]. Similar results were obtained in other studies involving hematological malignancies and breast cancer patients treated with standard dose chemotherapy [22]. Notably, troponins also provide valuable information when there is an absence of detectable levels, particularly in the case of troponin I, helping to identify patients who do not need close and long term follow-up for cardiovascular consequences [22]. Conversely, any troponin increase, which identify early patients at high-risk to develop cardiotoxicity, allows to plan in selected patients prophylactic strategies able to prevent the development of cardiac dysfunction and cardiac events [26].

Troponins also may be used to identify early cardiac injury in patients undergoing treatment with newer targeted cancer drugs, in breast cancer patients treated with trastuzumab, lapatinib [17,18,21], and in metastatic renal cancer patients treated with the tyrosine-kinase inhibitor sunitinib or sorafenib. [27] In these studies as well, increases in troponins predicted the development of late cardiac dysfunction and the occurrence of cardiac events. Our experience focused on the assessment of troponin I in 251 breast cancer patients treated with trastuzumab at our institution [28]. In these patients, troponin I was able to accurately identify patients at risk of developing cardiac dysfunction and, among them, those who will less likely recover from cardiotoxicity, despite optimized heart failure treatment. These findings suggest that troponins may be useful for assessing cardiotoxicity in patients treated with both conventional and newer cancer therapies. Possibly, the release of troponin reflects a final common event of multiple cardiotoxic mechanisms.

Table 1
Characteristic of an ideal cardiac biomarker.
Modified from Dolci et al. [6].

High-sensitivity
High concentration in myocardium after myocardial injury
Rapid release for early diagnosis
Long half-life in blood for late diagnosis
High specificity
Absent in non-myocardial tissue
No detectable in blood of non-disease subjects
Analytical characteristics
Measurable by cost-effective assay
Simple to perform
Rapid turnaround time
Sufficient precision and trueness
Clinical characteristics
Ability to influence therapy
Ability to improve patients outcome

5. Our approach at EIO (European Institute of Oncology)

On the basis of our overall clinical and research experience, we have suggested an approach focused on the identification of high-risk patients for cardiotoxicity by the evaluation of troponin levels during chemotherapy, coupled with a prophylactic treatment with enalapril to prevent its consequences [26]. This approach has been included in the latest version of the clinical practice guidelines on cardiovascular toxicity by the European Society for Medical Oncology (Fig. 1) [29]. In practical terms, we suggest a baseline evaluation before the beginning of chemotherapy, and a troponin evaluation before and soon after every chemotherapy cycle. In case of troponin positivity, we start a treatment with enalapril, without any interruption of the oncologic therapy. We closely monitor the patient during the first year after the completion of cancer therapy. On the other hand, in patients in whom troponin values remain below the cut-off value, we do not suggest close cardiac monitoring. We apply this approach in our daily clinical practice. We created an internal procedure to monitor patients undergoing oncologic therapy. This procedure has been shared also by our oncologist colleagues and it is available at our web site (www.ieo.it). We have used this approach in more than 2650 patients and the results have exceeded all expectations: during an 8-year follow-up, we have observed no significant reduction in systolic function from baseline neither in patients