



Anthracycline-induced cardio toxicity: Posing the right questions to find the correct answers

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Cardio toxicity in oncologic patients

Anthracyclines, such as Doxorubicin (Dox), are among the most effective anti-cancer agents but their clinical use is limited by cumulative dose-dependent cardiac toxicity, which leads to untreatable heart failure (HF) in a high percentage of patients. The primary problem posed by the harmful effects of these drugs are that their long-term use is impaired, leading to an incomplete exploitation of their anti cancer potential [1]. With increasing long-term cancer survivors, the number of patients experiencing anthracycline induced cardio toxicity is expected to grow [2]. According to estimates, there are, at present, several millions of cancer survivors in Western countries [3], many of which underwent chemotherapy treatments, thus being at risk of potential long-term cardiovascular toxicities. Indeed, the risk of cardiovascular death in these patients is higher than the actual possibility of tumor recurrence [4] with a seven-fold higher cardiac mortality rate in childhood cancer survivors [5]. The early identification of patients at risk for cardio toxicity is a current need for both oncologists and cardiologists, in order to counteract the development of cardiac impairment and its early

and late consequences. In the last years, the term Cardioncol-ogy has been coined to describe a new medical discipline with the aim of dealing with this important clinical need [6]. Anthracycline-induced cardio toxicity may manifest itself months or years after chemotherapy and can be categorized, by the time of presentation as acute, early-onset or late-onset. In acute anthracycline cardio toxicity, symptoms manifest within hours or days of administration, often presenting as disturbances in intracardiac conduction and arrhythmias. In rare cases, pericarditis and acute left ventricular (LV) failure can also occur [7]. Early-onset anthracycline-induced cardiac damage occurs within [1] year of treatment, and late-onset damage occurs ≥ 1 year after treatment. Early- and late-onset cardio toxicity are characterized by progressive LV dysfunction ultimately leading to HF. In many patients, subclinical echocardiographic abnormalities of LV structure and function are found in the first few years after anthracycline exposure, indicating that most patients experience cardiac injury soon after anthracycline administration and that the consequences of this injury worsen over time [8,9]. Susceptibility to toxicity varies in each patient suggesting possible genetic-based differences in processing anthracyclines [10].



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Cardio toxicity definition and assessment: A matter of the left ventricle

Despite the establishment of the harmful effect exerted by anthracyclines on the heart being now well in the past, there is still a huge controversy about the real definition of cardio toxicity. This issue is of no small consequence because it affects not only the way in which patients are treated, but also the way in which the research of new markers of toxicity is conducted. Indeed, the definition of cardio toxicity used in clinical and research settings can vary among different institutes. One widely accepted classification used in oncology is defined by the Cardiac Review and Evaluation Committee on trastuzumab-associated cardio toxicity and the ESMO Clinical Practice Guidelines. Cardio toxicity is defined as “a decrease of LVEF by 5% or more to less than 55% in the presence of symptoms of HF or an a symptomatic decrease in LVEF by 10% or more to less than 55%” [11]. Indeed, cardio toxicity can be defined as any heart injury (functional or structural) related to cancer treatment, and it usually equates (although not always) with the presence of left ventricular disease and HF onset. The ESC European Guidelines for the diagnosis and treatment of HF, published in 2016, classified HF into: reduced left ventricular ejection fraction (LVEF<40%), mid-range ejection fraction (LVEF 40-49%) and preserved ejection fraction (LVEF >50%) [12]. Many cardio toxicity-affected patients show HF with reduced ejection fraction, but there are probably also patients presenting HF with preserved ejection fraction. Indeed, currently there are clinical trials investigating the actual incidence of HF with preserved ejection fraction. Interestingly, in the last years, an increasing interest was registered regarding the effects of anthracyclines on right ventricular (RV) and left atrial (LA) function. The investigations involving the RV showed controversial results. Indeed, in some instances, partial functional impairment was detectable in patients even before treatment, possibly because of detrimental cardiac effects of the tumor itself. Additional studies, however, evidenced a negative effect of the drug on RV systolic function and remodeling.

Beside the RV, recent investigations clearly showed the functional impairment of the LA upon anthracycline treatment, thus introducing a new possible way of defining and diagnosing cardio toxicity. In particular, Shi and co-workers evidenced that early LA functional changes, detected by real-time three-dimensional echocardiography, can occur after doxorubicin exposure even inpatients with preserved LVEF [13]. Similarly, Yaylali et al. observed electromechanical delay (a predictor of atrial fibrillation measured by echocardiography) and mechanical function impairment after anthracycline-containing chemotherapy. The authors concluded that impaired left atrial electrical conduction could contribute to the development of atrial arrhythmias [14].

Circulating biomarkers of cardio toxicity

The current approach for detecting cardiotoxicity, based on the assessment of cardiac performance and cardiologic surveillance during and after chemotherapy completion by the evaluation of LVEF is not adequate for early stage assessment. This is largely due to the absence of a detectable change in LVEF until a critical amount of myocardial cell loss has already occurred. At that time cardiac damage is already present and, in most cases, not reversible, thus precluding any chance of preventing its development [15]. Indeed, complete recovery of cardiac function occurs in only around 40% of patients with chemotherapy-induced cardiomyopathy [16]. In addition, the evidence of a normal LVEF does not exclude the possibility of a late cardiac

deterioration. The gold-standard marker currently adopted in the clinical routine to identify patients at risk of cardio toxicity is cardiac Troponin (cTn). The presence of this protein in the plasma represents a reliable and quantitative established marker of the extent of myocardial injury. Several studies have demonstrated that cTn (and, to some extent, also BNP) can be used as a marker for myocardial injury in patients treated with anthracyclines and can partially predict the development of future left ventricular dysfunction, although not the time of its onset [17]. One limitation of cTn is the need to collect several blood samples at different time intervals after drug administration. In addition, very few patients show an increase in cTn levels during the first administration of chemotherapy, hinting to a need of progressive and cumulative damage during and after the therapy to observe a meaningful change in dysfunction markers. Further more, the best time point beyond which a negative value can assure that no further cTn release will occur is not predictable. The limitations of this marker hint at the need of new biomarkers to detect the onset of cardiac damage at a very early phase, possibly during the first cycle of therapy, allowing an early treatment and a possible increase in recovery rates.

Among all the possible contenders, circulating microRNAs (miRNA) represent very good candidate for this important task. miRNAs are short (22 to 24 nucleotides-long) non-coding RNAs, known to regulate complex biological processes by ‘fine-tuning’ the translation of specific messenger RNA targets [18]. They are pivotal modulators of mammalian cardiovascular development and disease, and can be stably found in the systemic human circulation and other animal species. Since their levels can change significantly upon different stimuli, circulating miRNAs have been successfully used as diagnostic biomarkers for several cardiac diseases [19-21] and can act as signaling molecules in response to specific stimuli and in the absence of cell damage such as during pregnancy [22]. Although many aspects of circulating and tissue miRNAs role and involvement in several cancers have been elucidated, to date there are only few studies linking circulating microRNAs and anthracycline cardiotoxicity [23]. One particularly interesting feature of the patient-based investigations is that cardiotoxicity was defined differently in each study, both in terms of cardiac damage onset evaluation (echography/troponin) and in terms of time of assessment post the initiation of anthracycline treatment. Indeed, the evaluation of miRNAs and other plasma markers was conducted from hours to months after chemotherapy administration. In these heterogeneous settings, a correct evaluation of toxicity onset and the correct identification of new biomarkers can become very difficult.

Conclusion

Cardiotoxicity is an old and established detrimental side effect of anthracyclines. Despite that, currently there is no clear and commonly accepted definition for this phenomenon. Indeed, the current guidelines for detection and treatment of cardio toxicity mostly rely on LV function assessment and on a few general biomarkers of heart damage and dysfunction. The lack of uniformity in the clinical assessment and response to cardio toxicity onset clearly hints to a strong change of direction. For this reason, future investigations should focus on better understanding the different involvement of all cardiac districts in cardio toxicity onset, possibly leading to the identification of new parameters to perform an efficient risk assessment before a real cardiac functional deficiency can start. In addition, the characterization of novel circulating markers will increase the ability

of assessing and answering to the detrimental effects of these important anti-cancer drugs.

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