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Review article

Troponins and natriuretic peptides for the prediction of anthracycline and/or trastuzumab-induced cardiotoxicity in cancer patients

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Abstract In recent decades, advances in oncology have remarkably improved cancer-related mortality rates. However, this has increased the spectrum of long-term sequelae from anti-cancer treatments including cardiovascular dysfunction. Cardiotoxicity has emerged as a leading cause of morbidity and mortality among cancer patients, specifically due to left ventricular dysfunction. The early detection of patients who are at increased risk of developing cancer therapy–related cardiovascular disease is required to establish appropriate preventive and therapeutic strategies. Cardio-specific biomarkers could predict cardiotoxicity during antineoplastic treatment. Troponins and natriuretic peptides are the preferred biomarkers for management of cardiovascular function in patients exposed to potential cardiotoxic anti-cancer drugs, particularly in individuals treated with anthracyclines and anti-human epidermal growth factor receptor 2 (HER-2) monoclonal antibodies. Further examinations are needed to evaluate novel surveillance clinical pathways integrating troponins (troponin I/T) and natriuretic peptides (NT-proBNP/BNP) for cancer patients receiving associated anthracycline and/or trastuzumab chemotherapy.

Kew words cardiotoxicity, anthracycline, trastuzumab, natriuretic peptides, troponin

Introduction

Cardiovascular disease in cancer patients represents leading medical problem, causing morbidity and premature mortality[1]. Age-standardized cancer incidence in the Europe is estimated to be 374 cases per 100 000 population (excluding non-melanoma skin cancer), and number of individuals with cancer is projected to increase to 4.75 million cases and 2.55 million deaths in 2040[2].

Cardiotoxicity rates may vary from 0% to 48% of patients, with heart failure (HF), coronary artery disease, atrial fibrillation, arterial hypertension, thromboembolic disease, valvular disease, pulmonary hypertension, stroke and peripheral vascular disease, being frequent clinical presentations[3]. Myocardial dysfunction, defined as a decrease in left ventricular ejection fraction (LVEF) > 10% from baseline to a final LVEF below the lower limit of normal (< 53%), and HF are the most frequently recognized therapy-related cardio-vascular problems[4]. Despite early (within one year) and late cardiovascular toxicities (years or even decades after chemotherapy termination) associated with various cancer therapies (chemotherapy, immunotherapy, radiotherapy), survival of cancer patients is improving due to earlier detection and effective treatment strategies[5,6]. Moreover, the average 5-year survival of malignant tumors has reached 54.2%[7].

Anthracyclines and anti-human epidermal growth factor receptor 2 (HER-2) monoclonal antibodies such as trastuzumab, are the agents most clearly associated with increased risk for developing cardiac dysfunction, although other newer antineoplastic drugs (vascular endothelial growth factor pathway inhibitors, proteasome inhibitors, and immune checkpoint inhibitors) have also been reported to cause cardiovascular complications[8]. Even in the era of targeted cancer treatments, anthracyclines, either alone or in combination, remain the cornerstone for many types of cancer therapies including pediatric cancers, breast, lymphoma, sarcoma, and leukemia[9,10].

Associated risk factors for developing treatment-related cardiac dysfunction include the existence of cardiovascular diseases, age and LVEF reduction before treatment[11]. There have been proposed risk scores on the basis of age, type of chemotherapy and comorbidities such as hypertension, diabetes mellitus, coronary disease, atrial fibrillation/flutter, and renal failure[12]. High-risk patients must not be treated with anthracycline, while low risk patients will receive normal doses of anthracycline and/or immunotherapy (monoclonal antibodies used in HER+ breast cancer)[13]. These drugs caused a dose-dependent and mainly irreversible

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Table 1. The most common biomarkers used in cardio-oncology

Cancer type	Treatment	Patient cohort	Biomarker	Reported cardiotoxicity	Author
diffuse large B-cell lymphoma or follicular lymphoma grade 3	epirubicin doxorubicin	100	hs-cTnT	16.1%	Xue et al., 2016[32]
breast	epirubicin trastuzumab	40	hs-cTnT	10.0%	Kitayama et al.,2017[41]
breast	doxorubicin trastuzumab	45	NT-proBNP	33.3%	Bouwer et al.,2019[55]
breast	doxorubicin trastuzumab	61	NT-proBNP	29.5%	El-Sherbeny et al.2018[44]
diffuse large B-cell lymphoma	doxorubicin	130	NT-proBNP	12.2%	Ferraro et al.,2019[49]
breast	trastuzumab anthracycline	66	NT-proBNP	27.3%	Blanqas et al., 2020[56]
breast	anthracycline	149	BNP	34.9%	Lu et al., 2019[51]
breast	anthracycline trastuzumab	56	hs-cTnT NT-proBNP	30.3%	Sendur et al.,2015[46]
leukemia lymphoma breast	doxorubicin trastuzumab	52	hs-cTnI NT-proBNP	9.6%	Mahjoob et al.,2019[48]
breast	doxorubicin trastuzumab	254	hs-cTnI NT-proBNP	19.3%	Demissei et al., 2020[39]
hepatoblastoma rhabdomyosarcoma myeloid sarcoma	anthracycline	131	cTnT NT-proBNP	1.5%	Hu et al., 2018
breast	doxorubicin	14	cTnI NT-proBNP	10.0%	Zhou et al., 2020
breast	trastuzumab anthracycline	50	cTnI NT-proBNP	14.0%	Benkridis et al., 2020

cardiotoxicity (e.g.,anthracyclines, specially doxorubicin with cumulative doxorubicin dose of ≥ 500 mg/m2 h) or mostly reversible form of cardiovascular toxicities (e.g.,anti-HER-2 antibodies)[14,15]. The incidence of cardiotoxicity in patients receiving trastuzumab alone is 3–7%, anthracyclines before trastuzumab 5%, and anthracyclines alone is reportedly 4–36% (6% have clinically overt cardiotoxicity)[15]. Therefore, many randomized clinical trials have demonstrated that dexrazoxane, ACEi/ARB and β-blockers therapy was beneficial to improve cardiac dysfunction and prevent HF induced by doxorubicin or trastuzumab[16-18].

Serial monitoring of circulating biomarker levels can estimate cardiotoxicity during and after treatment accurately and efficiently[19]. Recognition of cardiotoxicity at preclinical stage, through cardiac biomarkers such as cardiac troponins (cTn) and natriuretic peptides (NPs) would be pivotal for the application of preventive strategies (Table 1)[20]. Based on current guidelines, NT-proBNP and cTn in conjunction with cardiac imaging should be considered for monitoring patients at high risk of developing cardiotoxicity[21].

Cardiac troponin (cTn)

cTn represent a structural proteins that bind to the actin in myofilaments and regulate muscle contraction[22]. Detectable serum levels of cTnI/T are an indicator of of myocardial cells damage (with a peak serum concentration 12 h after myocardial injury)[23]. Measurement and interpretation of cTn are part of the diagnosis of acute myocardial infarction (AMI), HF, pulmonary embolism and arrhythmias. High-sensitive troponin assays improve time to diagnosis of AMI (elevated serum hs-cTn at the time of admission or at re-test above the 99th percentile of healthy individuals) and predict CVD in asymptomatic individuals or known CVD[23,24].

cTn as early marker of cancer cardiotoxicity may quantify both cardiomyocyte apoptosis and myofibril degradation more than necrosis. cTn elevation occurs in 21% - 40% of patients after anthracycline chemotherapy, regardless of assay type[25].

Hs-cTnI assays are extremely sensitive and precise, allowing for earlier and faster detection of cardiotoxicity compared with contemporary assays[26]. Anthracycline would induce oxidative stress and inhibit topoisomerase II causing myocardial damage, LVD, HF, ventricular arrhythmia in breast cancer patients and subsequent elevation of hs-troponin I[27-29]. Hs-cTnI concentration after only a single treatment dose cycle was a strong predictor of subsequent myocardial injury in study of Tzolos et al. Also, a threshold of 5 ng/l predicted following myocardial injury in the highest tertile before cycle 6, with a sensitivity of 69% and a specificity of 86% (c-statistic ¼ 0.80; 95% confidence interval 0.64-0.96)[30].

In comparative trial of CPOP-R (cyclophosphamide, doxorubicin, vincristine, prednisone– rituximab) versus CHOP-R (substituting doxorubicin for pixantrone) as first-line therapy in diffuse large B-cell lymphoma, doxorubicin demonstrated high long-term cardiotoxicity associated with declines in LVEF ≥15% and ≥20% from baseline and elevations in serum cTnT[31,32]. In PRADA

study was confirmed that there was a dose-dependent increase in hs-cTnI, hs-cTnT, and suggests that these biomarkers may be the best tools for monitoring the immediate cardiotoxic effects of anthracyclines. Moreover, a significantly less increase in hs-cTnI and hs-cTnT levels suggested that beta blockade with metoprolol may have anticardiotoxic effect through inhibition of beta-adrenergic–mediated proapoptotic pathways[33].

Treatment targeting HER2 has dramatically improved the survival of patients that overexpresses HER2, which is estimated to occur in up to 25% of breast cancer. Trastuzumab induces cardiomyocytes apoptosis, ultrastructural changes in the mitochondria and interferes with cell survival mechanisms[34]. But, this therapy may lead to development of congestive HF, LVD and systemic hypertension[35-37].

In the study by Yu et al. cardiac biomarker testing with contemporary cTnI assay wasn't correlated with clinically significant myocardial injury or volume or pressure overload in patients with metastatic breast cancer treated with dual anti-HER2 therapy[38]. Moreover, recent studies with repeated measures of hs-cTnT or hs-cTnI gave evidence that both troponin elevations were uncommon with trastuzumab therapy alone[39,40]

Although conventional cTnT assays could not predict chemotherapy-induced cardiotoxicity, study of Kitayama et al. showed normal LVEF and elevated hs-TnT levels after trastuzumab following anthracycline administration suggesting subclinical myocardial damage due to anthracycline, that would have otherwise remained unrecognized[41]. In the cohort of 206 patients, maximum hs-cTnT concentration after anthracycline treatment was a significant determinant for trastuzumab-induced LVEF decline. The amount of cTnT is expected to be a marker for the injury induced by anthracyclines because troponin T was derived from-by cardiac cells damaging, where trastuzumab is hypothesized to cause functional alterations in contractile proteins[42]. In contrast to anthracycline/trastuzumab-induced cardiomyocyte injury, trastuzumab alone may cause transient cardiac dysfunction without long-term consequences[43].

Brain natriuretic peptides (BNPs)

Natriuretic peptides (BNP or its amino-terminal cleavage equivalent- NT-proBNP), generated from ventricular myocardium during hemodynamic stress, are widely used to establish the presence and severity of HF and shown to be sensitive markers of LVD and powerful markers of morbidity and mortality in HF[44]. Studies on BNP/NT-proBNP in detecting cardiotoxicity are controversial[45-47].

The number of patients with elevated NT-proBNP, scheduled to undergo the first course of anthracycline-based chemotherapy, raised about 2-fold from baseline during the 4 months follow-up (cut off 304 pg/ml for baseline NT-proBNP with 97.8% specificity and 40% sensitivity). However, sensitivity doubled when considering the 3-week NT-proBNP concentrations (cutoff point: 490 pg/ml), but NT-proBNP was similar between the two groups of patients with and without cardiotoxicity. This may reflect that NT-proBNP would be used for revealing cardiac stress in long-term follow-up[48]. Ferraro et al. also reported that the cumulative incidence of cardiotoxicity in 130 patients with diffuse large B-cell lymphoma (DLBCL) is around 12% at 1 year and 27% at 10 years after starting therapy. In this study median time to development cardiotoxicity was 6.4 months, an overall 4-fold cardiotoxicity risk increase for adult DLBCL patients with NT-proBNP levels of 600 pg/mL or more at baseline[49].

Recent study in children with most common malignant tumors (hepatoblastoma, rhabdomyosarcoma, myeloid sarcoma) have also verified that abnormal NT-proBNP levels were significantly related to cumulative anthracycline dosage (>200 mg/m2) and showed its suitability in predicting delayed cardiotoxicity[50].

Recent data by Lu et al. demonstrated that elevation of serum BNP levels in cardiotoxicity diagnosis was not very effective, with considerable misdiagnosis or missed diagnoses (negative predictive value 0.762, positive predictive value 0.583), but detected BNP levels after the fourth dose (9 weeks after the initial chemotherapy course) of anthracycline chemotherapy could predict the cardiotoxicity for a median time period of 1.5 years[51]. In a multicenter controlled trial ICOS-ONE, BNP remained within the normal range during 3-years of follow-up, but in older and patients who received higher doses of anthracycline (were consistently elevated over time[52].

BNP/NT-proBNP for the identification of acute/subacute cardiotoxicity is limited because of overall low sensitivity (52.6%). A stronger association of BNP/NT-proBNP with LV dysfunction and higher sensitivity of 76.9% was within the small group of childhood cancer patients who received high-dose anthracycline treatment (≥240 mg/m2 of doxorubicin or doxorubicin-equivalent dose[53].

The NeoALTTO sub-study examined an anthracycline-naïve early breast cancer population receiving anti HER-2 antibodies and NT-proBNP was detected in few cases, so this biomarker wasn't useful in these patients[54]. Bower et al. concluded that NT-proBNP cannot be used as a monitoring tool for trastuzumab-induced cardiotoxicity during the first year of treatment, as the changes were too subtle and could barely be distinguished from normal intra-subject variability. In this study sample only patients with early-stage breast cancer treated with anthracycline before trastuzumab and individuals who showed an LVEF decline during pre-treatment appeared susceptible for trastuzumab-induced cardiotoxicity[55].

The latest a retrospective observational study involving 66 patients with HER2-positive breast cancer treated with trastuzumab (87.9% of them received anthracyclines before or in combination with trastuzumab) proposed a synergistic effect of both treatments on cardiac risk. In this setting, NT-proBNP levels above the upper limit of the normal range adjusted to age may correlated with the occurrence of cardiotoxicity[56].

Brain natriuretic peptides and cardiac troponins (BNPs/cTn)

Increased NT-proBNP values have been associated with cardiotoxicity in patients treated with anthracycline or

anthracycline in combination with trastuzumab with a normal or reduced LVEF, specially in long-term follow up. Furthermore, not every study demonstrated an association between NT-proBNP and cardiotoxicity possibly due to the type of treatment, sample size, the specific assay used, the wide biological variation (analytical and intra-individual), secretory burst, rapid turnover, cut-off values for clinically meaningful changes and timing of sampling and, probably most relevant, the definition of cardiotoxicity[55,57,58]. Increased cTn levels correspond to myocardial dysfunction, early cardiotoxicity and cardiac damage due to high doses of anthracyclines[59]. In contrast to anthracycline/trastuzumab-induced cardiotoxicity, cTn or BNP/NT-proBNP wasn't capable to predict adverse cardiovascular events in patients receiving trastuzumab.

Conclusion

NT-proBNP and cTn are the most promising screening tool for baseline risk assessment and early cardiac damage or strain which may predict decrease in LVEF and following HF in various cardiotoxic cancer therapeutics including anthracycline and trastuzumab. Cardiac biomarkers may be valuable for guiding primary prevention treatment or monitoring late side effects in survivors. Further studies are needed to clarify and optimize their role in routine clinical practice.

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Sažetak

Troponini i natriuretični peptidi u predviđanju kardiotokcičnosti izazvane antraciklinima i/ili trastuzumabom kod pacijenata obolelih od kancera

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Poslednjih decenija, napredak u onkologiji je u velikoj meri uticao na stopu smrtnosti od kancera. Međutim, povećao se i spektar dugotrajnih posledica koje uključuju i kardiovaskularne poremećaje, a koje su prouzrokovane antikancerogenim tretmanima,. Kardiotoksičnost, posebno disfunkcija leve komore, je postao vodeći uzrok mortaliteta i morbiditeta kod obolelih od kancera. Rano otkrivanje pacijenata kod kojih postoji povećan rizik od razvijanja kardiovaskularnog oboljenja nastalog usled primene antikancerogene terapije je potrebno kako bi se uspostavile odgovarajuće preventivne i terapijske strategije. Kardiospecifični biomarkeri mogu predvideti kardiotokcičnost nastalu tokom terapije. Troponini i natriuretični peptidi su odgovarajući biomarkeri za praćenje srčane funkcije kod pacijenata izloženih antikancerogenim lekovima, antraciklinima i monoklonskim antitelima na humani epidermalni factor rasta. Dalja istraživanja su neophodna kako bi se procenio novi klinički pristup koji obuhvata primenu troponina (troponin I/ T) I natriuretičnih peptida (proBNP/BNP) za obolele od kancera koji primaju antracikline i/ili trastuzumab.

Ključne reči: *kardiotoksičnost, antraciklini, trastuzumab, natriuretični peptidi, troponin*