

Biomarkers for the early detection of anthracycline-induced cardiotoxicity: current status

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Background. Cardiotoxicity is a well-known and potentially serious complication of anticancer therapy. Anthracycline-based chemotherapy represents the greatest risk. Early detection of cardiotoxicity is crucial for applying preventive and supportive therapeutic strategies.

Methods and Results. Various methods have been recommended for monitoring of cardiotoxicity. In our conditions, echocardiography and electrocardiography are routinely used. However, this approach shows low sensitivity for the early prediction of cardiomyopathy when the possibilities of appropriate management could still improve the patient's outcome. Recently, biomarkers of cardiac injury have been investigated in the assessment of chemotherapy-induced cardiotoxicity. Cardiospecific biomarkers, such as cardiac troponins, show high diagnostic efficacy in the early subclinical phase of the disease before the clinical onset of cardiomyopathy. Increase in their concentrations correlates with disease severity. As for natriuretic peptides, some studies, including ours, have shown promising results. Definitive evidence of their diagnostic and prognostic role in this context is still lacking and natriuretic peptides have not been routinely used for monitoring of cardiotoxicity in clinical practice. Other perspective biomarkers of cardiotoxicity in oncology are under study, especially heart-type fatty acid-binding protein (H-FABP) and glycogen phosphorylase BB (GPBB). Our studies using GPBB have provided encouraging results. However, the available data are limited and their practical use in this context cannot be recommended until their clinical efficacy is clearly defined.

Conclusions. This review covers the current status of biomarkers for the early detection of anthracycline-induced cardiotoxicity. The authors present in brief, their own experience with multiple biomarkers in the detection of cardiotoxicity.

Key words: biomarkers, cardiotoxicity, anthracyclines, chemotherapy

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INTRODUCTION

Cardiotoxicity is a well-known and potentially serious complication of anticancer therapy that can significantly impair the patient's quality of life and substantially increase health care costs. A wide range of chemotherapeutic agents are associated with cardiotoxicity. Of these, anthracyclines represent the greatest risk for development of cardiotoxicity. Despite conflicting reports, proposed risk factors for anthracycline cardiotoxicity include: 1. cumulative dose of the drug (the most important and independent risk factor), 2. age under 3 years or over 65 years, 3. irradiation of the mediastinum, 4. combination with other cardiotoxic chemotherapy (CT), 5. female gender, 6. heart damage caused by another disease (coronary atherosclerosis, arterial hypertension, diabetes mellitus, valvular heart disease), 7. bolus administration of the drug¹⁻³. High-dose chemotherapy (HD-CT) especially regimens containing high-dose Cyclophosphamide are also associated with high risk for development of cardiotoxicity^{4,6}.

In general, two forms of CT-induced cardiotoxicity⁷ may be distinguished: (1) Acute and subacute cardiotoxicity, found less frequently, can occur anytime from the initiation of CT up to 2 weeks after termination of treatment. In this form, the most common clinical findings range from abnormalities in ventricular repolarization and QT interval changes to supraventricular and ventricular arrhythmias or to acute coronary syndromes, acute heart failure, and pericarditis/myocarditis-like syndromes. (2) Chronic cardiotoxicity, the most frequent cumulative dose-dependent form, may be differentiated into 2 subtypes based on the timing of onset of clinical symptoms: early, within 1 year of the termination of CT, and late, after 1 year. The most typical sign of chronic cardiotoxicity is asymptomatic systolic and/or diastolic left ventricular (LV) dysfunction that leads to severe congestive cardiomyopathy and may eventually lead to death. The incidence of chronic cardiotoxicity depends on the presence of risk factors, time of follow-up, criteria used for cardiotoxicity definition and diagnostic methods used for cardiotoxicity identification, ranging in different studies from 5 to

65% of patients⁷⁻¹⁰. Anthracycline-induced cardiotoxicity is often divided into 4 subgroups: acute, subacute, chronic (occurring within 1 year of treatment) and late-onset (occurring more than 1 year after the completion of treatment).

DIAGNOSTIC METHODS FOR IDENTIFICATION OF CT-INDUCED CARDIOTOXICITY

Early identification of patients at risk for cardiotoxicity represents a primary goal for cardiologists and oncologists, considering personalized anticancer therapeutic strategies or interventions¹¹. For the detection of subclinical myocardial damage, time and expensive monitoring of cardiac functions is still recommended during and after CT (ref.^{7,12,13}). Nevertheless, most of the approaches commonly used in clinical practice – evaluation of left ventricular ejection fraction (LVEF) by echocardiography or radionuclide ventriculography¹⁴⁻¹⁹ – showed low diagnostic sensitivity and low predictive power in detecting subclinical myocardial injury^{9,20}. The use of some other techniques, such as endomyocardial biopsy, is troublesome in clinical practice owing to the invasiveness of the techniques^{12,13,21}.

Thus, there is a growing expectation for newer, non-invasive and cost-effective diagnostic tools for the early identification of patients susceptible to developing CT-induced cardiotoxicity²². The use of easily detectable cardiac biomarkers in blood has been evaluated in animal models and clinical studies²³⁻²⁷. Screening of high-risk patients is recommended for the detection of early subclinical cardiotoxicity.

Evaluation of cardiac biomarkers capable to specifically detect myocardial injury and to predict LV dysfunction could represent an alternative diagnostic tool for the early detection of cardiotoxicity²⁸. Previous reports consistently laid the theoretical basis for the possible use of cardiac troponins and natriuretic peptides in the early detection of cardiotoxicity in clinical practice, whereas creatine kinase MB (CK-MB) does not seem to be effective owing to a short time window of the serum elevation after myocardial injury and its imperfect cardiac specificity and sensitivity²⁹⁻³¹.

In 2011, a position statement from the Heart Failure Association of the European Society of Cardiology on “Cardiovascular side effects of cancer therapies” was published³². The main recommendations among others include that identification and validation of reliable biomarkers for the prediction and detection of cardiotoxicity of chemotherapeutic agents is urgently required. The use of simple biomarkers such as troponins and natriuretic peptides should be strongly considered but is not a substitute for objective evaluation by echocardiography or similar modalities. When designing clinical trials with potentially cardiotoxic agents, the routine use of currently available biomarkers (e.g. troponins and natriuretic peptides) should be strongly considered and their validation incorporated into the trial design, if possible.

The Expert Working Group on Biomarkers of Drug-Induced Cardiac Toxicity developed the following list of characteristics of “ideal biomarkers”, which includes specificity, sensitivity, kinetics of appearance in accessible media, robust assay, and ability to bridge between preclinical and clinical applications³³.

On this basis, we performed an analysis of the available scientific literature to define the clinical usability of cardiac biomarkers for the early detection of cardiotoxicity in oncology.

Cardiac troponins as markers of CT-induced cardiotoxicity

The clinical application of cardiac troponins as cardiotoxicity biomarkers was analyzed in several clinical studies with a consistent number of subjects monitored by cardiac troponin I (cTnI) or cardiac troponin T (cTnT), for the total number of almost 1 500 adult patients treated with CT for cancer³⁴⁻⁴⁰. The evidence emerging from these studies is that the percentage of patients with positive troponin values ranges from 15 to 34%. Thus, the increase in troponin concentrations in the blood underlines the occurrence of irreversible myocardial cell injury in patients treated with potentially cardiotoxic CT.

In our study on 23 patients treated with anthracycline-based CT for acute leukemia (mean age 47.0 ± 11.1 years, 14 males, mean total cumulative anthracycline dose 472.1 ± 115.0 mg/m²), cTnI became positive in 17.4% patients during CT and in 26.1% patients within 6 months after completion of CT. Our results suggest that evaluation of cTnI – in contrast with cTnT – during anthracycline treatment could identify patients at risk for development of anthracycline-induced cardiomyopathy in the future. CTnI seems to be superior to cTnT in the early detection of cardiac injury associated with anthracycline treatment in acute leukemia. The possible explanation could be the difference in molecular weight and release kinetics of cTnI and cTnT. Based on our preliminary data, a larger prospective and multicenter study would be most desirable⁴¹.

The agreement in defining the cut-off values for cardiac troponins (concentration measured with an analytic imprecision expressed as the coefficient of variation $\leq 10\%$), despite the availability of several methods for troponin determination, would lead to a useful unification of the definition of positive troponin results for the detection of myocardial injury related to cardiotoxicity. This cut-off provides the highest level of sensitivity for detection of myocardial injury at an acceptable level of analytic reliability. Adopting a univocal definition of positivity makes the troponin test very useful in clinical practice to monitor cardiac injury independent of the method used and of the laboratory performing the assay.

In contrast, the sampling protocol used in different studies is not as homogeneous as expected²⁵. It is important to note that the increase of troponin concentrations was detected at different intervals after administration of CT in various studies indicating that it may be necessary to collect several blood samples to demonstrate the possible increase of the marker⁴².

Clinical evidence derived from published studies can be summarized as follows: (1) Troponin determination is able to predict the occurrence of a clinically significant LV dysfunction at least 3 months in advance^{35,40}. (2) The early increase in the troponin concentrations also predicts the degree and severity of LV dysfunction in the future^{35,38}. (3) Among patients with positive troponin values, persistence of the increase within 1 month after the last CT is related to 85% probability of major cardiac events within the first year of the follow-up^{38,43}. (4) A persistently negative troponin test result can identify patients with the lowest cardiotoxicity risk (negative predictive value of 99%), who will not encounter cardiac complications at least within the first year after completion of CT.

From this scientific evidence, we can derive the main practical advantages of the use of troponin testing as a biomarker of cardiotoxicity, especially when it is compared with the low efficacy of any other method currently applied in this clinical setting: (1) Troponin determination detects the presence of cardiotoxicity very early, significantly before impairment of cardiac functions can be revealed by any other diagnostic method. (2) Immediately after the last CT, troponin determination allows the discrimination of patients at low risk from patients at high risk for cardiotoxicity requiring more careful long-term cardiac monitoring by imaging techniques.

The role of cardiac troponin determination to stratify the risk of cardiotoxicity is currently based on strong evidence clearly suggesting the routine use of this biomarker⁴⁴. Cardiac troponins have been incorporated into National Cancer Institute (NCI) classification of cardiotoxicity of anticancer therapy (Common Terminology Criteria for Adverse Events, CTCAE).

Natriuretic peptides as markers of CT-induced cardiotoxicity

Natriuretic peptides – atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and N-terminal pro brain natriuretic peptide (NT-proBNP) – are produced by the myocardium in response to wall strain and pressure overload. ANP is produced mainly in atria, BNP/NT-proBNP predominantly in ventricles. In cardiology, natriuretic peptides are routinely used in diagnostics and management of cardiac dysfunction and heart failure⁴⁵⁻⁴⁷. Normal plasma BNP/NT-proBNP concentrations practically exclude heart failure due to high negative predictive value of the test^{48,49}.

The applicability of natriuretic peptides (ANP, BNP, NT-proBNP) as markers for anthracycline-induced cardiotoxicity has been investigated in a limited number of studies. The results of some studies have suggested that natriuretic peptides could be of value in the detection of clinical and subclinical cardiotoxicity of anthracyclines⁵⁰⁻⁵⁴.

In our very first study, we evaluated the acute cardiotoxicity of the anthracycline agent, Idarubicin in induction CT for acute myeloid leukemia (15 patients, mean age 43.7 ± 10.6 years, 9 males). Our results suggested that induction CT for acute myeloid leukemia (Idarubicin 36 mg/m^2 and intermediate doses of Cytarabine) is in all

patients associated with acute neurohumoral activation (transient elevation of NT-proBNP) indicating acute subclinical cardiotoxicity. One patient experienced clinical cardiotoxicity within 2 weeks after induction CT. Since NT-proBNP elevations preceded the development of congestive heart failure after induction CT, we concluded that NT-proBNP seems to be a promising early marker and predictor of this complication. Hence, we suggest that serial measurements of plasma NT-proBNP could aid the early detection of cardiac dysfunction during anthracycline-based CT. Whether these acute changes are able to predict chronic and late cardiotoxicity is not clear. Studies are warranted in a greater number of patients and in patients with higher cumulative doses of anthracyclines and other risk factors for the development of anthracycline cardiotoxicity⁵⁵.

In another study, we evaluated acute and chronic cardiotoxicity of anthracyclines in 26 patients treated for acute leukemia (mean age 46.2 ± 12.4 years, 15 males, mean total cumulative anthracycline dose $464.3 \pm 117.5 \text{ mg/m}^2$). Our results showed that anthracycline-based CT is associated with acute and chronic neurohumoral activation of cardiac dysfunction that is manifested by a significant increase in NT-proBNP. NT-pro BNP correlated with LV dysfunction on echocardiography. It seems that NT-proBNP could be useful in the early detection of anthracycline-induced cardiotoxicity. Further studies on a larger number of patients and with a longer follow-up will be needed⁵⁶.

Recently published studies reported significant BNP/NT-proBNP elevations after HD-CT and hematopoietic cell transplantation⁵⁷⁻⁶⁰. Persistent BNP/NT-proBNP elevations early after HD-CT were observed in 33 – 47% patients and were associated with the development of cardiac dysfunction during the follow-up. The results suggest that monitoring of BNP/NT-proBNP could identify patients at risk for development of cardiac dysfunction after HD-CT and hematopoietic cell transplantation.

On the other hand, some studies using natriuretic peptides in the detection of CT-induced cardiotoxicity reported limited clinical usefulness of this method^{26,61,62}.

The published data are quite heterogeneous and often incomplete, lacking crucial information such as the ratio of patients with increased natriuretic peptide values, the methods used to measure natriuretic peptides and the cut-off values associated with the best diagnostic accuracy. Regarding the methods used to detect the occurrence of cardiac dysfunction, several articles reported the use of echocardiography or radionuclide ventriculography. Some authors studied the association and relationship between natriuretic peptides and diastolic LV dysfunction, and others simply checked systolic LV function. However, only a few studies^{55,63-67} evaluated the potential predictive value of natriuretic peptide concentrations to detect the ongoing development of cardiac dysfunction.

A lack of agreement in the conclusions of different studies is evident. Overall, studies were unable to confirm definitively the clinical usefulness of natriuretic peptides as cardiotoxicity biomarkers.

Even though there are some promising data available, it is not currently possible to recommend the routine use of the natriuretic peptides for monitoring of cardiotoxicity in clinical practice. New prospective studies on large cohorts of patients using validated, commercially available assays and comparing natriuretic peptides with well-established markers of cardiotoxicity are needed.

Perspective markers of CT-induced cardiotoxicity (under study)

Other potential markers of cardiotoxicity in oncology are under study, especially heart-type fatty acid-binding protein (H-FABP) and glycogen phosphorylase BB (GPBB).

H-FABP and GPBB are newer perspective markers for the early detection of myocardial ischemia and necrosis, recently evaluated in the diagnostics and risk stratification of acute coronary syndromes⁶⁸⁻⁷¹. H-FABP is a relatively small cytoplasmic protein for the oxidation of fatty acids that is quite specific for cardiac muscle. H-FABP is rapidly released from the myocardium after ischemic injury into the bloodstream. Plasma H-FABP increases above the reference limit within 2–3 h of the onset of myocardial injury and returns to normal values within 18–30 h. GPBB is a glycogenolytic enzyme providing glucose for the heart muscle tissue. During glycogenolysis in ischemic tissue, GPBB is released from the sarcoplasmic reticulum into the cytoplasm and then into the circulation through the damaged cell membrane. GPBB is released into the circulation 2–4 h after myocardial injury, returning to normal values within 24–36 h of damage occurrence. In the acute coronary syndrome setting, both markers are regarded as early markers of cardiac injury due to acute myocardial ischemia. The main mechanism of cardiac injury caused by anticancer therapy is mainly non-ischemic and prior cyclic exposure to anthracycline agents may play a role (chronic and late cardiotoxicity). Therefore, it is difficult to estimate the kinetics of release of these biomarkers from cardiomyocytes in this setting. Experience with these perspective biomarkers in the assessment of cardiotoxicity of anticancer therapy is very limited.

ElGhandour et al.⁷² studied H-FABP in 40 non-Hodgkin's lymphoma patients treated with 6 cycles of CT containing Doxorubicin (cumulative dose 300 mg/m²). The authors concluded that H-FABP may serve as a reliable early marker for prediction of cardiomyopathy induced by Doxorubicin.

Since 2007, we have published several papers dealing with multiple biomarkers of cardiac injury, including GPBB and H-FABP, to detect cardiotoxicity associated with CT for hematological malignancies – conventional CT containing anthracyclines and HD-CT followed by hematopoietic cell transplantation⁷³⁻⁷⁸.

In our study on 24 acute leukemia patients treated with anthracycline-based CT (mean age 48.1 ± 10.9 years, 13 males, mean total cumulative anthracycline dose 463.2 ± 114.3 mg/m²), we found significant elevations in GPBB after CT containing anthracyclines (in 16.7% and 20.8% patients, respectively). Increased release of GPBB from cardiomyocytes after administration of CT could be con-

sidered a sign of acute subclinical cardiotoxicity. Positivity of GPBB in patients with negativity of other cardiac biomarkers suggests that GPBB could be a more sensitive and promising marker for detection of acute cardiac injury caused by anthracycline-based CT, probably superior to cardiac troponins. Whether these acute changes will predict a development of cardiomyopathy in the future is not known and will be evaluated during a prospective follow-up. Further studies in a larger number of patients will be needed to define the potential role of new circulating biomarkers in the assessment of anthracycline-induced cardiotoxicity⁷⁵.

Other molecules have been proposed as markers for cardiovascular injury related to CT-induced toxic effect. Increase in markers of inflammation, such as cytokines, has also been described after CT. Mercuro et al.⁷⁹ and Mantovani et al.⁸⁰ reported a correlation between interleukine-6 increase and early changes in systolic LV function when analyzed by tissue Doppler imaging in a small sample of patients treated with Epirubicin containing CT. These preliminary results warrant confirmation by further investigations on a larger number of patients for a longer period of follow-up.

Several clinical studies have also analyzed endothelial damage in cancer patients. Nuver et al.⁸¹ reported an increased level of endothelial dysfunction markers in patients treated with CT several years before. Vaughn et al.⁸² also reported that long-term cancer survivors treated with CT showed increased markers of endothelial injury. These findings suggest that CT may induce endothelial dysfunction and accelerate atherosclerotic processes leading to an increased risk for future cardiovascular diseases⁸³. However, at present, no correlation with long-term cardiovascular events has been demonstrated and the predictive role of these markers is still unknown.

CONCLUSIONS

CT is a well-established therapeutic approach for several malignancies, but its clinical efficacy is often limited by CT-related cardiotoxicity which may lead to cardiomyopathy possibly evolving into heart failure. The most frequently adopted diagnostic method for detection of cardiac injury is evaluation of LVEF by echocardiography or radionuclide ventriculography. However, this approach shows low sensitivity for the early prediction of cardiomyopathy when appropriate management could improve the patient's outcome.

Cardiospecific biomarkers, such as cardiac troponins, show high diagnostic efficacy in the early subclinical phase of the disease, before the clinical onset of cardiomyopathy. The increase in their concentrations correlates with disease severity and may predict the occurrence of major cardiac events during follow-up. Negative troponin concentrations may identify patients with a low risk of cardiomyopathy. The role of cardiac troponin determination to stratify the risk of cardiotoxicity is currently based on strong evidence suggesting the routine use of this biomarker. Recently, natriuretic peptides have been investigated

in detection of CT-induced cardiotoxicity. Some studies, including ours, have shown promising results. However, definitive evidence of their diagnostic and prognostic role in this context is still lacking and natriuretic peptides have not been routinely used for monitoring of cardiotoxicity in clinical practice. Other perspective biomarkers of cardiotoxicity in oncology are under study, especially H-FABP and GPBB. Based on our data, a larger prospective and multicenter study will be needed to define the potential role of GPBB and other proposed biomarkers of cardiac injury in the assessment of cardiotoxicity induced by chemotherapeutic agents.

ABBREVIATIONS

ANP, Atrial natriuretic peptide; BNP, Brain natriuretic peptide; CK-MB, Creatine kinase MB; CT, Chemotherapy; cTnI, Cardiac troponin I; cTnT, Cardiac troponin T; GPBB, Glycogen phosphorylase BB; HD-CT, High-dose chemotherapy; H-FABP, Heart-type fatty acid-binding protein; LV, Left ventricular; LVEF, Left ventricular ejection fraction; NT-proBNP, N-terminal pro brain natriuretic peptide.

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