CME

Biochemical Markers for Prediction of Chemotherapy-Induced Cardiotoxicity

Systematic Review of the Literature and Recommendations for Use

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Upon completion of this activity you will be able to:
- define the most effective biochemical strategy to predict chemotherapy-induced cardiotoxicity in clinical practice.
- apply an evidence-based approach to biomarker utilization.
- examine the clinical evidence derived from published studies.

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Abstract

Chemotherapy is a well-established therapeutic approach for several malignancies, but its clinical efficacy is often limited by its related cardiotoxicity, which leads to cardiomyopathy, possibly evolving into heart failure. To detect cardiac damage, the adopted diagnostic approach is the estimation of left ventricular ejection fraction by echocardiography. This approach shows low sensitivity toward early prediction of cardiomyopathy, when the possibilities of appropriate treatments could still improve the patient's outcome. Cardiac troponins, however, show high diagnostic efficacy as early as 3 months before the clinical onset of cardiomyopathy. The increase in their concentrations is correlated with disease severity and may predict the new onset of major cardiac events during follow-up. Negative troponin concentrations may identify patients with a very low risk of cardiomyopathy (negative predictive value, 99%). Concerning cardiac natriuretic peptides, definitive evidence in regard to a diagnostic or prognostic role in predicting chemotherapy-induced cardiomyopathy is still lacking.

During the last 20 years, relevant improvements in the treatment of different malignancies have occurred, with a significant increase in the overall survival of patients with cancer.[1,2] Increasingly aggressive chemotherapy, however, has caused a comparable rise in serious adverse effects.

Bone marrow toxicity is successfully treated, in many cases, by blood cell growth factor infusion and/or hematopoietic stem cell transplantation. Conversely, cardiotoxicity remains a major limitation in standard and high-dose chemotherapy, strongly impacting the quality of life and the overall survival of many patients with cancer, regardless of the oncologic prognosis.

Moreover, owing to the increasing number of patients treated by chemotherapy and to the availability of new, more aggressive antineoplastic drugs (often administered in combination and at progressively higher cumulative doses) the incidence of cardiotoxicity is continuously growing.[3] However, our understanding of cardiotoxicity, from an epidemiologic perspective, remains inadequate for various reasons: investigations vary in methods and definition of cardiotoxicity; published data regarding risk factors are contradictory; longitudinal studies on well-defined cohorts, especially those treated with contemporary regimens restricting anthracyclines, are lacking; and knowledge of the relationship between abnormalities, identified by noninvasive cardiac testing, and clinical status of patient survivors is not well defined.[4]

The onset of cardiotoxicity, even if without symptoms, not only negatively affects the cardiologic outcome of patients with cancer, but largely reduces the range of suitable therapies.[5,6]

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Even subclinical cardiac impairment requires the use of less aggressive and, possibly, less effective antineoplastic drugs.

Commonly, 2 forms of chemotherapy-induced cardiotoxicity[5] may be distinguished: (1) Acute or subacute cardiotoxicity, found more infrequently, can occur anytime from the initiation of chemotherapy 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 in 2 subtypes based on the timing of onset of clinical symptoms: early, within 1 year of the termination of chemotherapy, and late, after 1 year. The most typical sign of chronic cardiotoxicity is asymptomatic systolic and/or diastolic left ventricular dysfunction that leads to severe congestive cardiomyopathy and may, in turn, ultimately lead to death. Incidence of chronic cardiotoxicity depends on different risk factors (eg, total administered dose of antineoplastic drugs, time of follow-up, patient age, sex, history of cardiac disorders, and previous mediastinal radiation) and on the criteria used for cardiotoxicity definition, ranging in different studies from 5% to 65% of patients.[5,7-9]

In the targeted therapy era of oncology, anthracyclines are still one of the most active cytotoxic drugs for the treatment of a wide variety of solid tumors and hematologic malignancies in adults and in children. Administration of anthracyclines, however, may induce cardiomyopathy and congestive heart failure, which is usually refractory to common medications.[7,8]

Although several drugs are potentially cardiotoxic **Table 1**, the drugs most commonly associated with cardiotoxicity are anthracyclines (doxorubicin and epirubicin), taxanes, alkylating agents, and trastuzumab, which belongs to the class of monoclonal antibodies against human epidermal receptor-2, that has recently been introduced in treatment of advanced breast cancer. Newly introduced nonreceptor tyrosine kinase inhibitors,[10] which induce modifications in cardiomyocyte cultures and in animal models,[11] can possibly determine cardiotoxicity in patients treated for cancer as well, but the question is still being debated.[12,13]

The mechanisms underlying acute heart failure and cardiotoxicity are not fully understood, but, in recent years, several hypothesized physiopathologic mechanisms leading to cardiotoxicity have been produced through basic and clinical research. For example, lipid peroxidation and the generation of free radicals by anthracycline-iron complexes have a major role; in fact, because protective antioxidant enzymes are present at lower levels than in other tissues, such as the liver and kidney, the heart is vulnerable to free radical injury, and the resulting damage to myocardial cells may eventually lead to irreversible heart failure. Following administration of different schemes of doxorubicin, changes in vascular endothelium–derived vasoactive mediators (endothelin-1 and cardiac nitric oxide), presumably involved in the development of cardiotoxicity, have been reported.[14] It has also been hypothesized that imatinib mesylate can induce cardiotoxicity by activation of the pathways of the endoplasmic reticulum stress response in exposed cardiomyocytes, leading to profound alterations of mitochondrial function and to cardiomyocyte death.[11]

Prevention of anthracycline-induced heart failure and clinically associated adverse events is critical in patients with cancer, particularly in children who can be expected to survive for decades after treatment. Attempts to minimize the cardiotoxicity of anthracyclines include dose limitation, schedule modification, use of less cardiotoxic analogues, and use of cardioprotective agents. Liposomal formulations of anthracyclines remain the best known alternative for improving the index and spectrum of activity with less cardiotoxicity of doxorubicin in clinical use.[15]

Some recent data have also emerged that deal with the role of various agents or drugs, such as erythropoietin;

Table 1
Chemotherapeutic Drugs With Potential Cardiotoxic Effects

Antibiotics cytotoxic
Anthracyclines
Doxorubicin
Daunorubicin
Epirubicin
Idarubicin
Mitoxantrone
Bleomycin
Alkylating agents
Cyclophosphamide
Ifosfamide
Cisplatin
Mitomycin
Busulfan
Antimetabolites
5-fluorouracil
Capecitabine
Methotrexate
Fludarabine
Cytarabine
Antimicrotubule agents
Paclitaxel
Docetaxel
Etoposide
Teniposide
Vinca alkaloids (vinorelbine)
Monoclonal antibodies
Trastuzumab
Rituximab
Tyrosine kinase inhibitors
Imatinib mesylate
Sunitinib
Miscellaneous
Tretinoin
Pentostatin
Interferon
Interleukin 2

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semisynthetic flavonoid; some free radical scavengers, like edaravone, and the use of antagonists of endocannabinoid receptors CB1 and phenylbutyrate, a histone deacetylase inhibitor, and their use as cardioprotectants against anthracycline-mediated cardiotoxicity.[16-19]

Diagnostic Strategy for Cardiotoxicity Identification

Early identification of patients at risk for cardiotoxicity represents a primary goal for cardiologists and oncologists, by allowing for the definition of personalized antineoplastic therapeutic strategies or interventions.[20] To detect subclinical myocardial damage, time and expensive monitoring of cardiac functions is still recommended, during and after chemotherapy.[5,21,22] Nevertheless, most of the approaches commonly used in clinical practice (echocardiographic left ventricular ejection fraction [LVEF] assessment and angiography with radionuclide) showed low diagnostic sensitivity and low predictive power in detecting subclinical myocardial injury. The use of some other techniques, such as endomyocardial biopsy, is troublesome in clinical practice owing to the invasiveness of the techniques.[5,21-25]

Hence, there is growing expectation for newer, noninvasive, and cost-effective diagnostic tools for the early identification of patients prone to developing drug-induced cardiotoxicity.[26] Use of easily detectable cardiac biomarkers in blood, such as cardiac troponins and cardiac natriuretic peptides (CNPs), has been evaluated in animal models and in clinical studies.[27-29] Screening of high-risk patients is recommended for the detection of early subclinical cardiotoxicity.

Conventional Strategies

At least 3 international consensus guidelines recommend evaluation of LVEF at the beginning of antineoplastic therapy, after administration of half the total anthracycline cumulative dose, and before every subsequent dose.[30-32] Moreover, during follow-up, LVEF evaluation 3, 6, and 12 months after the end of treatment is recommended.[5,25] A decline of LVEF by more than 10%, associated with an absolute LVEF value of less than 50%, is suggested as a criterion for suspending treatment.[33] Following this approach, the risk of developing clinically confirmed cardiac heart failure has been reduced, in some studies, to less than 5% in treated patients.[33,34]

However, some major limitations of this approach in clinical practice have been stressed.[26] Not all patients treated with chemotherapy require such frequently repeated LVEF monitoring as suggested by the guidelines because of the negative impact on patient management and cost-effectiveness ratio for the national health system.[35] Moreover, many doubts have been raised about the usefulness of monitoring cardiac function by LVEF evaluation only because the value of this monitoring seems to be neither sensitive nor specific enough to early predict development of cardiac dysfunction after chemotherapy. Thus, it permits the identification of cardiac damage only after the onset of cardiac dysfunction, not permitting any early interventional strategy able to prevent future cardiomyopathy.[8,36]

Biochemical Strategies

Searching for alternative diagnostic tools for early cardiotoxicity detection,[37] the evaluation of cardiac biomarkers able to specifically detect myocardial injury and to predict ventricular dysfunction could represent a valid strategy. Previous reports consistently laid the theoretical basis for the possible use of troponin and cardiac peptides in early detection of cardiotoxicity in clinical practice, whereas CK-MB does not seem to be effective owing to the short time window of the serum elevation after myocardial damage and its imperfect cardiac specificity.[38-41] However, by applying the established criteria of evidence-based medicine, it is clear that, before the clinical application of a new biochemical strategy to detect cardiotoxicity, we need to obtain well-defined scientific evidence about the following questions: What is the most effective biomarker? What is the most effective protocol for blood sampling? What is the marker cutoff concentration that gives the best diagnostic accuracy in terms of sensitivity, specificity, and predictive values?

On this basis, we performed an analysis of the available scientific literature to define the usefulness of well-standardized clinical use of cardiac biomarkers for detection of cardiotoxicity.

Cardiac Troponin as a Marker of Cardiotoxicity

After excluding a few articles based on personal, not standardized, anecdotal reports, the clinical application of cardiac troponin as a cardiotoxicity biomarker was analyzed in 7 studies with a consistent number of subjects (>40 patients enrolled) monitored by troponin I (cTnI) and T (cTnT), for a total number of almost 1,500 patients with cancer ▮**Table 2**▮.[42-48] The first strong evidence emerging from the comparative analysis of these studies is that in all the populations, with the exception of one that was markedly different in regard to the type of malignancies evaluated, the percentage of patients with positive troponin values ranges from 30% to 34%.[45] It appears evident, therefore, that in approximately one third of patients treated with potentially cardiotoxic chemotherapy, the increase in troponin concentrations in the blood underlines the occurrence of irreversible myocardial cell injury.

The second piece of evidence is that, even though cardiac troponin values are method-dependent, the cutoff values

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Table 2
Clinical Studies on Cardiac Troponin as a Marker of Chemotherapy-Induced Cardiotoxicity

Author/Year	Population Studied	No. (%) Troponin +	Troponin Type	Troponin Method	Cutoff (μg/L)	Comment
Cardinale et al,[42] 2000	Advanced neoplasia treated with HDC	204 (32)	I	Dade Stratus II	>0.50	No longer commercially available
Cardinale et al,[43] 2002	Breast cancer treated with HDC	211 (33)	I	Dade Stratus II	>0.50	No longer commercially available
Sandri et al,[44] 2003	Advanced neoplasia treated with HDC	179 (32)	I	Dade Stratus CS	>0.08	Cutoff established at the concentration measured with an imprecision CV ≤10%
Auner et al,[45] 2003	Blood cancers	78 (15)	T	Roche Elecsys (third generation)	>0.03	Cutoff established at the concentration measured with an imprecision CV ≤10%
Cardinale et al,[46] 2004	Advanced neoplasia treated with HDC	703 (30)	I	Dade Stratus CS	>0.08	Cutoff established at the concentration measured with an imprecision CV ≤10%
Lipshultz et al,[47] 2004	Acute lymphoblastic leukemia in children	76 (32)	T	Roche Elecsys (third generation)	>0.03	Cutoff established at the concentration measured with an imprecision CV ≤10%
Kilickap et al,[48] 2005	Advanced neoplasia treated with HDC	41 (34)	T	Roche Elecsys (third generation)	>0.01	Cutoff corresponding to detection limit of the method*

HDC, high-dose chemotherapy; CV, coefficient of variation.
* Detection limit of the method is the lowest concentration of the analyte, ie, cardiac troponin, truly measured by the method as significantly different from the noise of the analytic system.

applied in all studies except 1 are highly comparable, referring, in any case, to the troponin concentration measured with an analytic imprecision expressed as the coefficient of variation of 10% or less.[49] This cutoff provides the highest level of sensitivity for detecting myocardial damage at an acceptable level of analytic reliability. Any laboratory could monitor an imprecision profile of the troponin method in use on the site.[50]

This agreement in defining the cutoff, despite the availability on the diagnostic market of several methods for the troponin determination, leads to a useful harmonization of the definition of positive troponin results for the detection of myocardial injury related to cardiotoxicity. Adopting a univocal definition of positivity makes the troponin test very useful in clinical practice to monitor patients independent of the method used and of the laboratory performing the assay.

Conversely, the sampling protocol used in different studies is not as homogeneous as expected.[29] It is important to note that the increase of troponin concentrations was detected at different intervals after chemotherapy administration in the various studies, indicating that it may be necessary to collect several blood samples to demonstrate the possible increase of the marker.[51]

The mechanisms responsible for troponin release after chemotherapy are still being defined. Results of previous studies, such as the low incidence of coronary risk factors, the absence of history of coronary artery disease, and the lack of any symptom associated with typical electrocardiographic changes in the patients studied, support the nonischemic etiology of the serum troponin increase after chemotherapy.[46] Furthermore, the persistence of cTnI elevation, observed in some studies, after 1 month or more from the finish of chemotherapy, suggests the occurrence of a release pattern different from ischemic injury.[45,52] In acute coronary syndromes, indeed, troponin typically returns to baseline within 10 days and is associated with, not followed by, ventricular dysfunction.[53]

Although the increase of cTnI could possibly be elucidated by acute anemia and sepsis, in a large population, the incidence of these 2 complications after high-dose chemotherapy was equally distributed between troponin-positive and troponin-negative groups of patients.[46]

Clinical evidence derived from published studies can basically be summarized as follows: (1) Troponin determination is able to predict, at least 3 months in advance, the occurrence of a clinically significant dysfunction of the left ventricle.[43,48] (2) The early increase of the troponin concentrations also predicts the degree and severity of future left ventricular dysfunction.[43,46,54] (3) Among patients with positive troponin values, persistence of the increase 1 month after the last chemotherapy administration is related to an 85% probability of major cardiac events within the first year of follow-up.[46,55,56] (4) A persistently negative troponin test result can identify, with a predictive negative value of 99%, patients with the lowest cardiotoxicity risk, who will, most likely, never encounter cardiac complications, at least within the first year after the end of chemotherapy.

From this scientific evidence, we can derive the main practical advantages of the use of troponin testing as a cardiotoxicity biomarker, especially when it is compared with

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the low efficacy of any other strategy currently applied in this clinical subset: (1) Troponin determination detects the presence of cardiotoxicity very early, significantly before impairment of cardiac function can be revealed by any other diagnostic technique. (2) Immediately after the last chemotherapy administration, troponin determination allows for the discrimination of patients at high risk for cardiotoxicity (requiring strict monitoring of the cardiac function by imaging techniques) from patients at low risk (not requiring cardiac monitoring). (3) This determination can lead to a relevant economic impact in oncologic patient management, improving the cost-benefit ratio, because troponin-negative subjects can be safety excluded from long-term cardiac monitoring programs, which require high-cost imaging techniques.

Troponin peak value was observed at different intervals after high-dose chemotherapy, so that several samples were required to detect it. Furthermore, the time point at which a negative troponin value reached 100% of specificity for no further troponin releases cannot be defined. This represents a possible limitation for using the marker in clinical practice, but the cost of troponin measurement appears justified and absolutely cost-effective when negative values allow for the exclusion of most patients from a long-term monitoring program with expensive imaging methods such as echocardiography and radionuclide angiocardiography. In a recent work, high-dose chemotherapy–treated patients with a high risk of cardiotoxicity, defined by an increased cTnI value, showed that early treatment with enalapril seemed to prevent the development of a late form of cardiotoxicity.[56]

We emphasize that the need to frequently obtain blood samples for troponin testing could make this approach unsuitable in some ways for outpatients because they would need daily monitoring. However, the clinical subset most commonly monitored for cardiotoxicity is represented by hospitalized patients treated with high-dose chemotherapy.

In clinical practice, an interesting perspective that requires further scientific evidence is the ability of troponin to identify subclinical stages of cardiotoxicity, allowing for specific cardioprotective therapies aimed at slowing or blocking the evolution of left ventricular dysfunction due to cardiotoxicity.[57-59] In a recent study in pediatric patients affected by acute lymphoblastic leukemia and treated with doxorubicin, cTnT was evaluated in monitoring the cardioprotective efficacy of dexrazoxane, a drug known to reduce oxidative damage induced by free radicals.[47]

Cardiac Natriuretic Peptides as Markers of Cardiotoxicity

The recent development of the knowledge of CNP physiopathology and the improvement of the methods used to assay these molecules have clarified their diagnostic and prognostic role in cardiovascular diseases, particularly congestive heart failure.[60] The B-type natriuretic peptide (BNP) and the amino-terminal fragment of its precursor (NT-proBNP) represent efficient markers of ventricular dysfunction as they are rapidly produced and secreted by the heart in response to the ventricular wall distention.

It was, therefore, logical to associate the increased blood concentrations of these markers with the onset of chronic cardiotoxicity, which represents a pathophysiologic model of overload cardiomyopathy[27] evaluating B-type CNPs as markers of cardiotoxicity in a group of about 500 oncology patients **Table 3**.[61-73] The data, however, are quite heterogeneous. They mainly consider the different populations studied, adults and children, affected by hematopoietic cancers or solid malignancies, usually with a small population enrolled (>100 patients only in 1 study).[69] Furthermore, data reported are often incomplete, lacking crucial information such as the rate of patients with increased CNP values, the methods used to measure CNP**,** and the cutoff 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, some authors studied the association and relationship between CNP and diastolic dysfunction, and others simply checked ventricular function, but only a few studies[63,64,70,71,73] evaluated the potential predictive value of CNP concentrations in the blood to detect the ongoing development of cardiac dysfunction. Finally, only 3 reports used a commercially available, fully automated assay, producing results directly transferable in different clinical settings.[70,71,73]

Beyond the limitations reported herein, a lack of uniformity in the conclusions of different studies is evident. Some case reports showed small increases of CNP concentrations after chemotherapy, others reported fully or partially negative results; overall, studies were unable to definitively confirm the usefulness of CNPs as cardiotoxicity biomarkers.

Although the relevance of the inhibitory effect of doxorubicin on the genetic expression of BNP (shown in an animal experimental model[74]) is still unknown, recently reported preliminary data concerning a small cohort of patients seem to suggest a possible paradoxical effect with a reduction of the NT-proBNP concentration in patients treated with this drug.[75]

In lieu of definitive evidence, it is not currently possible to recommend the use of the CNP assay to assess cardiotoxicity in clinical practice, even if some results may suggest this possibility. New prospective studies, including large cohorts of patients, using well-validated and commercially available methods that compare BNP/NT-proBNP assays with well-established markers of cardiotoxicity, such as cardiac troponins, are needed. Furthermore, in a

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Table 3
Clinical Studies on B-Type Natriuretic Peptides as Markers of Chemotherapy-Induced Cardiotoxicity

Author/Year	Population Studied	No. (%) NP+	NP Evaluated	Method for BNP/NT-proBNP	Cutoff	Conclusions
Suzuki et al,[61] 1998	Blood cancers	27 (?)	BNP	Not defined	Not defined	Concentrations increased after treatment
Nousiainen et al,[62] 1998	Acute myeloid leukemia	10 (?)	BNP	RIA method, homemade	Not defined	BNP associated with diastolic dysfunction
Nousiainen et al,[63] 1999	Non-Hodgkin lymphoma	28 (25)	BNP	RIA method, homemade	8.5 pmol/L	BNP not predictive
Okumura et al,[64] 2000	Acute leukemia	13 (?)	BNP	Shonogi IRMA (manual)	40 ng/L	BNP not correlated with LVEF, but associated with future CHF
Hayakawa et al,[65] 2001	Pediatric cancers	34 (?)	BNP	Shonogi IRMA (manual)	Not defined	Concentrations increased in patients with diastolic dysfunction
Meinardi et al,[66] 2001	Breast cancer	39 (?)	BNP	Shonogi IRMA (manual)	Not defined	Concentrations increased after treatment, but not associated with ventricular dysfunction
Nousiainen et al,[67] 2002	Non-Hodgkin lymphoma	28 (?)	BNP	RIA method, homemade	Not defined	BNP associated with diastolic dysfunction
Poutanen et al,[68] 2003	Pediatric cancers	39 (?)	BNP	Shonogi IRMA (manual)	Not defined	No clinical usefulness
Daugaard et al,[69] 2005	Advanced neoplasia treated with HDC	107 (?)	BNP	RIA method, homemade	Not defined	Not useful to replace estimation of LVEF
Sandri et al,[70] 2005	Advanced neoplasia treated with HDC	52 (69)	NT-proBNP	Roche Elecsys	Male, >88 ng/L (≤50 y); >227 ng/L (>50 y); female, >153 ng/L (≤50 y), >334 ng/L (>50 y)	Persistent increase associated with development of cardiac dysfunction
Horacek et al,[71] 2005	Acute myeloid leukemia	15 (?)	NT-proBNP	Roche Elecsys	Not defined	Concentrations increased after treatment
Pichon et al,[72] 2005	Breast cancer	79 (49)	BNP	Shonogi IRMA (manual)	51.3 ng/L	To predict development of CHF, sensitivity, 83.3% (CI, 52%-97%); specificity, 90.2% (CI, 86%-94%)
Soker and Kervancioglu,[73] 2005	Blood cancers	31 (?)	NT-proBNP	Roche Elecsys	Not defined	Concentrations increased in patients with ventricular dysfunction

BNP, B-type natriuretic peptide; CHF, congestive heart failure; CI, 95% confidence interval; HDC, high-dose chemotherapy; IRMA, immunoradiometric assay; LVEF, left ventricular ejection fraction; NP, natriuretic peptide; NT-proBNP, B-type propeptide aminoterminal fragment; RIA, radioimmunoassay.

recent systematic review[76] that evaluated the effectiveness of different cardiac markers, mainly natriuretic peptides, to assess anthracycline-induced cardiotoxicity in children with cancer, results showed limited evidence, making conclusions problematic.

Conclusions

Cardiotoxicity has a strong impact on patients with cancer, in clinical and prognostic terms. Early detection is crucial for applying preventive and supportive therapeutic strategies. The role of cardiac troponin determination to stratify the cardiotoxicity risk is currently based on strong evidence clearly suggesting the routine use of this biomarker.

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