

Factors associated with the recovery of chemotherapy induced cardiomyopathy in HER2 overexpressing breast cancer

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ABSTRACT

Objective: Chemotherapy induced cardiomyopathy (CI-CMP) is an important and potentially deadly complication of chemotherapy. However, factors associated with the recovery of CI-CMP have not been studied adequately so far. In this study, determinants of the recovery of CI-CMP in HER2 overexpressing breast cancer patients who received a chemotherapy regimen consisting of Doxorubicin, Trastuzumab, Paclitaxel and Cyclophosphamide and developed CI-CMP were investigated.

Material and Methods: 88 patients with CI-CMP among 1.410 HER2 positive breast cancer patients were enrolled and followed up for a median of 64 months. A multivariate logistic regression analysis model was used to assess the association between recovery of CI-CMP and other variables

Results: The median age of the participants was 52, and similar between groups. CI-CMP was recovered in 52 patients (59.1 %). Hypertension, diabetes mellitus, clinical heart failure, ECG anomaly, visceral metastasis, heart rate and blood glucose were significantly lower in recovered patients. A multivariate logistic regression analysis revealed that diabetes mellitus (OR 0.030, CI 0.010-0.083, p<0.001), heart rate (OR 0.799, CI 0.700-0.913, p<0.001), minimum LVEF during follow-up (OR 1.115, CI 1.015-1.223, p=0.03), development of clinical heart failure (OR 0.238, CI 0.098-0.876, p=0.022) and visceral metastasis (OR 0.022, CI 0.002-0.226, p=0.001) were independent predictors of the recovery of CI-CMP.

Conclusion: According to our results, Diabetes mellitus, heart rate, minimum LVEF during follow-up, development of clinical heart failure, and presence of visceral metastasis were independently associated with the recovery of CI-CMP. Particularly, relationship between diabetes and recovery of CI-CMP is notable and deserves further research.

Keywords: cardiomyopathy, chemotherapy, Anthracycline, Trastuzumab, breast cancer

INTRODUCTION

Breast cancer is the most prevalent cancer type and the second leading cause of cancer mortality among women worldwide (1). Although new oncological therapies allow a prolonged lifespan for patients with breast cancer, one of the chemotherapy complications, chemotherapy induced cardiomyopathy (CI-CMP), may overshadow this benefit to some degree since it is the second cause of death in breast cancer survivors (2).

Anthracyclines and Trastuzumab are two commonly used chemotherapeutic agents in breast cancer despite having well-known cardiotoxic effects (3,4). Anthracyclines are not only one of the most effective anticancer treatments ever developed but also famous for their cardiotoxicity with a 5-fold greater risk than non-anthracycline chemotherapeutics (3). On the other hand, Trastuzumab is an Immunoglobulin G1 monoclonal antibody that targets human epidermal growth factor receptor 2 (HER 2) and is used exclusively in HER2 overexpressing breast cancer (4). While anthracyclines induce a dose-related and potentially irreversible cardiac toxicity, Trastuzumab induced cardiac toxicity is generally reversible and not related to dose. Nowadays, anthracyclines and Trastuzumab are often used sequentially and in combination with other potentially cardiotoxic agents like Paclitaxel and Cyclophosphamide in breast cancer in order to ensure enhanced effectiveness at the expense of cardiac safety which necessitates more attention for CI-CMP (5).

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Risk factors for the development of CI-CMP is generally well defined and includes but are not limited to factors such as age, hypertension, diabetes, coronary artery disease, atrial fibrillation, renal failure and type of chemotherapy (6). In order to develop a strategy to reduce the frequency of CI-CMP, determining the factors associated with the recovery of CI-CMP is also crucial but it has not been studied adequately so far. In the present study, we sought to investigate the determinants of recovery of CI-CMP in HER 2 overexpressing breast cancer patients who received a widely used chemotherapy regimen consisting of doxorubicin, Trastuzumab, Paclitaxel and Cyclophosphamide and developed CI-CMP as a result.

MATERIAL and METHODS

Study Population

Among 7.180 consecutive breast cancer patients who were referred to cardiology clinic as part of routine follow up in a tertiary oncology Center between January 2015 and January 2020, 1.410 patients were HER 2 positive. Most commonly used chemotherapy protocol was 4AC (Adriamycin [Doxorubicin]-Cyclophosphamide) -12 P (Paclitaxel) + Trastuzumab in this population and 1.248 patients who received this protocol was selected. Eighty-eight of these patients developed CI-CMP and formed our study population. Thirty-eight patients were excluded from the study due to preexisting heart failure, more than mild valvular heart disease, coronary artery disease and cardiomyopathy (**Figure1**). The study protocol was approved by the Institutional Ethics Committee.

Analysis of Patient Data

Medical history and demographic information of the patients were obtained from hospital records. Venous blood samples were taken from all patients for hematologic and biochemical analysis at the time of CI-CMP diagnosis. A 12 lead ECG was recorded in each patient. Transthoracic echocardiography was performed before initiation of chemotherapy, before starting Trastuzumab and then once 3 months if the ejection fraction is in normal range and once a month if the ejection fraction drops below 55%. All patients underwent a comprehensive examination, including M-mode, two-dimensional and Doppler echocardiography (Ultrasound AS, Horten, Norway). Left ventricular ejection fraction was calculated by using Modified Simpson's method. All examinations were performed by an experienced cardiologist who had no knowledge of the patients' clinical information.

Definitions

Chemotherapy induced cardiomyopathy was defined as a decline in left ventricular ejection fraction (LVEF) of at least 10% to less than 50% (5). CI-CMP recovery was defined as, at least two consecutive LVEF measurements \geq 50%. Hypertension was defined as systolic blood pressure \geq 140 mmHg or diastolic blood pressure \geq 90 mmHg or current antihypertensive medicine use. Diabetes mellitus was defined as a fasting blood glucose \geq 126 mg/dL, HbA1c \geq 6.5 or current antidiabetic medicine use.

Chemotherapy protocol

The chemotherapy protocol which used in the present study consisted of doxorubicin 60 mg/m² and Cyclophosphamide

600 mg/m² per each cycle, for four cycles with 3-week intervals, followed by Paclitaxel 80 mg/m² and Trastuzumab 4 mg/kg loading dose and 2 mg/kg weekly for 12 weeks. After that, Trastuzumab 6 mg/kg 3 weekly was continued to 1 year for non-metastatic patients and over one year in metastatic patients. If necessary, radiotherapy was started only after completing anthracycline and Cyclophosphamide therapy with a dose of 50 Gray. If CI-CMP develops, chemotherapy was stopped and treatment with an ACE inhibitor and beta blocker was started in the absence of specific counter indications to these drugs. Other heart failure medications were given, if necessary, in accordance with the current heart failure guidelines.

Statistical analysis

SPSS Statistics version 18.0 for Windows (SPSS Inc., Chicago, IL) was used for statistical analysis. Distribution pattern of the continuous variables was determined by using The Kolmogorov-Smirnov method. Continuous data was presented as mean and standard deviation or median and interquartile range according to distribution pattern. The Student's T test was used to compare data with normal distribution and Mann-Whitney U test was applied to compare the data without normal distribution. Categorical data was presented as frequencies and percentages and analysed using chi-square test. A multivariate logistic regression analysis model was used to assess the association between recovery of CI-CMP and other variables. In this model, variables with a p value $<$ 0.25 in univariate logistic regression analysis were selected for multivariate model. A two tailed p value $<$ 0.05 was considered significant.

RESULTS

Totally 88 patients with chemotherapy induced cardiomyopathy were included to the study. Cardiomyopathy was recovered in 52 (59.1 %) patients and not recovered in 36 (40.9 %). The median follow-up time was 64 months. The median age of the participants was 52 and similar between groups. In patients with recovered CI-CMP, rates of hypertension, diabetes mellitus, clinical heart failure, ECG anomaly and visceral metastasis were significantly lower. Mean heart rate and blood glucose were also significantly lower in recovered CI-CMP group.

Admission LVEF, rate of smoking, median blood pressures, previously used medications and heart failure medications except furosemide started after CI-CMP diagnosis were similar between groups. All patients received the same doses of doxorubicin (240 mg/m²), Cyclophosphamide (2400 mg/m²) and Paclitaxel (960 mg/m²) according to chemotherapy protocol. Median Trastuzumab dose was not different between groups (**Table 1**).

A multivariate logistic regression analysis revealed that diabetes mellitus (OR 0.030, CI 0.010-0.083, $p<$ 0.001), heart rate (OR 0.799, CI 0.700-0.913, $p<$ 0.001), minimum LVEF during follow-up (OR 1.115, CI 1.015-1.223, $p=$ 0.03), development of clinical heart failure (OR 0.238, CI 0.098-0.876, $p=$ 0.022) and visceral metastasis (OR 0.022, CI 0.002-0.226, $p=$ 0.001) are independent predictors of the recovery of CMP (**Table 2**).

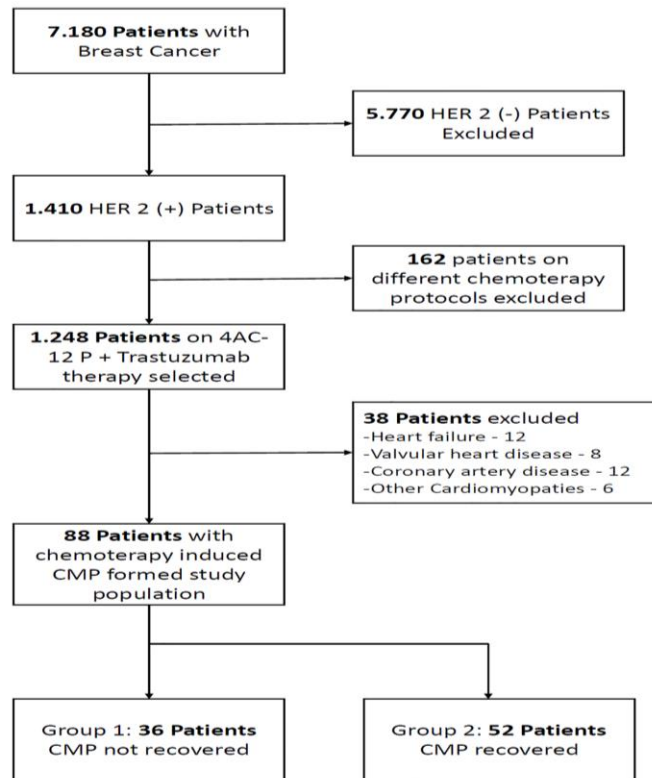


Figure 1. Patient selection algorithm

Table 1. Demographic, clinical, and laboratory characteristics of study participants.

	All CMP n=88	CMP not recovered n=36	CMP recovered, n=52	P value
Age (years)	52 (16)	53 (17)	50 (13)	0.308
Hypertension – n (%)	28 (31.8)	12 (33.3)	16 (30.7)	0.117
Diabetes – n (%)	36 (40.9)	24 (66.7)	12 (23.1)	<0.001
Hyperlipidemia – n (%)	41 (46.6)	18 (50)	23 (44.2)	0.384
Smoking – n (%)	19 (21.6)	8 (22.2)	11 (21.2)	0.407
BMI (kg/m ²)	27.6 (8.2)	27.9 (9.3)	27.4 (8.4)	0.434
Heart rate (min ⁻¹)	84.5 (18.8)	93 (12)	80 (10)	<0.001
Systolic BP (mmHg)	122 (26)	126 (22)	123 (25)	0.258
Diastolic BP (mmHg)	72 (20)	76 (18)	72 (16)	0.310
Glucose (mg/dl)	93.5 (18.3)	102 (26)	92 (14)	0.035
BUN (mg/dl)	13.0 (4.4)	13.0 (6.0)	13.0 (3.0)	0.115
Creatinine (mg/dl)	0.70 (0.16)	0.70 (0.23)	0.68 (0.13)	0.180
Hemoglobin (g/dl)	12.7 (1.5)	12.6 (2.9)	12.7 (1.5)	0.393
Platelets (x1,000/ml)	271 (96)	280 (106)	271 (97)	0.839
WBC (x1,000/ml)	6.80 (2.35)	7.10 (2.35)	6.7 (2.43)	0.398
Previous Medications				
Beta Blockers-n (%)	8 (9.1)	3 (8.3)	5 (9.6)	0.865
ACE Inhibitors-n (%)	12 (13.6)	5 (13.9)	7 (13.5)	0.988
Spirolactone-n (%)	2 (2.3)	1 (2.8)	1 (1.9)	0.789
Calcium antagonist-n (%)	10 (11.4)	4 (11.1)	6 (11.5)	0.767
Trastuzumab dose	72 (22)	76 (24)	70 (18)	0.594
Radiotherapy-n (%)	38 (43.1)	18 (50)	20 (38.5)	0.282
Visceral metastasis-n (%)	26 (29.5)	18 (50)	8 (15.4)	<0.001
Estrogen receptor (+)-n(%)	54 (61.4)	24 (66.7)	30 (57.7)	0.528
Progesterone receptor(+)-n(%)	38 (43.2)	14 (38.9)	24 (46.2)	0.311
Time to CI-CMP (months)	10 (20)	11 (22)	10 (12)	0.544
Clinical heart failure	14 (15.9)	10 (27.8)	4 (7.7)	0.009
ECG anomaly – n (%)	31 (35.2)	14 (38.9)	18 (32.7)	0.248
LVEF - Admission (%)	62.0 (4.0)	62.0 (5)	62.0 (4.0)	0.878
LVEF - Minimum (%)	40 (5.0)	38 (10)	43(5)	0.027
LVEF - Last (%)	55.0 (11.5)	45 (5)	58 (5)	<0.001
Heart failure medications given				
Beta Blockers – n (%)	80 (90.9)	33 (91.6)	47 (90.4)	0.511
ACE Inhibitors – n (%)	75 (85.2)	31 (86.1)	44 (84.6)	0.457
Spirolactone– n (%)	8 (9.1)	6 (16.6)	2 (3.8)	0.067
Furosemide– n (%)	14 (15.9)	10 (27.8)	4 (7.7)	0.009

BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; WBC, white blood cell; ACE, angiotensin converting enzyme; CI-CMP, chemotherapy induced cardiomyopathy; ECG, electrocardiography; LVEF, left ventricular ejection fraction.

Table 2. Multivariate logistic regression analysis demonstrating the association between chemotherapy induced cardiomyopathy recovery and other factors.

Variables	Univariable		Multivariable	
	OR (95 % CI)	p value	OR (95 % CI)	p value
Age	0.976 (0.933-1.020)	0.281	-	-
Hypertension	0.471 (0.186-1.195)	0.113	0.546 (0.235-1.145)	0.108
Diabetes	0.080 (0.017-0.386)	<0.001	0.030 (0.010-0.083)	0.001
Heart rate	0.883 (0.834-0.934)	<0.001	0.799 (0.700-0.913)	0.001
BUN	0.860 (0.748-0.990)	0.035	0.871 (0.686-1.116)	0.096
Creatinine	0.911 (0.831-1.231)	0.432	-	-
ECG anomaly	0.729 (0.299-1.775)	0.486	-	-
LVEF - Minimum	1.084 (1.012-1.161)	0.021	1.115 (1.015-1.223)	0.03
Clinical heart failure	0.217 (0.062-0.759)	0.017	0.238 (0.098-0.876)	0.022
Visceral metastasis	0.182 (0.067-0.493)	0.001	0.022 (0.002-0.226)	0.001
Radiotherapy	0.625 (0.265-1.476)	0.284	-	-

OR, odds ratio; CI, confidence interval; BUN, blood urea nitrogen; ECG, electrocardiology; LVEF, left ventricular ejection fraction.

DISCUSSION

In the present study, we investigated the factors associated with the recovery of CI-CMP in a group of patients who received an anthracycline and Trastuzumab based chemotherapy protocol for HER2 positive breast cancer and found out that diabetes mellitus, heart rate at the time of CI-CMP diagnosis, minimum LVEF during follow-up, development of clinical heart failure and presence of visceral metastasis were independently associated with recovery of CI-CMP. The unique aspect of the present study was its homogenous population in terms of both cancer diagnosis and chemotherapy protocol which renders a healthy analysis of independent predictors of the recovery of CI-CMP possible with minimal confounding factors. Despite the advancements in cardio-oncology in recent years, exact mechanism of chemotherapy induced cardiotoxicity remains to be elucidated. Doxorubicin, which classic example of cardiotoxic chemotherapeutics, and Trastuzumab have different mechanisms for cardiotoxicity with proposed common points. Oxidative stress has long been believed to be the major cause of doxorubicin induced cardiotoxicity (7). However, additional mechanism such as DNA damage, mitochondrial dysfunction, defects in apoptosis, iron handling and dysregulation of autophagy which proposed cause of antioxidants were shown to be ineffective in preventing cardiac side effects of doxorubicin (7,8). On the other hand, Trastuzumab suppresses autophagy in cardiomyocytes by suppressing HER2 signalling and trigger accumulation of reactive oxygen species (9). Furthermore, doxorubicin activates HER2 signalling pathway and increases HER2 protein levels in cardiomyocytes and render them dependent to HER2 signalling for survival in stressed conditions. Thus, cardiomyocytes become more sensitive to Trastuzumab after doxorubicin treatment (10). Cyclophosphamide cardiotoxicity is rare and primarily seen in patients receiving high doses before bone marrow transplantation (11). Total bolus dose, older age, mediastinal irradiation and combination therapy with other cardiotoxic drugs are risk factor for Cyclophosphamide cardiotoxicity (12). Taxanes are frequently used together with other cardiotoxic drugs in breast cancer treatment and contribution of individual drugs to cardiotoxicity in such multidrug regimens is difficult to assess.

The absolute cardiotoxic risks of taxans are unknown and some reports suggest that they may be safe alternatives to anthracyclines in patients with preexisting left ventricular dysfunction (13). Factors associated with the recovery of CI-CMP have not been clearly identified so far despite the fact that non-recovery of left ventricular function is associated with worse survival (14). Decreased ejection fraction, enlarged left ventricular size, pulmonary hypertension, introduction of heart failure treatment and older age were associated with recovery in previous studies (14-16). Similarly, the results of the present study demonstrated that minimum LVEF during follow-up, development of clinical heart failure and heart rate at the time of CI-CMP diagnosis which may be an indicator of neurohormonal activation and progression of heart failure are independently associated with CI-CMP recovery. Diabetes mellitus was another predictor of CI-CMP recovery in our study. Diabetes is a well-known risk factor for chemotherapy induced CMP in both patients receiving Trastuzumab and doxorubicin but its predictive value for recovery of CI-CMP was demonstrated for the first time in the present study (5,6). Actually, there is growing evidence about the relationship between doxorubicin cardiotoxicity and cardiac metabolic alterations as a result of imbalanced insulin signaling and cardiac insulin resistance (6,1). Moreover, studies about two antidiabetic agents, metformin and empagliflozin, revealed that these agents have promising protective effect against the development of doxorubicin induced cardiotoxicity (17,18). Thus, relationship of non-recovery of CI-CMP and diabetes is not surprising and diabetic patients who receive cardiotoxic chemotherapy need special attention. Surely, further studies are required in order to elucidate the association of diabetes, antidiabetic medications, and the development and recovery of CI-CMP. Interestingly, advanced cancer may contribute to impairment of cardiac insulin signaling via reduced pancreatic insulin production secretion of insulin-degrading enzymes, which may explain the findings of the present study, which suggested that presence of visceral metastasis is related to recovery of CI-CMP (19). In addition, other cancer related mechanisms such as proteolysis by ubiquitin-proteasome pathway, also mitochondrial dysfunction and release of proinflammatory cytokines may further contribute to heart failure development in advanced cancer (20).

The present study has several limitations. First, it is a single center study. Second, only HER2 positive breast cancer patients receiving a single chemotherapy protocol were included and results of the study cannot be generalized to all breast cancer patients. In addition, study participants received four different chemotherapeutic agents, and individual contribution of individual drugs to cardiotoxicity was not possible to assess.

CONCLUSION

In conclusion, diabetes mellitus, heart rate at the time of CI-CMP diagnosis, minimum LVEF during follow-up, development of clinical heart failure, and presence of visceral metastasis were independently associated with recovery of CI-CMP in HER2 positive breast cancer patients who received a chemotherapy protocol consisting of doxorubicin, Cyclophosphamide and Paclitaxel. Further studies are required to elucidate the factors associated with the recovery of CI-CMP. Particularly, relationship between diabetes and recovery of CI-CMP is notable and deserves further research.

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