Journal of Translational Science

Mini Review

ISSN: 2059-268X

Determination of early tumoricidal drug-induced cardiotoxicity with biological markers

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Abstract

Cardiotoxicity due to tumoricidal drug use is defined as an asymptomatic reduction in left ventricular (LV) ejection fraction (EF) of ≥ 10% to <55% or as a reduction of the LVEF of ≥ 5% to <55% with symptoms of heart failure (HF). The implementation in routine practices the highly tumoricidal anthracycline drugs, taxanes, and trastuzumab cause progressive LV dysfunction and symptomatic HF in dose-dependent manner. Despite there is potent reversibility of tumoricidal drug-induced cardiotoxicity, this adverse effect frequently consists continuously and might lead to limited response to medical treatment and worse survival sufficiently. The aim of the mini review is consideration the clinical evidence that supports the use of cardiac biomarkers for early detection of cardiotoxicity. The review is reported that the identification of cancer patient with increased risk of early cardiotoxicity would allow not only prevention and diagnosis of chemotherapy related cardiotoxicity but also administration of optimal dose and duration of chemotherapy. The predictive role of brain natriuretic peptides, cardiac troponins, microRNAs, S100A1 and inflammatory biomarkers (C-reactive protein) is discussed.

Introduction

Cardiotoxicity as resulting in anti-neoplastic chemotherapy, radiation therapy, and targeted agents is well recognized and frequently considered an expected adverse effect [1]. The implementation in routine practice the highly tumoricidal anthracycline drugs, taxanes, and trastuzumab cause progressive left ventricular (LV) dysfunction and symptomatic heart failure (HF) in dose-dependent manner [2,3]. The improved survival rate raises the likelihood that patients will experience wide spectrum cardiotoxicity: from asymptomatic diastolic dysfunction to acute severe HF [4]. Although reversibility of tumoricidal drug-induced cardiotoxicity is possible [5,6], in generally, this adverse effect frequently consists continuously and might lead to limited response to medical treatment and worse survival sufficiently [7,8]. Despite the majority of patients with LVEF decline from cancer therapy could achieve full LVEF recovery and complete their cancer therapy, there is no consensual agreement regarding strategy to management cardiac dysfunction in this patient population [9]. Additionally, there are no developed clinical guidelines for early detection of cardiotoxicity too. It has been suggested that biomarkers, most prominently brain natriuretic peptides (BNPs), cardiac troponins, inflammatory biomarkers (C-reactive protein, soluble ST, galectin-3) and signature microRNAs might have utility to stratify the patients at risk of potential cardiac dysfunction at early stage before clinical manifestation [10,11]. The aim of the mini review is consideration the clinical evidence that supports the use of cardiac biomarkers for early detection of cardiotoxicity.

Definition of cardiotoxicity

According Cardiac Review and Evaluation Committee criteria cardiotoxicity due to tumoricidal drug use is generally characterized by an asymptomatic reduction in LVEF of ≥ 10% to <55% or, less often, as a reduction of the LVEF of ≥ 5% to <55% with symptoms of HF [12]. The cardiac dysfunction associated with anthracycline therapy leads to significantly decline of LVEF and frequently associates with asymptomatic and symptomatic HF, whereas trastuzumab-induced cardiotoxicity is most often reversible upon discontinuation of treatment and initiation of standard medical care for HF [13,14].

Molecular pathogenic mechanisms underlying anthracycline-induced cardiac toxicity

It is well known that pivotal role in anthracycline-induced cardiotoxicity belongs to oxidative stress, which mediates worse of myofilament protein synthesis, destroying structured protein, and cytoskeleton, and as well as apoptosis of cardiac myocytes [15-17]. Therefore, anthracycline is able to suppress reparative capable of cardiac myocytes via inhibition of cardiac progenitor cells mobbing and differentiation [18,19]. It has been suggested that calcium overload resulting in alterations in cardiac myocites metabolism leads to ultrastructural changes in cytoskeleton and mediates development of asymptomatic myocardial dysfunction and subsequently clinically manifested HF [20,21]. Thus, molecules that are able reflect these multiple faces of pathophysiology of cardiotoxicity are considered potent surrogate candidates in biomarkers with diagnostic and predictive value.

Biomarkers of cardiotoxicity

Radiotherapy and drug exposure with anthracyclines, monoclonal

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Key words: *cardiotoxicity, anti-neoplastic chemotherapy, biomarkers, natriuretic peptides, C-reactive protein, troponins, risk stratification*

Received: January 07, 2016; **Accepted:** January 23, 2016; **Published:** January 26, 2016

antibodies, fluoropyrimidines, taxanes, alkylating agents, vinka alkaloids were reported to induce different clinical manifestations of cardiotoxicity including development of cardiac dysfunction. In this context, some biomarkers may be used to evaluate cardiac damage and clinical events in follow up. The promising biomarkers of cardiotoxicity are reported in Table 1.

Brain natriuretic peptides

Because of assessment of the LVEF fails to detect subtle alterations in cardiac function in chemotherapy-treated patients, BNPs could predict future cardiac dysfunction. Current clinical guidelines serve measurement of BNP as a marker of biomechanical stress for diagnostic and predictive value in generally population patients at high risk of HF development and in those who have acute or symptomatic chronic HF with volume overload [22-25]. Theoretically, cardiac dysfunction as result in chemotherapy might reflect in stretching of cardiac wall and secretion of BNP in circulation. However, the received results were controversial and frequently relate to treatment regime, the adjuvant setting and concomitant therapy. Sawaya *et al.* [26] reported that NT-proBNP did not predict cardiotoxicity patients treated with anthracyclines and trastuzumab. Fallah-Rad *et al.* [27] were not able to find sufficient changes in serum concentrations of troponin T, C-reactive protein, and BNP among trastuzumab-treated patients with human epidermal growth factor receptor II-positive ($HER2^+$) breast cancer.

Contrary, Cil *et al.* [28] have found a closely association between higher NT-proBNP levels and reduced LVEF in asymptomatic breast cancer patients after doxorubicin administration. Authors have shown that NT-proBNP could be an early indication of subclinical acute anthracycline cardiotoxicity. Ürun *et al.* [29] have believed that women with $HER2^+$ breast cancer treated with trastuzumab could early stratify at risk of cardiotoxicity with of NT-proBNP (>300 ng/ml). Moreover, Horácek *et al.* [30] have reported that transient elevation of NT-proBNP may indicate acute subclinical cardiotoxicity in anthracycline-treated patients with acute myeloid leukemia. Thus, it seems to be that NT-proBNP could be useful in the early detection of anthracycline cardiotoxicity [31], while trastuzumab-induced cardiotoxicity is probably not defined by measurement of serum NT-proBNP [32].

High-sensitivity cardiac troponins

The results regarding predictive value of high-sensitivity cardiac troponins in anthracycline and trastuzumab cardiotoxicity are controversial. This controversial relates that anthracyclines, even in higher cumulative doses, do not usually cause detectable acute injury to cardiomyocyte structure. Indeed, Horacek *et al.* [32] reported that high-sensitivity cardiac troponin T was not elevated in patients treated for acute leukemia with anthracycline, although serum level of NT-proBNP was elevated sufficiently and could be useful in the early detection of anthracycline cardiotoxicity. In another study, in contrast to BNP, elevated high-sensitivity cardiac troponin I level was proposed an independent predictor of the development of cardiotoxicity at 6 months in cancer patients treated with anthracyclines and trastuzumab [25]. Additionally, there are evidences regarding that the early increase in high-sensitivity cardiac troponin I might offer additive information about the cardiotoxicity risk in cancer patients undergoing doxorubicin and trastuzumab therapy [33-35]. Interestingly, there was not a sufficient correlation between cTnT and oxidative stress parameters [36]. In this context, commonly used biomarkers of oxidative stress cannot reliably predict cardiovascular dysfunction, whereas circulating cardiac troponins remained attractive as a marker of cardiotoxicity. Overall, biochemical markers of structural and functional myocardial damage, such as cardiac troponins, might have utility in cardiotoxicity monitoring in doxorubicin- and trastuzumab-treated individuals.

High-sensitivity C-reactive protein

High-sensitivity C-reactive protein (hs-CRP) is discussed a predictive biomarker of increased risk of cardiotoxicity among cancer patients treated with anthracycline and trastuzumab [37]. Onitilo *et al.* [38] reported that elevated hs-CRP (≥ 3 mg/L) predicted decreased LVEF with a sensitivity of 92.9% and specificity of 45.7% in patients with early $HER2^+$ breast cancer. Interestingly, author found that the maximum hs-CRP value was observed a median of 78 days prior to detection of cardiotoxicity by decreased LVEF, and those with normal levels were at lower risk for cardiotoxicity. This result opens a perspective to regular monitoring of hs-CRP level for identifying women with early-stage breast cancer at low risk for asymptomatic trastuzumab-induced cardiotoxicity. In contrast, Lipshultz *et al.* [39] did not find closely association between increased hs-CRP and any echocardiographic variables in doxorubicin-treated subjects with acute lymphoblastic leukemia, although cardiac troponin T and NT-proBNP were related to an abnormal LV thickness-to-dimension ratio, suggesting LV remodeling. In general, definitive validation studies are required to fully establish clinical utility of hs-CRP in cancer patients as biomarker of cardiotoxicity.

S100A1

S100A1 is a Ca^{2+} binding protein of the EF-hand type that belongs to a family of multifunctional proteins characterized by predominantly specific expressions in heart, to a lesser degree in skeletal muscle, and at low levels in most normal tissues [40]. There is evidence regarding ability of S100A1 to improve cardiac contractile performance both by regulating sarcoplasmic reticulum Ca^{2+} handling and myofibrillar

Table 1. The promising biomarkers of cardiotoxicity.

Biomarkers	Relation to pathophysiological process	Clinical relevance	References
NPs	Biomechanical stress	Could indicate acute subclinical cardiotoxicity	[28-30]
Troponins	Cardiac injury	Independent predictor of the cardiotoxicity	[25,32]
Oxidative stress components	Cardiac injury, inflammation	Lack of evidence regarding prediction of cardiotoxicity	[36]
hs-CRP	Inflammation	Prediction in decreased LV pump function and early cardiotoxicity	[37,38]
S100A1	Cardiomyocyte integrity	Prognostication in heart failure and early cardiotoxicity	[42-44]
miRNAs	Regulators of expression of protein-coding genes	Prognostication in early cardiotoxicity	[47-49]
Placental growth factor	Angiogenesis, neovascularization	Unknown	-
Soluble FMS-like tyrosine kinase receptor-1	Vascular remodeling	Unknown	-

Abbreviations: NPs, natriuretic peptides; hs-CRP, high-sensitivity C-reactive protein; LV, left ventricular.

Ca^{2+} responsiveness [41]. In animal studies down-regulation of S100A1 protein was shown to contribute to cardiac failure after acute myocardial infarction via impaired Ca^{2+}cycling, β adrenergic signaling, induce oxidative stress and mitochondrial dysfunction and [42,43].

Eryilmaz *et al.* (2015) [44] reported that trastuzumab and lapatinib could induce cardiotoxicity via free-radical-induced alteration of the expressions affected both troponin I and S100A1. Because S100A1 is up-regulated only in cancers of kidneys, skin and ovary, authors concluded that S100A1 might become promising biomarker in assessing the state of myocardium exposed to toxicity accompanying to hs-CRP and cardiac troponins [44]. Whether S100A1 might help to detect subclinical cardiotoxicity at early stage is not clear.

MicroRNAs

MicroRNAs (miRNAs) are endogenous, small noncoding RNAs that are able to modulate post-processing in target cells via regulating expression of protein-coding genes [45]. Wide spectrum of skeletal muscle- and cardiac-specific miRNAs (miRNA-12, miRNA-133a, miRNA-124 and miRNA 208) miRNAs has been investigated as circulating biomarkers of myotoxicity [46]. Because several miRNAs have exhibit tissue specificity, stability in extracellular space, high conservation between preclinical test species, and might express as response on direct tissue injury, it has been suggested that signature of microRNAs might be useful as biomarkers of cardiac injury [47,48]. Calvano, et al. [47] reported that miRNA-133a/b are sensitive and specific markers of skeletal muscle and cardiac toxicity and that miRNA-208 used in combination with miRNA-133a/b can be used to differentiate cardiac from skeletal muscle toxicity. Desai *et al.* [49] using a chronic doxorubicin cardiotoxicity mouse model found that pro-apoptotic miRNA-34a showed a significant dose-related up-regulated and was associated with down-regulation of hypertrophy-related miRNA-150. Authors suggested that these findings may lead to the development of biomarkers of earlier events in doxorubicin-induced cardiotoxicity that occur before the release of cardiac troponins [49]. By now, the development of miRNAs as clinical biomarkers has been hindered by the lack of standardization [50]. In this context, extracellular miRNA-based biomarkers have not been embraced as diagnostic tools, while their implication in early drug toxicity is considered as very attractive.

Future perspectives

Because of biomechanical stress biomarkers (BNP, NT-proBNP), markers of myocardial injury (cardiac troponis) and inflammation (hs-CRP) are not specific for cardiotoxicity and might not help to sufficiently individualize treatment by immediately identifying cardiac injury and HF, novel biomarkers are discovered widely. It has been suggested that several cardiac biomarkers reflected inflammatory reactions and oxidative stress, *i.e.* growth differentiation factor-15, myeloperoxidase, galectin-, miRNAs, and S100A1 could useful for prediction of the risk of early cardiotoxicity. Probably, biomarkers of angiogenesis (placental growth factor), vascular remodeling (soluble FMS-like tyrosine kinase receptor-1) might be demonstrated the benefit in this setting too. In this context, more investigations are required to consolidate our knowledge regarding utility of biomarkers of cardiotoxicity in cancer patients.

Conclusion

In conclusion, one can suggest that the identification of cancer patients with increased risk of early cardiotoxicity would allow not only prevention and diagnosis of chemotherapy related cardiotoxicity but also administration of optimal dose and duration of chemotherapy. However, the determining optimal biomarker(s) for risk stratification strategy is not completely clear and requires more investigations.

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