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THE ROLE OF CARDIAC BIOMARKERS AS PREDICTORS OF TRASTUZUMAB CARDIOTOXICITY IN PATIENTS WITH BREAST CANCER

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***Aim*: Identification of patient with increased risk of cardiotoxicity would allow not only prevention and early diagnosis of chemotherapy related cardiotoxicity but also administration of optimal dose and duration of chemotherapy. *Materials and methods*: Fifty-two women with HER2$^+$ breast cancer treated with trastuzumab were included in this study. Patients were prospectively followed with routine cardiac evaluation. Before and after administration of trastuzumab blood samples for NT-proBNP were also taken. *Results*: The median age was 48.5 year (range: 26–74). Hypertension and obesity were two most common co-morbidities. The median duration application of trastuzumab was 52 weeks. During median 14.5 (3–33) months follow-up cardiac adverse events occurred in 5 (9.6%) patients and 2 out of 5 was grade III–IV heart failure. Both patients had preserved left ventricular ejection fraction and no symptom of heart failure before trastuzumab but older than 65 years old and had diabetes mellitus and obesity. High level of NT-proBNP (> 300 ng/ml) was observed in both patients and heart failure recovery was not observed. There was statistically significant difference regarding body mass index ($p = 0.004$) and diabetes mellitus ($p = 0.002$) between patients with and without cardiotoxicity. *Conclusion*: Although, cardiac biomarkers still cannot replace routine cardiac monitoring, natriuretic peptides may provide additional tool for detection of patients with high risk of cardiotoxicity and early detection of cardiotoxicity.**

***Key Words*: breast cancer, trastuzumab, heart failure, left ventricular dysfunction, natriuretic peptides.**

Breast cancer (BC) is most common cancer and second leading cause of cancer death among women in developed countries [1]. BC is heterogeneous disease with different genetic and clinicopathologic features. Almost one-fourth of the patients show overexpression of human epidermal growth factor receptor 2 (HER2) [2, 3]. Treatment targeting HER2, such as trastuzumab, has dramatically changed clinical course of those patients [4, 5]. Although, the exact mechanism is still unclear, trastuzumab is associated with cardiotoxicity in subset of patients [4–9]. According to recent Cochrane meta-analysis, trastuzumab significantly increases the frequency of left ventricular ejection fraction decline and the risk of symptomatic heart failure (HF) [10, 11]. American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines classify patients receiving cardiotoxins as stage A HF, and recommend aggressive control and treatment of modifiable risk factors [12]. For that reason, optimal cardiac management is crucial for both prevention and early diagnosis of chemotherapy related cardiotoxicity. In addition, because the optimal survival benefit of adjuvant trastuzumab achieved with one-year treatment, it is also important for optimal dose and duration of chemotherapy [13–15].

Clinical trials usually include selected patients who are usually under 65 and without serious co-morbidities. Nonetheless, the median age of patients with BC is over the 60, and 40% of patients are over 65, and 20% over 75 [1, 10, 11, 16]. Older women has higher risk of cardiotoxicity. Therefore, clinical trials may not represent real world. In additionally, median survival of patients with BC has been improved. The estimated 5 year overall survival is also reached to 80–85% for patients who were diagnosed between 1999–2005 [1, 17]. Finally, number of cancer survivors has been increased and late toxicities become more important for those patients.

HF is a complex clinical syndrome. According to underlying cause, while half of patients present with HF with reduced ejection fraction (HFrEF), second half have HF with preserved ejection fraction (HFpEF). The diagnosis of HFpEF is more challenging. HFpEF are usually observed in obese older women with a history of hypertension, diabetes mellitus (DM), and hyperlipidemia [12, 18]. There is no single test for the diagnosis of HF but ejection fraction (EF) is considered important in classification of patients with HF and response to treatments. Also clinical trials usually selected patients based on EF. However, measurement of EF is dependent operator, imaging technique, and method of analysis. B type natriuretic peptides (BNP) are secreted by ventricular cardiomyocytes in response to increased ventricular stretch.

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Abbreviations used: BMI – body mass index; BC – breast cancer; CAD – coronary arterial disease; DM – diabetes mellitus; EF – ejection fraction; HF – heart failure; HFpEF – heart failure with preserved ejection fraction; HFrEF – heart failure with reduced ejection fraction; LVEF – left ventricular ejection fraction; MUGA – multiple-gated acquisition scanning.

After release of propeptide (proBNP), it converts in to biologically inert amino terminal (NT-proBNP) and biologically active BNP [19]. The role of BNP and NT-proBNP has been well defined in diagnosis of both HFrEF and HFpEF [12, 20, 21]. EF alone may not predict cardiotoxicity of chemotherapy for all patients and the optimal monitoring and treatment algorithm for trastuzumab related cardiotoxicity remain to be established. The purpose of this study was to evaluate the role of serum biomarker in early diagnosis or prediction of trastuzumab related cardiotoxicity.

MATERIALS AND METHODS

Patients. All patients with HER2-positive BC who were treated with trastuzumab either single-agent or combined with chemotherapy agents were included in this study. Demographic and clinical data of patients were reported on case record forms designed for data collection for this study. Patient characteristics considered relevant for cardiotoxicity were age, Eastern Cooperative Oncology Group (ECOG) performance status, prior anthracycline therapy, prior radiotherapy, hypertension, DM, hyperlipidemia, obesity, and renal failure. This study was approved by the Institutional Review Board of Ankara University School of Medicine and was conducted according to Helsinki Declaration and good clinical practice.

Biochemical measurements. All blood samples were collected after 5 min supine rest and 30 min before and 30 min after trastuzumab administration. Samples were immediately centrifuged and separated sera were stored at −80 °C at the hospital laboratory until assayed. Before assay performed all samples were anonymized. NT-proBNP was measured using the commercially available electrochemiluminescence immuno-assay (Roche Cobas e601, Roche Diagnostics GmbH, D-68298 Mannheim, Germany). The staff that performed assay was masked to the patient's diagnosis and cardiac status.

Cardiac tests. Routine cardiac evaluation of all patients was performed before trastuzumab treatment and follow-up echocardiography or Multiple-Gated Acquisition scanning (MUGA) scan were performed every 3 months during treatment and also in case of HF related symptoms. A cardiac event was defined as the development of symptomatic HF or more than 10% decline of left ventricular ejection fraction (LVEF). Grading of all toxicities was done according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 4.0, published May 28, 2009).

Statistical analysis. Statistical analysis was carried out using the computer program Statistical Package for the Social Sciences 11.5 for Windows (SPSS, Inc, Chicago, IL, USA). Frequency (percent) or median (minimum-maximum) was given as descriptive statistics. Chi-square test was used to determine differences in proportions. *p* Value of less than 0.05 was considered as statistically significant.

RESULTS

The median age of patients was 48.5 year (range: 26–74). Hypertension and obesity were two most common co-morbidities. Patients' basal and pre-trastuzumab characteristics were summarized at Table 1 and 2.

Table 1. Patients' basal characteristics

Parameters	n (%)
Age, year	
Median, range	48.5 (26.0–74.0)
Menopausal status, n (%)	
Pre-	26 (50.0)
Peri-	4 (7.7)
Post-	22 (42.3)
Hypertension	11 (21.2)
DM	8 (15.4)
Coronary arterial disease (CAD)	1 (1.9)
Hyperlipidemia	6 (11.5)
Smoking	5 (9.6)
Body mass index (BMI), kg/m^2	
Median, range	28 (18.0–41.1)
< 25	9 (17.3)
25–30	25 (48.1)
> 30	18 (34.6)
Creatinin, mg/ml	0.77 (0.36–1.0)
Glucose, mg/ml	95 (77.0–202.0)
Triglyceride, mg/ml	113.5 (44.0–256.0)
High-density lipoprotein, mg/ml	50.5 (34.0–75.0)
Uric acid, mg/ml	3.6 (2.4–6.2)

Table 2. Pretrastuzumab patients' BC features

Features	Number patients	
	n = 52	%
ECOG performance status		
0	45	86.5
1	7	13.5
Laterality		
Right	20	38.5
Left	32	61.5
Stage		
Metastatic	14	26.9
Non-metastatic	38	73.1
Estrogen receptors		
Positive	35	67.3
Negative	17	32.7
Progesterone receptors		
Positive	40	76.9
Negative	12	23.1
HER2		
İmmunohistochemistry (+3)	51	98.0
FISH/CISH	1	2.0
Pre-trastuzumab anthracycline[#]		
No	13	25.0
Yes	39	75.0
Radiotherapy (n = 25)		
Right breast	9	36.0
Left breast	16	64.0
Hormonal treatment (n = 46)		
Tamoxifen	34	73.9
Aromatase inhibitor	12	26.1

[#]Total anthracycline dose, median (mg/m^2): doxorubicin – 240, epirubicin – 300. Time from last anthracycline administration to trastuzumab, median (range), month: 1 (1–110). Trastuzumab therapy duration, median (range), week: 52 (9–120).

The median duration of trastuzumab application was 52 weeks. None of patients was given concurrently anthracycline and trastuzumab. During median 14.5 (3–33) months follow-up cardiac adverse events occurred in 5 (9.6%) patients. Grade III–IV HF observed in 2 (3.8%) patients. Although both patients had normal EF and no symptom of HF before trastuzumab, high level of NT-proBNP was observed for both before and post trastuzumab. Asymptomatic LVEF decrease was observed in 3 (5.6%) patients. After discontinuation of trastuzumab cardiac recovery was observed

in 3 patients with asymptomatic EF decrease. However, in 2 patients with symptomatic HF recovery was not observed and both patients was older than 65 years-old and had DM and obesity (Table 3 and 4). Overall, there was statistically significant difference regarding BMI ($p = 0.004$) and DM ($p = 0.002$) between patients who have manifested and not manifested cardiac toxicity.

Table 3. Cardiac characteristics of patients

Cardiac characteristics	Median (range)	
	Pretrastuzumab	Posttrastuzumab
Heart rate, per minute	78 (56–104)	76 (62–108)
EF, %	65 (55–75)	62 (40–77)
NT-proBNP level, pg/ml	50 (5–694)	49 (5–829)
CK-MB level, ng/ml	1.33 (0.49–2.82)	1.35 (0.09–3.12)

DISCUSSION

The data from this study show that, a higher level of NT-proBNP is associated with cardiotoxicity even in patients with preserved baseline LVEF. Older patients with high BMI and with history of DM have higher risk trastuzumab related cardiotoxicity. Although HF is usually reversible after discontinuation of trastuzumab and appropriate treatment of HF, patients with NT-proBNP higher than 300 pg/ml were unlikely recovered from HF.

Cancer and CAD are two leading causes of death. These two diseases combined accounted for approximately half of deaths in the developed countries. While overall CAD mortality has shown a downward trend, the incidence and prevalence of HF has still exhibited an upward trend [22]. In the last 2 decades, new classes of treatment provided improvement in survival and have been approved for the treatment of various type of cancer. On the other hand, new type of toxicities has been also witnessed. While these toxicities were mostly associated with morbidity and affect quality of life, treatment related mortality was also reported [23]. In addition, these toxicities lead to treatment interruptions and discontinuation that results in inferior treatment outcome.

Cardiotoxicity is well known anthracyclines related toxicity and usually dose dependent, predictable, and irreversible. Although, it may occur during relatively new treatment such as trastuzumab, bevacizumab, and tyrosine kinase inhibitors [24–26]. The cardiotoxicity of these drugs usually dose independent and reversible. Trastuzumab is a monoclonal antibody against HER2 receptor, which over expressed in 20–25% of BC. Although the exact mechanism is not clear yet, trastuzumab related cardiotoxicity has been well established in randomized clinical trials and meta-analysis. Age, obesity, history of heart disease and use of anthracyclines are known risk factors for trastuzumab related cardiotoxicity. Although lifetime risk of BC is increased with age, in our population we see BC at earlier age than US women. Almost half of patients with BC are under 50 in our country [27]. Likewise, median age was 48.5 years old in present study. However, both groups of patients with irreversible HF were older than 65 years old.

In early study, Slamon et al. [5] showed the survival advantage of adding trastuzumab to chemotherapy in patients with advanced BC. However, in this study also carditoxicity was frequently observed. The frequency of New York Heart Association (NYHA) class III–IV cardiac dysfunction was 27 and 13% in patients who were treated with anthracycline, cyclophosphamide plus trastuzumab and paclitaxel plus trastuzumab, respectively. After these results, baseline and follow-up cardiac monitoring were added subsequent trial. Despite strict inclusion criteria, carditoxicity is still occurred in clinical trials. According to recently published Cochrane review, in patient with early BC, who has high chance of cure, trastuzumab increased risk of HF 5 fold and LVEF decline 2 fold [11]. Randomized controlled trials have generally excluded older patients with major comorbidities. Therefore, frequency of cardiotoxicity is expected to be more common in the real world. Recently, Bowles et al. [6] reported population based retrospective cohort study of 12 500 women with BC. At median 4.4 years follow up time, the risk of HF/cardiomyopathy was 4 to 7 fold higher in patients with trastuzumab alone or anthracycline plus trastuzumab. In addition, the risk of HF has been continued to increase during follow — up. In another population based study from Italian Cardio-Oncologic Network, trastuzumab cardiotoxicity rate was 27% and also treatment interruption rate was higher than clinical trials [28].

Due to, patients on chemotherapy were considered as stage A HF, patient with risk of developing HF, preventive intervention, early detection and treatment of chemotherapy-induced cardiotoxicities are

Table 4. Characteristics' of 5 patients with cardiotoxicity

Clinical characteristics	Patient				
	1[a]	2[a]	3[a]	4[b]	5[b]
Pretrastuzumab age, years	66	72	48	52	44
Menopausal status	Post-	Post-	Post-	Pre-	Pre-
Hypertension	No	Yes	No	No	No
DM	Yes	Yes	Yes	Yes	No
BMI, kg/m^2	30.92	31.39	31.08	30.22	25.31
Total anthracycline dose, mg/m^2	600 (E)	No	60 (A)	240 (A)	180 (A)
Radiotherapy	No	No	No	Yes	No
Chemotherapy[#]	6EC→5TH	6TCH→7H	A→6TH→14H	4AC→4TH→13H	3AC→3TH→5H
Creatinin, mg/dl	1.0	0.97	0.8	0.55	0.73
Pretrastuzumab, EF, %	55.0	60.0	62.5	55.0	60.0
Pretrastuzumab, NT-proBNP level, pg/ml	370	694	41	49	72
Posttrastuzumab, EF, %	35	40	48	49	52
Posttrastuzumab, NT-proBNP level, pg/ml	426	829	43	44	104
Cardiac status after discontinuation of trastuzumab	Symptomatic HF	Symptomatic HF	Recover after 2 months EF: 65%	Recover after 4 months EF: 55%	Recover after 3 months EF: 60%

[a]Metastatic disease. [b]Adjuvant treatment. [#]Chemotherapy was administered every 3 weeks. A – adriamycine; C – cyclophosphamide; E – epirubicine; H – trastuzumab; T – docetaxel.

needed for reducing severe, irreversible, late onset cardiotoxicity and optimal treatment of cancer. In daily clinical practice calculation of EF, by echocardiography or MUGA scan, is most widely used method [29]. However, because of EF does not usually decrease in early stage HF, EF has some limitations for early detection or prediction of late onset left ventricular dysfunction. In addition, half of patients with HF have HFpEF despite lower risk of death than patient with HFrEF, those patients mortality rate is still high [30–32]. As well as, echocardiography is mostly operator dependent and MUGA scan causes radiation exposure. Therefore, non-invasive predictive and prognostic tests of HF for patients on chemotherapy are needed. The role of serum biomarker such a troponin, natriuretic peptides has been well established by meta-analysis and both BNP and NT-proBNP are endorsed in current guidelines plus clinical evaluation [20, 33–36]. The normal level of BNP/NT-proBNP are very low and increased myocardial wall stress lead to elevation of serum level [21, 34, 37]. In contrast to the echocardiography and MUGA scan, HFpEF and diastolic HF may cause elevated BNP/NT-proBNP. However, not only CAD but advancing age and renal dysfunction might cause higher levels, while lower levels may be detected in patients with obesity and overt HF [21, 37]. Although, adjusted cutoff values are proposed for renal dysfunction and obesity, <30–50 pg/ml of BNP and <300 pg/ml of NT-proBNP have high accuracy for excluding HF. In additionally, the prognostic value of natriuretic peptides has also been reported and higher values were associated with worse prognosis [21]. Likewise, patient without history of HF and with elevated natriuretic peptides levels are at higher risk for cardiovascular events [38]. In two recent meta-analysis Felker et al. and Porapakkham et al. reported that biomarker guided treatment of HF was associated with 31% and 24% reduction in all causes of mortality compared to routine daily practice in patients with HF [33, 39]. Therefore, not only for diagnosis but also for optimizing treatment and reduction in mortality, natriuretic peptides may have additional value.

This study has several limitations: our cohort has smaller sample size and possibly fewer events, so the analyses were primarily exploratory, so, no definitive conclusions cannot be drawn. However, it supports of the potential clinical application of NT-proBNP as a predictive marker to consider cardiac management of patients treated with trastuzumab.

In conclusion, although, cardiac biomarkers still cannot replace routine cardiac monitoring, natriuretic peptides may provide additional tool for detection of patients with high risk of cardiotoxicity and early detection of cardiotoxicity.

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DISCLOSURE

None of the authors had a conflict of interest.

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