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Biochemical and echocardiographic markers for the early detection of cardiotoxicity under monoclonal antibodies therapy

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ABSTRACT

The progress made over the past years in the field of cancer therapy has led to a significant decrease in cancer mortality, but these therapies have many adverse effects, cardiovascular effects being among the most frequent ones. For increasing lifelong expectancy of surviving cancer patients, cardiac monitoring represents an important task. Current studies and practice recommend echocardiography using strain analysis for monitoring the cardio toxic effects of cancer therapy. The potential of combining imaging techniques with biomarkers for the early detection and diagnosis seems a promising path for future research.

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Introduction

The progress made over the past years in the field of cancer therapy has led to a significant decrease in cancer mortality. However, these therapies have many adverse effects, cardiovascular effects being among the most frequent ones. In addition to the fact that they decrease the quality of life, they can lead to a reduction in the overall survival rate, independently of the prognosis of cancer disease [1]. In fact, the term cardiotoxicity refers to myocardial dysfunction and heart failure (HF), the most redoubtable complications of these therapies, which occur in variable proportions, being estimated at 1.7-20.1% for trastuzumab and 1.6-4% for bevacizumab [2].

Currently, efforts are aimed at the early detection of left ventricular dysfunction (LVD) for the initiation of prompt treatment, without compromising cancer therapy. Many studies investigate the role of biomarkers in the early detection of LVD, before this becomes severe enough to induce a decrease in the left ventricular ejection fraction (LVEF). Among the most studied markers, there are cardiac troponins and natriuretic peptides [3].

Discussions

Troponins

Troponins represent a complex formed by 3 subunits: troponin T (cTnT), troponin I (cTnI), and troponin C (cTnC). Isoforms T and I have cardiac specificity, while cTnC is present in the myocardium as well as in striated muscles [4,5]. Most frequently, their measurement is performed in case of acute coronary syndrome, being essential for the diagnosis and guidance of the therapeutic approach [6]. However, any myocardial lesion, regardless of its mechanism of occurrence, which induces myocyte membrane damage, also induces intracellular depletion of troponins and its subsequent release into the blood [7-11]. Drugs that induce progressive/chronic myocardial injury cause a small but persistent increase in troponins, which is

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directly proportional to the duration of the therapy [12-16]. Many studies investigate their utility in LVD screening in cancer patients. For this review, 16 studies have been analyzed. Their characteristics and the main results obtained are summarized below (Table 1) [17-22].

All studies included samples of patients with HER-positive breast carcinoma. One study [7] included patients who did not receive anthracycline prior to trastuzumab therapy.

Regarding the patients sequentially treated with anthracyclines and trastuzumab, studies report divergent results. Some authors consider that increased or detectable troponin values observed during the treatment with trastuzumab might be the result of anthracycline toxicity because they occur shortly after the initiation of trastuzumab therapy and subsequently tend to normalize [8,11,12,21]. A possible explanation could be the different cardiotoxicity mechanisms of the two groups of drugs [23].

Table 1. The characteristics and the main results of the studies investigating cardiac troponin modifications in HER2+ breast cancer patients treated with trastuzumab

Study (year)	Troponin type	Troponin measurement	Main results
Ponde N et al. (2018) [7]	cTnT[1]	Baseline, 2 wks[2] 18 wks	2.9% elevation at 18 wks
Zardavas et al. (2017) [8]	us-cTnI[3] hs-cTnT[4]	Baseline, 13,25,52 weeks 18,24,30 mo	No significant increase; high troponin levels at baseline are predictive of LVEF drop[5]
Goel S et al. (2011) [9]	cTnI	Before and 24h after	No troponin elevation
Sawaya H et al. (2011) [10]	hs-cTnI[6]	Baseline 3,6 mo[7]	High hs-cTnI levels at 3 mo predictive of cardiotoxicity at 6 mo
Sawaya H et al. (2012) [11]	us-cTnI	Baseline, every 3 mo during treatment	Elevated usTnI concentrations at 3 mo are predictive of subsequent cardiotoxicity
Ky B et al. (2014) [12]	cTnI	Baseline 3,6 mo	Values at 3 mo predictive of cardiotoxicity (HR=1.36; p=0.012) Changes in TnI values from baseline compared to 3 mo are predictive of cardiotoxicity (HR[8]=1.38; p=0.02)
Fallah-Rad et al. (2011) [13]	cTnT	Baseline 3,6,9,12 mo	No increases over time
Putt M. et al. (2015) [14]	hs-cTnI	Baseline 3,6,9,12,15 mo	Maximum hs-cTnI values at 6 mo (12x baseline value) Not predictive for concurrent (p=0.30) or subsequent cardiotoxicity (p=0.14)
Kitayama H et al. (2017) [15]	hs-cTnT	Baseline Every 3 to 6 mo	Patients with cardiotoxicity had elevated hs-cTnT values Stable troponin values in patients without cardiotoxicity
Katsurada K et al. (2014) [16]	hs-cTnT hs-cTnI	Baseline 3,6,9,12,15 mo	Maximum hs-cTnT levels at 3 and 6 mo hs-cTnT changes at 6 mo correlate with LVEF drop at 15 mo ($r = -0.56$, $p < 0.05$)
Mokuyasu S et al. (2015) [17]	hs-cTnI		8.9% of anthracycline treated patients and 3% of trastuzumab treated patients had hs-cTnI elevations
Onitilo AA et al. (2012) [18]	cTnI	Baseline; every 3 wks up to 1 year	No elevations
Morris PG et al. (2015) [19]	cTnI	Every 2 wks during ChT and then at 6,9,18 mo	Detectable cTnI at 2 weeks after anthracycline Detectable cTnI before maximum LVEF drop but not an independent predictive factor

de Vries Schultink AHM et al. (2018) [20]	hs-cTnT	Baseline 3,12,24,36,52,64,78,92 wks	Maximum values of hs-cTnT at 3 wks after anthracycline treatment
Cardinale D et al. (2010) [21]	cTnI	Every 1-3 wks	cTnI strongest independent predictive factor for cardiotoxicity (HR=17.6; p=0.001) patients with high cTnI who develop HF[9] are less likely to recover despite the treatment (HR=2.88; p<0.001)
Dhir V et al. (2019) [22]	hs-TnI	Before trastuzumab	No correlations between with LVEF drop

cTnT[1] – troponin T; wks[2] - weeks; us -cTnI[3] – ultra-sensitive troponin I; hs-cTnT[4] – high-sensitive troponin T; LVEF[5] - ; hs-cTnI[6] – high-sensitive troponin I; mo[7] - months; HR[8] – hazard ratio; HF[9] – heart failure

For example, Mokuyasu et al. [17] compared cTnI values in patients treated with anthracyclines and patients treated with trastuzumab. The results show that 8.9% of the patients who were also treated with anthracyclines had an increase in cTnI values compared to 3% of the patients treated with trastuzumab. The patients who received no anthracyclines did not have increased hs-cTnI values.

Zardavas et al. [8] demonstrated that in patients with high cTn values, these were already present before the initiation of the therapy with trastuzumab and did not increase significantly afterwards, and that these patients had a 2.4-4.5 times higher risk of a decrease in LVEF. Similarly, Sawaya et al. [11] showed that the highest us-cTnI values were recorded shortly after the completion of the treatment with anthracyclines, followed by their decrease during trastuzumab therapy. According to this study, us-cTnI measurement after the completion of anthracycline treatment has a sensitivity of 48% and a specificity of 73% as a predictor of subsequent cardiotoxicity. The usefulness of troponins I as a prognostic marker of cardiac dysfunction was also demonstrated in the study conducted by Ky B et al. [12].

The study carried out by Cardinale et al. [21] also reported increased troponin values in the majority of the patients (23 of the 36 patients with increased values) at the beginning of the treatment with trastuzumab, with their normalization over the following 3 months. In addition, the authors showed that cTnI values represent the strongest independent predictor of cardiotoxicity. Furthermore, the authors indicated that patients with high troponin levels who develop cardiotoxicity have lower chances of LVEF recovery compared to patients with normal cTnI values (36% vs. 100%) under optimal medical treatment.

The study performed by Katsurada K et al. [16] showed that hs-cTnT values at 6 months represent a predictive factor of the 10% LVEF reduction at 15 months, suggesting that this would be a more useful marker than hs-cTnI. A more recent study [20, 23] also demonstrated the predictive value of hs-cTnT at 3 weeks after the treatment with anthracyclines regarding the trastuzumab-induced decrease in LVEF.

In some studies, [14,19], despite an increase in the troponin values recorded during treatment, the authors could not demonstrate their predictive value in the early detection of cardiotoxicity. On the other hand, there are studies in which the increase in troponins during therapy was not demonstrated [9,13,18,22].

The only study comprising patients treated exclusively with trastuzumab [7] suggests that high troponin values occur in a small number of patients and their measurement is not useful for monitoring trastuzumab-induced cardiotoxicity, but it should be taken into consideration that the small sample and the reduced number of cardiac events did not allow statistical analysis.

In conclusion, although there are many studies that show the usefulness of troponin measurement for the early detection of cardiac toxicity or for the identification of patients at risk of developing HF during the therapy with trastuzumab after anthracycline treatment, further studies with larger samples and standardized measurement methods are required for the implementation of this method in clinical practice. Comparing the results is difficult since different cut-off values for troponin as a marker of cardiotoxicity have been chosen. Moreover, troponin measurement presents a high variability because of the different assays that are used. The imprecision of a typical troponin assay that was used in the past was between 10-20% at the 99th percentile. The new hs-assays managed to lower this imprecision below 10% [24].

Brain Natriuretic Peptide

The family of natriuretic peptides includes the atrial natriuretic peptide, brain natriuretic peptide (BNP), and C-type natriuretic peptide (a peptide secreted by the vascular endothelium). BNP is released mainly by atrial myocytes under normal conditions, and by ventricular myocytes in the presence of congestive HF. Thus, increased BNP values are the hallmark of ventricular dysfunction. The precursor pre-proBNP is cleaved into the biologically active BNP molecule and the inactive N-terminal proBNP (NT-proBNP) fragment. In patients with HF, BNP is more increased than the atrial natriuretic peptide and has a half higher half-life (20 min vs. 2 min), while NT-proBNP has the highest half-life (approximately 120 min) and thus

persists more in circulation [25]. BNP values are under the influence of several factors. Higher BNP values are seen in older patients (the cut-off point for HF jumps from 450 to 900 pg/ml in patients over 50 years) and in females, but obesity leads to significantly lower BNP. Cut-off points for diagnosing HF need to be higher if the estimated glomerular filtration rate is lower than 60 mL/min/1.73 m2 [25,26].

The widespread use of BNP in clinical practice has led to its study in various chemotherapy regimens. In anthracycline-based therapy, LVD, symptomatic HF, or acute coronary syndrome were associated with BNP values above 100 pg/mL. NT-proBNP elevations correlate with diastolic and systolic dysfunction after high dose chemotherapy [27,28].

So far, studies have not shown a useful role for BNP/NT-proBNP monitoring during trastuzumab treatment. This might be explained by the low cardiotoxicity of trastuzumab compared to anthracyclines and the difference in assays and cut-off values used in various studies [28]. Table 2 provides a summary of the results [8-11,13,14,18,20,29-34]. Studies have not looked specifically for the influence of bevacizumab therapy on BNP in breast cancer patients. Two to four percent of the subjects on bevacizumab treatment develop LVD that associates increased BNP levels [35].

Table 2. NT-proBNP[1]/BNP[2] changes during the trastuzumab treatment

Study (year)	NT-proBNP/BNP measurement	Main results
Zardavas et al. (2016) [8]	baseline; wks[3] 13,25,52; mo[4] 18,24,30,36	Elevated NT-proBNP does not predict a significant LVEF[5] drop
Goel et al. (2011) [9]	baseline, after 24 hours	No significant change in NT-proBNP
Sawaya et al. (2011) [10]	baseline, 3 and 6 mo	Changes in NT-proBNP do not predict cardiac toxicity
Sawaya et al. (2012) [11]	baseline; 3,6,9,12,15 mo	No association between NT-proBNP and cardiac toxicity
Fallah-Rad et al. (2011) [13]	before anthracycline and trastuzumab; 3 wks after the final cycle; 12 mo after trastuzumab	No difference between the patients who developed cardiomyopathy and those who did not
Putt et al. (2015) [14]	baseline; 3,6,9,12,15 mo	No significant increase in NT-proBNP
Onitilo et al. (2012) [18]	baseline; every 3 wks up to a year	No difference in NT-proBNP associated with a LVEF[3] drop
de Vries Schultink et al. (2018) [20]	before anthracycline, baseline before trastuzumab, up to 92 wks after trastuzumab	Prior treatment with anthracyclines followed by trastuzumab does not elevate NT-proBNP
Advani et al. (2017) [29]	at baseline, days 1,2,3, and 7 during 1st and 2nd cycle	Transient increase in NT-proBNP in the first two days of the second cycle
Yu et al. (2016) [30]	baseline 6,12,18,24 and 30 wks	No significant increase in BNP
El-Sherbeny et al. (2019) [31]	baseline 3,6,9 and 12 mo	No significant increase in NT-proBNP
Şendur et al. (2015) [32]	at 9 and 52 wks	No difference in NT-proBNP after the treatment; cardiac toxicity associated higher NT-proBNP
Matos et al. (2016) [33]	baseline, after 4,8,12 mo during trastuzumab	No significant difference between patients with and without a LVEF drop
Grover et al. (2013) [34]	baseline and 4 mo	No difference in NT-proBNP after anthracyclines or trastuzumab

NT-proBNP[1] - N-terminal pro-hormone brain natriuretic peptide; BNP[2] - brain natriuretic peptide; wks[3] – weeks; mo[4] – months; LVEF[5] – left ventricular ejection fraction

Galectin-3

Galectins are β-galactoside-binding lectins with at least one carbohydrate recognition domain. There are 15 types of galectins, distinguished from one another by the type of carbohydrate recognition domain. Galectin-3 is involved in numerous cellular processes such as cellular differentiation, inflammation, fibrosis, and angiogenesis. Cardiovascular diseases such as HF, ischemic heart disease, atrial fibrillation, and renal dysfunction are associated with increased serum galectin-3 values. At the same time, breast tumor tissue has an increased expression of galectin-3, and triple negative breast cancer expresses more galectin-3 than other types of breast cancer [36].

Patients with breast cancer have higher serum galectin-3 levels compared to healthy subjects (18.41 ng/mL in cancer patients and 6.73 ng/mL in controls ($p<0.0001$). After 3 and 6 months of trastuzumab, anthracycline and taxane treatment, galectin-3 levels were increased compared to baseline. At the same time, HER2- patients had higher galectin-3 values than HER2+ patients [37]. In contrast, in another study, galectin-3 levels did not increase from baseline after 15 months of trastuzumab, doxorubicin, and paclitaxel treatment [14].

Echocardiographic markers of cardiac dysfunction

Advances in cancer treatment over the last decades have remarkably improved the survival rates of patients diagnosed with solid and hematologic malignancies.

Unfortunately, several chemotherapeutic agents (e.g., trastuzumab, bevacizumab) are known to have cardio toxic effects [37]. Ventricular dysfunction and heart failure, as a complication of cancer therapy, have become major public health concerns, as they are associated with poor prognosis and long-term morbidity and mortality [38]. The development of a subclinical left ventricular dysfunction (cancer therapy–related cardiac dysfunction [CTRCD]), defined by a threshold change in LV ejection fraction (LVEF), may be seen in up to 42% of the patients with cancer in selected treatment groups [39].

Therefore, the early diagnosis and control of cancer therapy-related cardiac dysfunction CTRCD is of crucial importance in patients undergoing therapies. In the absence of robust risk prediction models, cardiologists are very interested in the use of more sensitive markers to detect early myocardial dysfunction [40], for CTRCD prevention.

The most frequent echocardiographic markers used in cancer patients are as follows: LVEF by 2D TTE; VTI: lateral S wave in both LV and RV; DTI: the detection of strain (GLS versus GCS versus GRS) and free wall RV strain.

One of the conventional methods for monitoring cardiac function in patients receiving cancer therapy is the determination of 2D left ventricular ejection fraction (LVEF) with serial transthoracic echocardiography (TTE). A value <53% of LVEF or a decrease >10% in LVEF during cancer treatment is consistent with cardiac systolic dysfunction [41].

However, this strategy fails to detect early subtle alterations in LV systolic function, as LVEF is dependent on hemodynamic conditions. Tissue velocity imaging (TVI) and strain imaging are novel, sensitive, non-invasive echocardiographic techniques that allow the early detection of LV systolic dysfunction, before a decrease in conventional LVEF [42]. Tissue velocity imaging has been validated in murine models of chemotherapy-induced cardiac dysfunction [43] and more recently, evaluated in the clinical setting of trastuzumab-induced cardiac dysfunction [13]. Neilan et al. demonstrated that a decrease in LVEF, detected by conventional echocardiographic measures (2D LVEF), was observed on day 5 in mice treated with chemotherapy, whereas DTI indices, such as S wave maximal velocity, dropped significantly earlier, on day 2. These findings were corroborated by Jassal et al. [44] in a study conducted in 2009, in which DTI parameters decreased within 24 hours in mice treated with doxorubicin plus trastuzumab, while a decreased LVEF was observed only on day 4.

In the echocardiographic assessment of both left and right ventricular inotropy, tissue Doppler measures, such as S or E wave maximal velocities, can be used to quantify regional systolic and diastolic function with greater accuracy than conventional measures such as LVEF or RV FAC [45]. However, we should acknowledge that systolic velocities, being Doppler derived measures, are angle-dependent. Thus, a good alignment of the Doppler interrogation line with the region of interest is mandatory in order to obtain the correct peak velocities. Nonetheless, peak systolic tissue Doppler velocities can be affected by the overall motion of the heart and the afterload pressures, particularly in the RV [46]. Several investigators have demonstrated an early reduction in lateral E velocity of the mitral annulus in patients receiving anthracyclines [47] but not trastuzumab, which remained reduced during the treatment and for several years thereafter. In a study by Negishi et al., [48] a 10% reduction in E velocity was observed in patients who developed CTRCD. Nevertheless, the reduction was neither statistically significant nor predictive of subsequent reduction in LVEF. In a recent study concerning the RV dysfunction, Keramida et al. [49] showed a global and uniform effect of trastuzumab on myocardial function, affecting both the left and right ventricles. The RV dysfunction was demonstrated by a decrease in both TAPSE and S wave, criteria of an abnormal longitudinal function. Both techniques (M-mode echography and Doppler tissue imaging) are angle-dependent, but also load-dependent.

Among the measures of myocardial function, echocardiography-measured peak systolic global longitudinal strain (GLS) is the most extensively studied

marker and it provides an easy, inexpensive, and quantitative assessment of the global long-axis systolic function [50]. As a general idea, strain is defined as a percentage change in myocardial deformation and strain rate as the speed of deformation of myocardial segments. Neither the strain nor the strain rate derived parameters represent pure myocardial contractility, and none of them is load-independent [51,52]. Several studies have linked threshold changes in GLS or an absolute GLS value during cancer treatment with the subsequent development of CTRCD [11]. However, the greatest limitation is that these studies differ in the GLS cut-off values, depending on the vendors used and the populations studied. The cardio-oncology expert consensus document of the American Society of Echocardiography (ASE) and the European Association for Cardiovascular Imaging (EACVI) recommends the routine use of GLS in monitoring patients during cancer therapy whenever possible. In patients with available baseline strain measurements, a relative percentage reduction in GLS of less than 8% is not meaningful, whereas a change greater than 15% is likely to indicate subclinical LV dysfunction (2,52). GLS measurements based on 3 apical views is the preferred technique for the detection of cardiotoxicity, according to Thavendiranathan et al., even though single view LS is less time consuming [53].

Longitudinal strain seems to be affected when cardiotoxicity occurs. Bergamini et al. demonstrated that 2D GLS was the only parameter significantly modified across the studies after 12 months, while, overall, 2D GCS was not significantly reduced. Concerning the 2D GRS, the analysis demonstrated a significant reduction of this parameter, but not all the involved studies showed a coherent result after the same follow-up period [54].

Given the established prognostic significance of the RV dysfunction [55] for the outcome of the patients with heart failure, the finding of concurrent RV impairment at the time of diagnosis of LV cardiotoxicity makes RV GLS a useful measurement during trastuzumab therapy. In the recent study performed by Keramida et al., in patients treated with trastuzumab, the RV FWLS (free wall longitudinal strain) changes were modest. On the other hand, the insignificant change of RV FWLS raises the possibility that the detected impairment of RV GLS is attributed mainly to the intraventricular septum that both ventricles share. Also, the optimal cut-off value of the relative percent change in the RV GLS to predict cardiotoxicity was ≥14.8%, almost identical to the established LV GLS cut-off. We should also point out that both RV GLS and RV FWLS are size-independent estimates of contraction, as opposed to peak S velocity and TAPSE. But all the parameters proposed to detect early changes in RV systolic function are load-dependent; therefore, the presence of pulmonary hypertension may affect them [56].

Data concerning bevacizumab-related cardiotoxicity are scarce in the literature, but the same echocardiographic markers as for trastuzumab are proposed in the follow-up of patients, while the myocardial dysfunction induced seems reversible [57].

To conclude, the most sensitive marker of the early myocardial dysfunction in patients during and after the chemotherapy treatment with either trastuzumab or bevacizumab is global longitudinal strain GLS, having an important prognostic value in the development of end-stage HF [58].

Abbreviations

BNP - brain natriuretic peptide
ChT –chemotherapy
cTnC - troponin C
cTnI - troponin I
cTnT - troponin T
CTRCD - cancer therapy–related cardiac dysfunction
DTI - One-dimensional tissue Doppler
FWLS - free wall longitudinal strain
GCS - global circumferential strain
GLS - global longitudinal strain
GRS - global radial strain
HF - heart failure
hs-cTnI - high-sensitive troponin I
hs-cTnT - high-sensitive troponin T
LV - left ventricle
LVD - left ventricular dysfunction
LVEF - left ventricular ejection fraction
NT-proBNP - N-terminal pro-hormone brain natriuretic peptide
RV - right ventricle
RVD - right ventricular dysfunction
us-cTnI - ultra-sensitive troponin I

Conclusions

To conclude, the most sensitive marker of the early myocardial dysfunction in patients during and after the chemotherapy treatment with either trastuzumab or bevacizumab is global longitudinal strain GLS, having an important prognostic value in the development of end-stage HF [58].

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant

bodies and that such approvals are acknowledged within the manuscript.

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