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ORIGINAL PAPER

Impacts of non-recovery of trastuzumab-induced cardiomyopathy on clinical outcomes in patients with breast cancer

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Abstract

Objectives The impacts of non-recovery of trastuzumab-induced left ventricular dysfunction (LVD) on clinical outcomes in breast cancer have been poorly studied. We investigated the predictors of LV-functional non-recovery and its impacts on clinical outcomes in breast cancer patients with trastuzumab-induced LVD.

Methods and results A total of 243 patients with trastuzumab-induced LVD were divided into the recovered LVD group ($n=195$) and non-recovered LVD group ($n=48$). Major adverse clinical events (MACEs) including death, symptomatic heart failure (HF), and HF hospitalization (HHF) were compared. Hemoglobin and albumin levels were significantly lower in non-recovered LVD than in recovered LVD group. Non-recovered LVD group showed significantly larger LV end-diastolic and systolic dimension, higher pulmonary artery systolic pressure, lower LV ejection fraction (EF), and decreased global longitudinal strain than in recovered LVD group. Decreased LVEF, enlarged LV size, pulmonary hypertension, and anemia were independent predictors of LV-functional non-recovery. During 45.9 ± 23.5 months of follow-up, MACEs were developed in 32 patients: 15 deaths, 28 symptomatic HF, and 22 HHF. In Kaplan–Meier survival analysis, MACE free survival was significantly lower in non-recovered LVD group than in recovered LVD group (log rank $p=0.002$).

Conclusion LV-functional non-recovery was not uncommon in breast cancer patients with trastuzumab-induced cardiomyopathy, and non-recovered LVD was significantly associated with MACEs. Decreased LVEF, enlarged LV size, pulmonary hypertension, and anemia were independent predictors of LV-functional non-recovery. Careful monitoring for MACEs and intensive medical management should be considered in trastuzumab-induced cardiomyopathy with these characteristics.

Keywords Trastuzumab · Cardiomyopathy · Cardiotoxicity · Recovery

Introduction

Chemotherapy-induced cardiomyopathy (CMP) or left ventricular dysfunction (LVD) has been one of the major obstacles in the treatment of patients with cancer [1, 2]. Because anthracyclines are the most effective and widely used anticancer agents in breast cancer, anthracyclines have been major causative agents for chemotherapy-induced LVD in patients with breast cancer for several decades [3]. With the introduction of new therapeutic agents such as trastuzumab, the incidence, pathomechanism, or prognosis of chemotherapy-induced LVD in breast cancer is also changed [4].

Trastuzumab, a humanized monoclonal antibody which binds to extracellular domain of Human Epidermal Growth Factor Receptor-2 (HER2), inhibits the proliferation of HER2-dependent cancers. The usefulness of adjuvant therapy with trastuzumab in conjunction with cytotoxic agents in patients with HER2-positive breast cancer has been well established [5]. However, the usefulness of trastuzumab is counterbalanced by a risk of cardiotoxicity attributable to cardiomyocyte dysfunction [6, 7]. Trastuzumab-related cardiotoxicity encompasses wide ranges of cardiac dysfunction from asymptomatic decrease in LV ejection fraction to clinically overt heart failure [8, 9]. Cardiotoxicity depends on various factors, including the types of chemotherapeutic regimens, combined use of other drugs, radiotherapy (RT),

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or comorbidities of the patients. Trastuzumab-related LVD is generally known to be transient, reversible, and unrelated to the cumulative doses as compared to anthracycline related cardiotoxocity [10, 11]. However, in the study of Slamon et al. [12], non-recovery of cardiac dysfunction which developed by the addition of trastuzumab to anthracycline-based chemotherapy was not uncommon even after the cessation of trastuzumab and standard care of heart failure. Furthermore, LVD was aggravated in some cases. The identification of contributing factors for LV-functional recovery in patients with trastuzumab-induced LVD would be useful in the risk stratification and in clinical decision making of therapeutic strategy, but it has been poorly studied. Therefore, the aim of this study was to investigate the predictors of LV-functional non-recovery in breast cancer patients with trastuzumab-induced LVD. We also investigated the impacts of non-recovery of LV function on future clinical outcomes in breast cancer patients with trastuzumab-induced LVD.

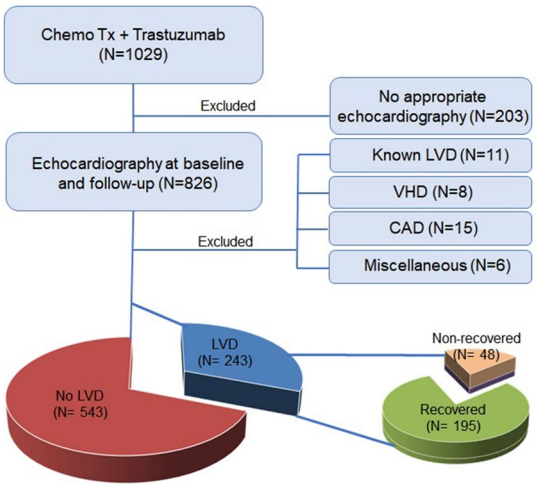

Fig. 1 Flow charts for the selection of study population. *Tx* therapy, *LVD* left ventricular dysfunction, *VHD* valvular heart disease, *CAD* coronary artery disease

Materials and methods

Study design and population

The present study was a single-center retrospective observational study, and the study protocol was approved by our institutional review board (No. 2015-05-092).

From January 2003 to December 2010, adjuvant target therapy with trastuzumab was given in 1029 female patients with breast cancer after the completion of anthracycline or taxene-based chemotherapy at our institution. After excluding 786 patients, a total of 243 patients who were diagnosed as trastuzumab-induced de novo LVD and had follow-up echocardiography were finally enrolled. The reasons of exclusion were as follows; no development of LVD ($n=583$), no appropriate echocardiographic studies ($n=203$), de novo LVD after chemotherapy and before the initiation of trastuzumab ($n=11$), significant valvular heart diseases ($n=8$), known coronary artery diseases ($n=15$), and miscellaneous ($n=6$) (Fig. 1).

According to the LV-functional recovery on follow-up echocardiography, the patients were divided into 2 groups: non-recovered LVD group ($n=48$, 49.6 ± 10 years) vs recovered LVD group ($n=195$, 51.4 ± 10 years). The development of major adverse cardiac events (MACE) including death, symptomatic HF, and hospitalization due to HF (HHF) during clinical follow-up was compared between the groups.

Treatment of breast cancer

All the patients received four-to-six cycles of anthracycline or taxene-based chemotherapy [13, 14]. Modified radical mastectomy or breast conservative surgery was performed in patients who had no evidence of disease progression. RT using conventional techniques after considering the clinical tumor size and/or staging was performed for patients treated with conservative breast surgery. Trastuzumab (Herceptin®) was administered for 1 year in patients with HER-2 overexpression at the discretion of the physician in charge after the completion of the scheduled cycles of chemotherapy [15, 16].

Echocardiographic examination

Comprehensive 2 dimensional and Doppler echocardiographic examinations were performed in accordance with the recommendation of the current guideline [17]. Echocardiographic images from various echocardiographic windows were obtained using a digital ultrasonographic equipment system (Vivid 7, GE Vingmed Ultrasound, Horten, Norway). Digital cine loops were obtained for subsequent offline analysis. All of the data were analyzed using the computerized offline software package (EchoPAC PC 6.0.0, GE Vingmed Ultrasound, Horten, Norway).

Echocardiographic examinations were performed at least 3 times in all patients. Pre-chemotherapy echocardiography was done in all patients before initiating anthracycline or taxene-based chemotherapy. First follow-up echocardiography was performed just after finishing all scheduled cycles of the chemotherapy including target therapy with trastuzumab. In cases of symptoms (dyspnea or edema) or signs (cardiomegaly on chest X-ray or changes in electrocardiography) of heart failure (HF), however, first follow-up echocardiography was performed as soon as possible, even though all the scheduled cycles of chemotherapy or target therapy were not completed. In case of trastuzumab-induced

LVD, the additional second follow-up echocardiography was performed at 6 months from the diagnosis of trastuzuamb-induced LVD to evaluate the changes of LV function.

Global longitudinal strain (GLS) of the LV was measured by automate function imaging (AFI) at a frame rate of 65.2 ± 10.5 frames/s. After selecting the optimal 2D image, the timing of aortic valve closure was derived from the pulse wave Doppler of the aortic valve, and the three-point click method in three apical planes (apical four-chamber, two-chamber, and long-axis view) was used. The LV in each apical view was divided into three levels (basal, mid, and apical), and each level was subdivided into two segments (septal and lateral); thus, the LV was divided into six segments for each apical plane. Two points placed at the base along the mitral valve annulus and one at the apex triggered the automated process. AFI non-invasively tracked and analyzed GLS based on the 2D speckle tracking method and displayed the combined results of GLS of the three planes in a single bull's eye summary. The mean value of GLS was calculated by dividing the sum of the GLS of each segment by [18].

Study definitions

According to the current guideline (Cardiac Review and Evaluation Committee of Trastuzumab-associated Cardiotoxicity), trastuzumab-induced LVD was defined as the LVEF < 55% or the decrease in LVEF > 10% on follow-up echocardiography after trastuzumab therapy as compared to the LVEF on baseline echocardiography [19].

Non-recovered LVD was defined as the persistence of LVEF < 55% on follow-up echocardiography or the failure of LVEF improvement ≥ 10% on follow-up echocardiography in cases of LVEF ≥ 55% on echocardiography at the time of diagnosis of trastuzumab-induced LVD.

Recovered LVD was defined as the LVEF ≥ 55% on follow-up echocardiography in cases of the LVEF was < 55% on echocardiography at the time of diagnosis of trastuzumab-induced LVD or the improvement of LVEF ≥ 10% on follow-up echocardiography in cases of LVEF ≥ 55% on echocardiography at the time of diagnosis of trastuzumab-induced LVD.

Anemia is defined as the level of hemoglobin less than 12 g/dL for women and less than 13 g/dL for men [20]. The patients checked laboratory parameters serially. We collected the laboratory finding at diagnosis of LVD.

Statistical analyses

The Statistical Package for Social Sciences version 18.0 for Windows (SPSS Inc, Chicago, USA) was used for the statistical analysis. Data are presented as percentages or mean ± standard deviation. The differences in the categorical variables were evaluated using the Chi-square test, and the continuous variables were compared using the independent *t* test. Event-free survival rate was evaluated using the Kaplan–Meier analysis, and event rates were compared using the log-rank test. To identify the independent predictor of chemotherapy-induced LVD, multivariate logistic regression analysis was applied to the significant variables in the univariate analysis. A p value of < 0.05 was considered as statistically significant.

Results

Baseline clinical characteristics

Among 826 patients treated with trastuzumab after standard chemotherapy for breast cancer, trastuzumab-induced LVD was developed in 243 patients. On follow-up echocardiography, trastuzumab-induced LVD was improved in 195 patients (80.2%), whereas LVD was persisted in 48 patients (19.8%) (Fig. 1).

Baseline characteristics between the groups are summarized in Table 1. Mean age was 50.9 year, and mean body mass index was 23.6. The patients were showed 10.3% of diabetes and 18.6% of hypertension. There were no significant differences in baseline characteristics including chemotherapy and radiation therapy between the groups.

Laboratory findings

Laboratory findings between the groups are summarized in Table 2. The levels of hemoglobin and albumin at diagnosis of LVD were significantly lower in the non-recovered LVD group than in the recovered LVD group. Other laboratory findings were not different between the groups.

Echocardiographic findings

Pre-chemotherapy echocardiographic findings are summarized in Table 3, and pre-chemotherapy echocardiographic findings were not different between the groups.

Echocardiographic findings at the time of LVD diagnosis and at 6 months from LVD diagnosis are summarized in Table 4.

In echocardiographic examination at the time of LVD diagnosis, LV end diastolic and systolic dimensions were significantly larger, whereas LV EF and GLS were significantly decreased in the non-recovered LVD group than in the recovered LVD group. Late diastolic velocity of mitral inflow and early diastolic velocity of septal annular velocity were significantly lower, whereas right ventricular systolic pressure was significantly higher in in the non-recovered LVD group than in the recovered LVD group.

Table 1 Baseline characteristics of the patients

	Recovered LVD ($n=195$)	Non-recovered LVD ($n=48$)	p value
Age (years)	51.4 ± 10.2	49.6 ± 10.9	0.304
Body mass index (kg/m^2)	23.9 ± 4.2	23.0 ± 2.8	0.206
Hypertension (%)	48 (24.1)	9 (18.8)	0.531
Diabetes (%)	22 (11.3)	4 (8.3)	0.270
Cancer stage III–IV (%)	64 (32.8)	26 (54.2)	0.060
HRT (%)	87 (44.6)	23 (47.9)	0.254
Doxorubicin (%)	92 (47.2)	33 (68.8)	0.118
Epirubicin (%)	42 (21.5)	18 (37.5)	0.531
Paclitaxel (%)	90 (46.2)	31 (64.6)	0.208
Doxorubicin (mg/m^2)	340.6 ± 59.2	356.0 ± 55.2	0.614
Epirubicin (mg/m^2)	108 ± 192.7	135.1 ± 197.1	0.452
Paclitaxel (mg/m^2)	324.9 ± 727.3	343.1 ± 464.6	0.387
RT (%)	117 (60.0)	32 (66.7)	0.243
RT dosage (cGy)	5360.7 ± 1530.8	5682.0 ± 1011.4	0.119

LVD left ventricular dysfunction, *HRT* hormone replacement therapy, *RT* radiation therapy;

Table 2 Laboratory findings of the patients

	Recovered LVD ($n=195$)	Non-recovered LVD ($n=48$)	p value
WBC (mg/dL)	5587.7 ± 2487	4416.7 ± 2155	0.006
Hb (g/dL)	12.1 ± 1.6	11.1 ± 1.7	0.043
Glucose (g/dL)	110.9 ± 43.2	104.3 ± 27.3	0.408
Creatinine (mg/dL)	0.83 ± 0.33	0.87 ± 0.41	0.499
GFR (ml/min)	81.8 ± 33.7	79.9 ± 28.7	0.746
Albumin (mg/dL)	4.4 ± 0.56	3.4 ± 0.56	0.029
TC (mg/dL)	187.2 ± 43.8	185.36 ± 28.3	0.828
TG (mg/dL)	119.6 ± 73.6	25.6 ± 82.1	0.715
LDL (mg.dL)	344 ± 40.3	390 ± 49.2	0.251
CEA (ng/ml)	4.69 ± 21.6	2.33 ± 1.86	0.552

WBC white blood cell, *Hb* hemoglobin, *GFR* glomerular filtration rate, *TC* total cholesterol, *TG* triglyceride, *LDL* low-density lipoprotein cholesterol, *CEA* carcinoembryonic antigen

Table 3 Pre-chemotherapy echocardiographic findings of the patients

	Recovered LVD ($n=195$)	Non-recovered LVD ($n=48$)	p value
LVEDD (mm^2)	46.6 ± 5	47.9.0 ± 6.1	0.344
LVESD (mm^2)	35.8 ± 5.3	36.3 ± 6.0	0.451
EF (%)	67.6 ± 5.3	66.4 ± 8.6	0.222
LAD (mm)	33.7 ± 4.9	34.2 ± 5.2	0.255
GLS (%)	− 19.2 ± 3.38	− 18.7 ± 4.15	0.314
E (cm/s)	0.72 ± 0.26	0.70 ± 0.20	0.822
A (cm/s)	0.74 ± 0.61	0.81 ± 0.32	0.089
DT (ms)	220 ± 41.2	217 ± 48.9	0.077
E′ (cm/s)	0.067 ± 0.19	0.062 ± 0.25	0.515
S′ (cm/s)	0.082 ± 0.08	0.079 ± 0.04	0.442
E/*E′*	9.6 ± 3.9	10.2 ± 4.2	0.371
RVSP (mmHg)	28.9 ± 7.8	27.9 ± 7.8	0.332

LVD left ventricular dysfunction, *LVEDD* left ventricular end diastolic dimension, *LVESD* left ventricular end systolic dimension, *LAD* left atrial dimension, *EF* ejection fraction, *GLS* global longitudinal strain, *E* early mitral inflow velocity, *A* atrial contraction, *DT* deceleration time, *E′* early diastolic velocity of mital septal annulus, *S′* systolic velocity of mitral septal annulus, *RVSP* right ventricular systolic pressure

In echocardiographic examination at 6 months from LVD diagnosis, LV end diastolic and systolic dimensions were significantly larger, whereas LV EF and GLS were significantly decreased in the non-recovered LVD group than in the recovered LVD group. Other echocardiographic findings were not different between the groups (Table 4).

Management of trastuzumab-induced LVD

Trastuzumab therapy was discontinued in 27 patients of the recovered LVD and 17 patients of the non-recovered LVD (13.8% vs 35.4%, $p=0.005$). Mean duration of trasuzumab therapy was 10.7 months (3–15 months), and cycle was 16.2 (1–36) in this population. Angiotensin converting enzyme inhibitors or receptor blockers were used in 23 patients of the recovered LVD and 14 patients of the non-recovered LVD (11.8% vs 29.1%, $p=0.008$), and beta-blockers were used in 17 patients of the recovered LVD and 14 patients of the non-recovered LVD (8.7% vs 29.1%, $p=0.004$).

Independent predictors of non-recovery of LVD

To identify the independent predictors of non-recovery of LVD, multivariate regression analysis including

Table 4 Echocardiographic findings at LVD diagnosis and 6 months from LVD diagnosis

	At LVD diagnosis		*p* value	At 6 months from LVD		*p* value
	Recovered LVD ($n=195$)	Non-recovered LVD ($n=48$)		Recovered LVD ($n=195$)	Non-recovered LVD ($n=48$)	
LVEDD (mm^2)	48.6 ± 4.9	51.0 ± 8.0	0.014	48.3 ± 4.1	52.9 ± 7.1	0.001
LVESD (mm^2)	34.8 ± 4.3	39.3 ± 8.0	0.001	32.0 ± 3.3	38.9 ± 6.5	0.001
EF (%)	54.7 ± 6.0	44.8 ± 10.5	< 0.001	60.4 ± 5.6	47.0 ± 12.6*	< 0.001
LAD (mm)	32.7 ± 4.7	33.8 ± 6.1	0.262	33.0 ± 5.1	36.4 ± 9.9	0.072
GLS (%)	− 15.2 ± 3.18	− 10.7 ± 5.05	0.014	− 18.6 ± 3.59	− 11.8 ± 5.40	0.026
E (cm/s)	0.74 ± 0.20	0.74 ± 0.23	0.893	0.67 ± 0.12	0.73 ± 0.80	0.329
A (cm/s)	0.74 ± 0.18	0.65 ± 0.23	0.009	0.71 ± 0.12	0.61 ± 0.170	0.110
DT (ms)	197.2 ± 48.9	178.3 ± 68.9	0.057	206.0 ± 59.9	184.8 ± 58.1	0.235
E′ (cm/s)	0.087 ± 0.09	0.072 ± 0.05	0.004	0.078 ± 0.2	0.140 ± 0.19	0.123
S′ (cm/s)	0.076 ± 0.07	0.061 ± 0.02	0.218	0.070 ± 0.08	0.112 ± 0.01	0.292
E/*E′*	11.3 ± 4.9	12.3 ± 5.2	0.270	9.77 ± 1.6	12.32 ± 4.2	0.043
RVSP (mmHg)	30.6 ± 6.5	34.6 ± 9.5	0.005	31.9 ± 7.5	35.9 ± 8.7	0.109

LVD left ventricular dysfunction, *LVEDD* left ventricular end diastolic dimension, *LVESD* left ventricular end systolic dimension, *LAD* left atrial dimension; *EF* ejection fraction, *GLS* global longitudinal strain, *E* early mitral inflow velocity, *A* atrial contraction, *DT* deceleration time, *E′* early diastolic velocity of mital septal annulus, *S′* systolic velocity of mitral septal annulus, *RVSP* right ventricular systolic pressure

Table 5 Independent predictors of the non-recovery of left ventricular dysfunction

	RR	CI	*p* value
Anemia	2.149	1.091–4.232	0.027
Hypoalbuminemia	7.000	0.362–13.551	0.198
LVEDD > 55 mm	3.739	2.082–11.993	0.017
LVESD > 40 mm	6.242	2.704–14.409	< 0.001
LVEF < 50%	13.68	6.458–29.018	< 0.001
GLS > − 18%	1.556	0.000-1.053	0.997
RVSP > 35 mmHg	2.409	1.081–5.369	0.031
ACEI or ARB	1.796	0.504–6.406	0.367
BB	2.382	0.712–7.972	0.159

RR relative risk, *CI* confidence interval, *LVEDD* left ventricular end diastolic dimension, *LVESD* left ventricular end systolic dimension, *LVEF* left ventricular ejection fraction, *GLS* global longitudinal strain, *ACEI* angiotensin converting enzyme inhibitor, *ARB* aldosterone receptor blocker, *BB* beta blocker

significant variables in univariate analysis was performed. Anemia (HR = 2.149, CI = 1.091–4.232, $p = 0.027$), decreased LVEF (HR = 13.68, CI = 6.458–29.018, $p < 0.001$), larger LV end-diastolic (HR = 4.997, CI = 2.082–11.993, $p < 0.001$) and systolic dimension (HR = 6.242, CI = 2.704–14.409, $p < 0.001$), and pulmonary hypertension (HR = 2.409, CI = 1.081–5.369, $p = 0.031$) at diagnosis of LVD were independent predictors of non-recovery of LV function in patients with trastuzumab-induced LVD (Table 5).

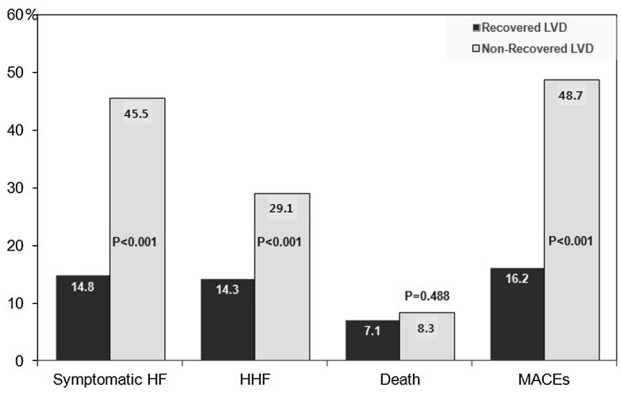

Fig. 2 Major adverse cardiac events (MACEs) during clinical follow-up between the non-recovered left ventricular dysfunction (LVD) and recovered LVD group. *HF* heart failure, *HHF* hospitalization due to heart failure

Clinical outcomes

During 45.9 ± 23.5 months of clinical follow-up, MACEs were developed in 32 patients (15 deaths, 28 symptomatic HF, and 22 HHF). MACEs were significantly higher in the non-recovered LVD than in the recovered LVD [$n = 15$ (31.3%) vs $n = 17$ (10.9%), $p = 0.001$]. Death was not different between the groups [4 deaths (8.3%) in the non-recovered LVD vs 11 deaths (5.6%) in the recovered LVD, $p = 0.488$], but symptomatic HF [$n = 20$ (45.5%) vs $n = 8$ (14.8%), $p < 0.001$] and HHF [$n = 14$ (29.1%) vs $n = 8$ (14.3%), $p < 0.001$] were significantly higher in the non-recovered LVD than in the recovered LVD (Fig. 2). In Kaplan–Meier analysis, event-free survival was significantly

lower in the non-recovered LVD group than in the recovered LVD group (log rank $p = 0.002$) (Fig. 3b).

Discussion

The authors investigated the predictors of LV-functional non-recovery and its impacts on future clinical outcomes in breast cancer patients with trastuzuamb-induced LVD and demonstrated several important findings. First, non-recovery of LV function was not uncommon (19.8%) in breast cancer patients with trastuzumab-induced LVD, even after the discontinuation of trastuzumab. Second, non-recovered LVD was associated with poor clinical outcomes as compared to those of recovered LVD. Third, anemia, decreased LVEF, larger LV dimension, and pulmonary hypertension were independent predictors of non-recovery of LV function in patients with trastuzumab-induced LVD. Therefore, careful monitoring for the development of adverse events and intensive medical management for LVD should be considered in trastuzumab-induced cardiomyopathy with these clinical and echocardiographic characteristics.

Trastuzumab, an anti-HER2 humanized monoclonal antibody, is the standard treatment for both early and metastatic HER2-positive breast cancer. In addition to other chemotherapeutic agents, trastuzumab significantly improves response rate and survival in HER2-positive early and metastatic breast cancer. Although trastuzumab therapy is closely associated with both symptomatic and asymptomatic cardiotoxicity, it has known to Type II cardiotoxicity, considered as reversible [12]. Large-scale clinical studies with trastuzumab have shown that up to 7% or 28% of patients suffer from cardiac dysfunction when trastuzumab is used in monotherapy, or in combination with anthracyclines, respectively [12]. Trastuzumab-induced LVD was noted in 30.6% of patients after chemotherapy in our study, and the incidence of trastuzumab-induced cardiotoxicity seems to be higher as compared to those of the review article of Onitilo et al. [21]. The used chemotherapeutic agent might be a possible explanation of this relatively higher incidence of trastuzumab-induced cardiotoxicity in our study. In the study of Slamon et al., the incidence of trastuzumab-induced cardiotoxicity is about 7% when used as a monotherapy, but the incidence significantly increased up to 28% when use in combination with anthracyclines. Because all patients in our study received chemotherapy before initiating trastuzumab therapy and the majority of them received anthracycline-based chemotherapy, the higher incidence of trastuzumab-induced cardiotoxicity might be explained. The cardiotoxicity of antibodies has been associated to trastuzumab, which induces cardiac dysfunction when used in monotherapy, or in combination with anthracyclines. The exact mechanism of cardiotoxicity by ErbB2 inhibition is not clear, but trastuzumab-induced cardiotoxicity can be due to blockage of HER2 signaling in cardiac myocytes. It is believed that ErbB2 plays a critical role in the developing embryonic heart and it has been shown that deletion of this gene in a preclinical mouse model was responsible for early death [22]. Furthermore, recent retrospective studies

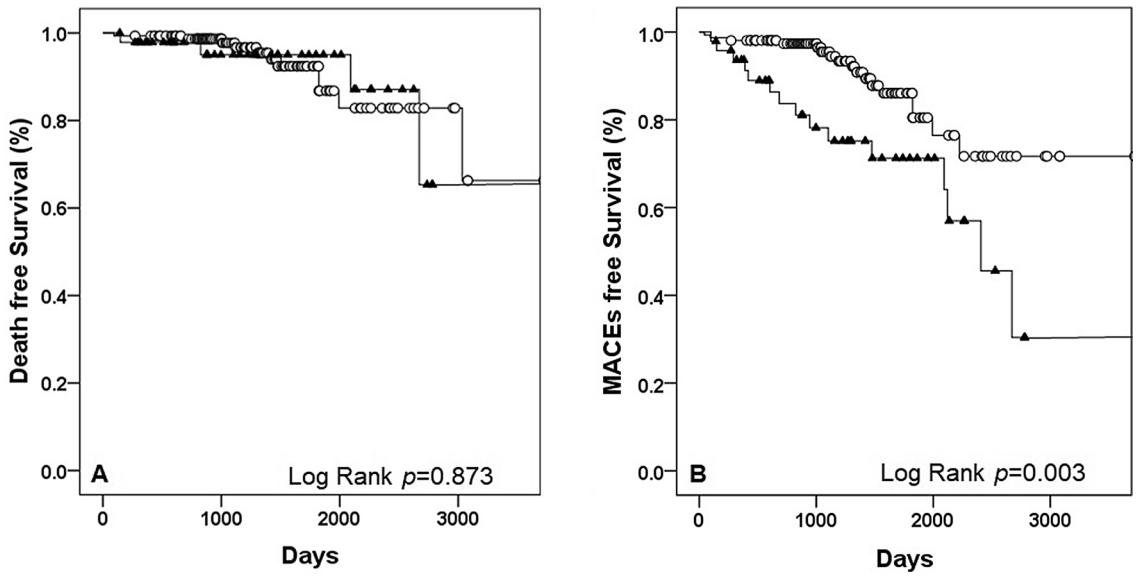

Fig. 3 Death (A) and major adverse cardiac event (MACE)-free survival on Kaplan–Meier curve according to the left ventricular (LV)-functional recovery in patients with trastuzumab-induced LV dysfunction (LVD). Open circle signifies the recovered LVD group, and closed triangle signifies the non-recovered LVD group

have shown an increased incidence of heart failure and/or cardiomyopathy in patients treated with trastuzumab that can persist many years after the conclusion of the therapy, thus suggesting that the side toxic effects are not always reversible, as it was initially proposed [23]. Non-recovery of LV function in breast cancer patients with chemotherapy and trastuzumab-induced LVD was not uncommon (19.8%) after quit the agents in our study. It was not shown reversible course during follow-up duration. Recent report suggests that early initiation of standard medical treatment for HF may lead to LV-functional recovery in chemotherapy-induced cardiotoxicity. However, it is not clear the time of medication or spontaneously recovery [24].

Recently, some studies have shown an increased incidence of HF in patients treated with trastuzumab in monotherapy or in combination with anthracyclines, particularly in elderly breast cancer patients with a history of other diseases [25, 26]. In our previous reports, chemotherapy-related LV dysfunction was associated with lower body mass index and concomitant trastuzumab target therapy [27]. Severe LVD, pulmonary hypertension, and anemia were independent predictors of sustained LV dysfunction in our populations in this study. Age was not related to development and recovery of LV function. It may be a cause that patients in this study were relatively younger than other previous reported groups. It was not clear about contributable factors associated with recovery of LV function after anti-cancer therapy. Data were insufficient about associated factors of sustained LVD until now.

Chronic anemia may also contribute to high-output states. Over the last decade, the prevalence, as the potential treatment options of anemia in HF have received increasing clinical interest and epidemiological studies have indicated a wide variation in the prevalence of anemia in patients with chronic HF [28–30]. More specifically, the prevalence of anemia in HF patients varies in published studies from 4 to 55%, due to heterogeneous patient populations and the lack of specific definition. However, it was not found about the relation between anemia and LVD. In this population, anemia at the point of LVD was the poor prognostic factor of recovery of LV function. Pulmonary hypertension was also bad prognostic factor for functional recovery of LV. Usually, pulmonary hypertension regarded as significant parameter of diastolic dysfunction. Severe LVD, decreased EF less than 45%, was another associated factor of sustained LVD. It might be possible that the large amount of myocardial injury presented to markedly decreased EF. Therefore, the early identification of high-risk patients for sustained LVD in patients with breast cancer underwent chemotherapy and target therapy would be clinically important. On the other hand, the chemotherapy-related cardiotoxic side effects progressively increased after the end of treatment with trastuzumab, thus suggesting that the cardiotoxicity onset could occur even post treatment and the patients were not appropriately subjected to follow-up inspections.

The present study has several potential limitations. First, the present study has all limitations of a retrospective analysis. Second, some patients who developed asymptomatic LVD after chemotherapy and before trastuzumab therapy might be included in the present study, and thus, the results of this study might be affected by these patients to some extent. However, the subjects in this category may be small in number, because the patients with symptoms or signs of HF were excluded in this study. Third, the impacts of anthracyclines on the development of LV dysfunction cannot be excluded in the present study, even though we excluded the patients who developed de novo LVD before the initiation of trastuzumab therapy. Because anthracycline-induced LVD can occur during target therapy, or after the termination of target therapy as a late effect, anthracyclines would be an important contributing factor for the development LV dysfunction after trastuzumab therapy. Fourth, because the presence of coronary artery disease is not routinely evaluated in this study, the impacts of coronary artery disease on the development of trastuzumab-induced cardiotoxicity cannot be evaluated accurately. However, the impacts of coronary artery disease would be minimal, because the subjects enrolled in our study are relatively young female who are low-risk group. Fifth, follow-up duration was not even in this population groups. Because the timing of the follow-up echocardiography was not the same among the patients, the onset of chemotherapy-induced LVD could not be estimated in the present study. It may be possible recover of LVD after final follow-up point. This may suggest that non-recovered LVD was more frequent than that under definition in index period. As for today, assessment of baseline risk factors prior to treatment initiation and cardiac imaging before and during treatment remains the optimal way to prevent cardiac dysfunction. Sixth, the use of angiotensin converting enzyme inhibitors or receptor blockers or beta-blockers is very low in this study, and thus, the effects of cardioprotective agents on LV-functional recovery cannot be evaluated. Many physicians, not in HF specialist, were involved in the treatment of the study population, and the use of these cardioprotective agents was heterogeneous in timing or doses.

Conclusions

Despite these potential limitations, the results of the present study demonstrated that LV-functional non-recovery was not uncommon in breast cancer patients with trastuzumab-induced cardiomyopathy, and non-recovered LVD was significantly associated with adverse clinical events. Decreased LVEF, enlarged LV size, pulmonary hypertension, and anemia at diagnosis of LVD were independent predictors of

LV-functional non-recovery. Therefore, careful monitoring for the development of adverse events and intensive medical management should be considered in trastuzumab-induced cardiomyopathy with these characteristics.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

Ethics approval This study has been approved by our institutional review board (No. 2015-05-092).

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