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ORIGINAL PAPER

Cardioprotective effect of renin–angiotensin inhibitors and β-blockers in trastuzumab-related cardiotoxicity

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Abstract

Background Trastuzumab-related cardiotoxicity (TRC) has been considered as reversible. However, recent studies have raised concern against reversibility of left ventricular (LV) systolic dysfunction in breast cancer patients treated with trastuzumab. In addition, the efficacy of medical treatment for heart failure (HF) including renin–angiotensin inhibitors and β-blockers has not been defined in TRC.

Methods and results We retrospectively studied 160 patients with breast cancer receiving trastuzumab in the adjuvant ($n=129$) as well as metastatic ($n=31$) settings in our institution from 2006 to 2015. During the median follow-up of 3.5 years, 20 patients (15.5%) receiving adjuvant trastuzumab and 7 patients (22.6%) with metastatic breast cancer developed TRC with a mean decrease in LV ejection fraction (EF) of 19.8%. By the multivariate analysis, lower LVEF before trastuzumab (OR 1.30; 95% CI 1.16–1.48; $P=0.0001$) independently predicted subsequent development of TRC. LV systolic dysfunction was reversible in 20 patients (74.1%) with a median time to recovery of 7 months, which was independently associated with lower dose of anthracyclines (OR 1.03; 95% CI 1.01–1.07, $P=0.020$) and an introduction of renin–angiotensin inhibitors and β-blockers (OR 19.0; 95% CI 1.00–592.2, $P=0.034$).

Conclusions Irreversible decline in LVEF occurred in patients who underwent trastuzumab in combination with anthracyclines with a relatively high frequency. The lower cumulative dose of anthracyclines and HF treatment including renin–angiotensin inhibitors and β-blockers were both independent predictors to enhance LV functional reversibility in patients with TRC.

Keywords β-blockers · Cardiotoxicity · Reversibility · Heart failure · Renin–angiotensin inhibitors · Trastuzumab

Introduction

Breast cancer is the most common and frequently diagnosed cancer among women in the world. Approximately 25–30% of breast cancers have overexpression of human epidermal growth factor receptor 2 (HER2), which confers an aggressive clinical phenotype including increased growth and proliferation, early systemic metastasis, and high risk of recurrence [1, 2]. Trastuzumab, a monoclonal antibody targeting against HER2, has achieved a major breakthrough in the treatment of early-stage and metastatic HER2-positive breast cancer that reduced cancer recurrence and improved survival [3–6]. It, alone and in combination with anthracycline-based chemotherapy, has become a mainstay in the treatment of HER2-positive breast cancer for both curative adjuvant and metastatic settings [4, 5, 7].

Despite its adoption in the management of breast cancer, the use of trastuzumab, especially when given with anthracyclines, has led to an unexpectedly high incidence of cardiotoxicity, usually manifested as congestive heart failure (HF) or asymptomatic decrease in left ventricular ejection fraction (LVEF). The incidence of trastuzumab-related cardiotoxicity (TRC) has been reported as high as 43.6%, which varies depending on the definition used, patient comorbidity, and different regimens [8]. Its mechanisms remain to be clarified; however, cardiac dysfunction can be attributed to

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cardioprotective HER2 signaling blockade [9] and increased oxidative stress in cardiomyocytes [10, 11]. In contrast to the cardiotoxicity induced by anthracyclines, TRC constitutes an entity known as a type II chemotherapy-related cardiac dysfunction, characterized by a largely reversible cardiac damage with benign myocardial structural change and no cumulative dose relationship [12]. Despite the reversibility of TRC, this cardiotoxicity frequently leads to premature discontinuation of trastuzumab therapy which resulted in suboptimal cancer treatment and thereby may increase the chance of cancer recurrence [13]. This is a particular concern in the metastatic setting where benefits of prolonged trastuzumab administration may weigh cardiac harms. Additionally, the recent reports raise fundamental doubts about the reversibility of TRC by showing that 40% of TRC patients represented sustained systolic dysfunction [14–16] and failed reversibility of systolic dysfunction was associated with adverse cardiac events [14].

Despite a high incidence of TRC, knowledge about early diagnosis and optimal treatment is limited. Although several risk factors for TRC have been described [8, 17], it remains uncertain whether those are consistently applied to all patients with various clinical backgrounds. Advances have been made in reducing anthracyline-induced cardiotoxicity [18, 19], but little is known about optimal management for TRC. Recent randomized studies provided a potential of HF medical treatment including renin–angiotensin inhibitors and β-blockers to prevent TRC. However, the role of HF treatment in TRC was not established and predictors of LV function reversibility were poorly characterized. Defining the consequences of TRC is mandatory as physicians are encountered to weigh the risks versus benefits of trastuzumab therapy in patients with breast cancer. Accordingly, we examined the demographic and clinical characteristics, the incidence of TRC, the clinical parameters which may predispose patients to adverse cardiac events and irreversibility in both adjuvant and metastatic settings.

Methods

Study cohort

All consecutive patients with HER2-positive breast cancer received trastuzumab in the adjuvant (stage I through III) or metastatic (stage IV) settings from January 1, 2006, to December 31, 2015, were included in our institution. Patients were excluded if breast cancer was not the initial primary cancer or serial echocardiographic assessments were not performed to assess diagnostic accuracy over time. Previous chemotherapy included regimens with or without anthracyclines. The typical adjuvant regimen consisted of FEC100 (epirubicin 100 mg/m^2, 5-FU 500 mg/m^2, and cyclophosphamide 500 mg/m^2) followed by four cycles of weekly paclitaxel (80 mg/m^2) and trastuzumab (initial dose of 4 mg/kg, followed by 2 mg/kg). Adjuvant trastuzumab therapy was conducted for 12 months. Maintenance trastuzumab therapy was conducted for metastatic setting depending on the disease progression. Irradiation of the mediastinal internal mammary node was received if applicable. All patient data were encrypted and de-identified before the statistical analysis and this protocol was approved by Kyushu University Hospital Institutional Review Board.

Definition of TRC

The cardiotoxicity was defined and graded according to the expert consensus statement [20] and the National Cancer Institute Common Toxicity Criteria for Adverse Event, version 4.0 (CTCAE4), respectively. In brief, TRC was defined as a decrease in the LVEF of 10% points from baseline, to a value < 53%. In patients with a reduced LVEF (< 53%) at baseline, a drop in LVEF of more than 10% points was defined as TRC. This decrease was confirmed by repeated echocardiography 3–4 weeks after the diagnostic study. Severity grading systems of TRC were as follows; Grade I asymptomatic decline in LVEF of 10% points from baseline, Grade II asymptomatic decline in LVEF of < 50% or < 20% points compared with baseline, Grade III symptomatic decline in LVEF of < 40% or ≥ 20% points compared with baseline, Grade IV severe heart failure requiring intensive therapy, Grade V death.

Cardiac evaluation

Patients with serial echocardiographic assessments performed before chemotherapy, at baseline (before trastuzumab initiation), during trastuzumab therapy, yearly after drug discontinuation were identified. The LV cavity dimensions and LVEF were measured from the modified biplane Simpson's method. Tissue Doppler Imaging velocities were measured from the septal annulus in the apical four-chamber view. All echocardiograms were reviewed by two independent investigators.

Reversibility of cardiac dysfunction

Reversibility of cardiac dysfunction was defined as an increase in LVEF > 10% points from the nadir, and irreversibility when an increase in LVEF < 10% points from the nadir and remaining > 5% points below the baseline [20].

Discontinuation of trastuzumab and introduction of HF medical treatment

Trastuzumab was discontinued in patients who developed an asymptomatic decrease in LVEF or overt HF according

to the discretion of oncologists. HF therapy including renin–angiotensin inhibitors or β-blockers was instituted and up-titrated in patients who were referred to cardiologists. Additional cardiac treatment including diuretics or anticoagulants was given based on the clinical situation. The decision to resume trastuzumab was left to the discretion of the oncologists after careful evaluation of the risks and potential benefits of trastuzumab therapy.

Data extraction

Data were obtained for enrolled patients regarding demographics, comorbidities, cardiac diseases including ischemic heart disease, valvular heart disease, arrhythmia, and congenital heart disease, breast cancer features including stage at diagnosis, tumor size, histology, hormone receptor, concurrent chemotherapy regimens, surgery, and site of radiation therapy, and clinical status.

Statistical analysis

Categorical data are presented as numbers with percentages. Continuous data which are non-normally distributed are presented as medians with first and third quartiles, and data which are normally distributed are presented as a mean and standard deviation. Normality was analyzed by the D'Agostino-Pearson test. Comparison between continuous variables was assessed using the Mann–Whitney *U* test or Student's *t* test as appropriate. Comparison between categorical variables was analyzed using Fisher's exact test. Time-to-TRC was calculated using the Kaplan–Meier method and compared by log-rank test. Independent correlates of TRC were identified by multivariable logistic regression analysis, adjusting for confounders. Covariates with a *P* value of less than 0.10 in the univariate analysis and predefined baseline covariates were entered in the multivariate model, and non-significant factors were removed by a stepwise selection procedure. All-probability values were two-tailed, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed with the use of JMP statistical package and GraphPad Prism.

Results

Study population

This study included 160 breast cancer patients that received trastuzumab as adjuvant ($n = 129$) or metastatic maintenance ($n = 31$) therapy. Their mean age at diagnosis was 56 years. The median time of trastuzumab treatment was 12 months [interquartile range (IQR) 11–14 months] and 18 cycles (IQR 17–18 cycles). The majority of patients (76.4%) received anthracycline-based chemotherapy prior to trastuzumab therapy. Median time from the last anthracycline administration to the initiation of trastuzumab was 32 days (IQR 21–66 days).

Trastuzumab-related cardiotoxicity (TRC)

During the median follow-up of 18 months (IQR 14–30 months) from the start of chemotherapy to last echocardiography, 27 patients (16.9%) developed TRC (Table 1). Twenty patients (12.5%) experienced Grade I and II asymptomatic LVEF decrease and 7 patients (4.4%) developed Grade III symptomatic HF (Table 1). Overall, 7 out of the 27 patients (25.9%) diagnosed as TRC were symptomatic. Figure 1a shows the Kaplan–Meier curve of onset of TRC after trastuzumab therapy and the median time to develop TRC was 4 months (IQR 3–6 months). Maximum LVEF decline was $19.8 \pm 9.8\%$ (Fig. 1b).

Table 2 summarizes the clinical characteristics of patients who developed TRC or not. Univariate analysis showed that there was no difference in the stage and phenotype of breast cancer, cumulative dose of prior anthracyclines, time from last anthracyclines to trastuzumab administration, trastuzumab cycle, concomitant chemotherapy, or left chest radiation therapy between the groups. The prevalence of underlying cardiovascular risk factors and cardiac comorbidities also did not differ between groups. In contrast, LVDs, LVEDVI, and LVESVI before trastuzumab therapy were significantly larger in patients with TRC than those with No TRC. Corresponding with these findings, LVEF and S' before trastuzumab therapy were significantly lower in patients with TRC. By multivariate analysis, lower LVEF before trastuzumab independently predicted subsequent development of TRC (Table 3).

At the last follow-up of 3.5 years, 14 (8.8%) patients had died. All the patients died of tumor-related causes, and no cardiac death was identified. When stratified by TRC, cumulative all-cause mortality rates were not significantly different between patients who developed TRC and those who did not.

Table 1 Trastuzumab-related cardiotoxicity

Characteristics	No. of patients	%
Trastuzumab-related cardiotoxicity	27	16.9
Grade		
I	10	6.3
II	10	6.3
III	7	4.4
IV	0	0
V	0	0

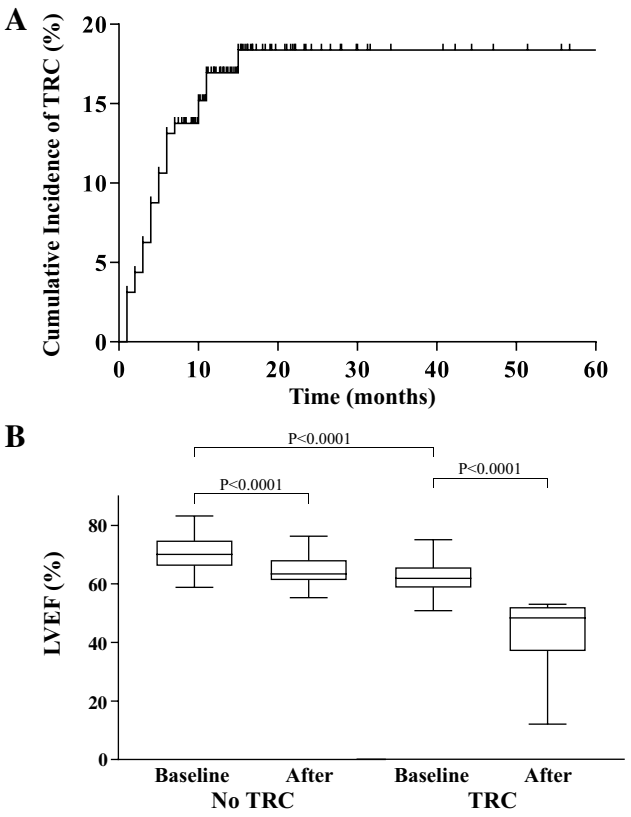

Fig. 1 **a** Cumulative incidence of trastuzumab-related cardiotoxicity (TRC) after trastuzumab therapy. **b** Time-dependent changes of left ventricular ejection fraction (LVEF) at baseline and after trastuzumab therapy for patients with TRC or No TRC. Box-plot values are expressed as the median (horizontal line in each box) and 25th and 75th percentiles (top and bottom of each box), with whiskers (top and bottom of each bar) drawn to the minimum and maximum values

Reversibility of LV systolic dysfunction

Among the patients who experienced TRC, 19 patients (70.4%) had trastuzumab therapy withheld due to the decrease in LVEF or the development of clinical HF. The median interruption period was 69 days (IQR 44–84 days). Among 15 patients, trastuzumab therapy was conducted again after LVEF recovery; however, 8 patients experienced further decrease in LVEF, leading to the second discontinuation of trastuzumab therapy. On the other hand, trastuzumab therapy was permanently discontinued in 4 patients (14.8%) owing to the sustained decrease in LVEF even after the discontinuation of trastuzumab.

Among the 27 patients who developed TRC, 19 (70.4%) patients were referred to cardiologists and HF treatment including renin–angiotensin inhibitors and/or β-blocker was introduced in 14 (51.9%) patients. In 20 (74.1%) patients who developed TRC, LV systolic dysfunction was reversible by trastuzumab discontinuation or initiation of HF treatment after a median time of 7 months (IQR 4–9 months). The mean LVEF of those with reversibility or irreversibility at last follow-up was 60.6% and 48.1% ($P=0.0007$, Fig. 2), respectively. Of note, the LVEF of those with reversibility did not fully restore to the pre-chemotherapy baseline level ($P=0.024$). Table 4 shows the clinical characteristics of patients who had reversibility of cardiac dysfunction and those who had an irreversible cardiac dysfunction. LVEF before trastuzumab, at TRC, and at the lowest value were not different between reversibility and irreversibility. By univariate analysis, lower cumulative doxorubicin dose and HF treatment including renin–angiotensin inhibitors and β-blockers were associated with reversibility of cardiac dysfunction (Table 4). By multivariate analysis, lower cumulative doxorubicin dose and HF treatment independently predicted reversibility of cardiac dysfunction (Table 5).

There was no difference in the clinical characteristics of patients who received HF treatment or not. LVEF significantly increased after discontinuation of trastuzumab without HF treatment (47.8 ± 9.7–$56.6\pm11.4\%$, $P<0.0004$, Fig. 3). The lowest LVEF in patients who received HF treatment was lower than that in patients who did not ($38.5\pm11.4\%$ vs $47.8\pm9.7\%$, $P=0.032$); however, the LVEF at last follow-up was not significantly different between the patients with HF treatment or not ($58.0\pm5.9\%$ vs $56.6\pm11.4\%$, $P=0.64$, Fig. 3). Discontinuation of trastuzumab therapy as a result of LV dysfunction was not observed in patients with the introduction of HF treatment.

Discussion

This retrospective analysis demonstrated that cardiotoxicity developed in 16.9% of patients treated with trastuzumab, with or without preceding anthracycline therapy and lower LVEF before trastuzumab therapy was independently associated with the development of TRC. In addition, LV systolic dysfunction was reversible in 74.1% of patients who developed TRC, which was independently associated with the lower anthracycline dose and the introduction of HF treatment.

In our study, 15.5% of patients received trastuzumab with adjuvant chemotherapy and 22.6% of those with palliative chemotherapy developed TRC. Overall, symptomatic HF and asymptomatic decline of LVEF occurred among 4.4% and 12.5% of patients who received trastuzumab, respectively. The incidence of TRC in previous reports varied according to its definition, study types, study populations, and concomitant chemotherapy regimens. Randomized controlled trials (RCTs) including only patients who met stringent cardiac eligibility criteria and received rigorous monitoring of cardiac function reported symptomatic HF in 0.8–14.2% of patients, and total TRC in 5.7–35.4% of patients. Community-based cohort studies including more heterogeneous

Table 2 Baseline characteristics of studied patients according to the occurrence of TRC

Characteristics	Total $N=160$	TRC $N=27$	No TRC $N=133$	P value
Demographics				
Age at diagnosis, year	56 ± 12	52 ± 12	57 ± 12	0.51
Body mass index	22.6 ± 4.6	21.8 ± 4.9	22.8 ± 4.5	0.31
Breast cancer stage				0.41
Early	95 (59.4)	13 (48.1)	82 (65.4)	
Advanced	34 (21.3)	7 (25.9)	27 (20.3)	
Metastatic	31 (19.4)	7 (25.9)	24 (18.0)	
Affected breast				0.73
Right	74 (46.3)	11 (40.7)	63 (47.4)	
Left	83 (51.9)	16 (59.3)	67 (50.4)	
Bilateral	3 (1.9)	0 (0)	3 (2.3)	
Tumor grade				
Estrogen receptor+	90 (56.3)	17 (63.0)	73 (54.9)	0.53
Progesterone receptor+	65 (40.6)	12 (44.4)	53 (39.8)	0.67
HER2+	100 (160)	27 (100)	133 (100)	1.00
Cancer type				0.36
Invasive ductal carcinoma	146 (91.3)	26 (96.3)	120 (90.2)	
Invasive lobular carcinoma	2 (1.3)	1 (3.7)	1 (0.8)	
Invasive micropapillary carcinoma	2 (1.3)	0 (0)	2 (1.5)	
Medullary carcinoma	2 (1.3)	0 (0)	2 (1.5)	
Others	8 (5.0)	0 (0)	8 (6.0)	
Prior chemotherapy				
Anthracyclines	125 (76.4)	23 (85.2)	102 (76.7)	0.45
Doxorubicin	7 (4.4)	0 (0)	7 (5.3)	0.60
Epirubicin	118 (73.8)	23 (85.2)	95 (71.4)	0.16
Cumulative dose				
Doxorubicin, mg/m^2	240 ± 0	0	240 ± 0	
Epirubicin, mg/m^2	393 ± 66	423 ± 91	386 ± 56	
Doxorubicin equivalents, mg/m^2	199 ± 34	212 ± 45	198 ± 30	0.095
Time from last anthracycline administration to trastuzumab initiation, days	32 (21–66)	39 (28–85)	31 (21–61)	0.32
Trastuzumab cycle	18 (17–18)	17 (17–18)	18 (17–18)	0.098
Concomitant anti-cancer agent				
Microtubule-targeting agent	129 (80.6)	20 (74.1)	109 (82..0)	0.42
Antimetabolites	93 (58.1)	13 (48.1)	80 (60.1)	0.29
Alkylating agent	119 (74.4)	21 (77.8)	98 (73.7)	0.81
Selective estrogen-receptor modulators	29 (18.1)	5 (18.5)	24 (18.0)	> 0.99
Left chest radiation therapy	38 (23.8)	6 (22.2)	32 (24.1)	> 0.99
Cardiovascular risk factors				
Hypertension	30 (18.8)	3 (11.1)	27 (20.3)	0.42
Diabetes mellitus	11 (6.9)	1 (3.7)	10 (7.5)	0.69
Hypercholesterolemia	15 (9.4)	2 (7.4)	13 (9.8)	> 0.99
Smoking	30 (18.8)	4 (14.8)	26 (19.5)	0.79
Cardiac disease	11 (6.9)	1 (3.7)	10 (7.5)	0.69
Echocardiographic data before trastuzumab therapy				
LVDd, mm	45.5 ± 4.4	46.7 ± 4.7	45.3 ± 4.3	0.20
LVDs, mm	27.7 ± 3.8	30.9 ± 4.6	27.1 ± 3.3	< 0.0001
LVEDVI, mL/m^2	63.5 ± 13.5	69.1 ± 18.2	62.5 ± 12.1	0.040
LVESVI, mL/m^2	19.7 ± 6.8	26.9 ± 9.0	18.5 ± 5.1	< 0.0001
LVEF, %	69.3 ± 6.6	61.6 ± 6.9	70.4 ± 5.5	< 0.0001

Table 2 (continued)

Characteristics	Total $N=160$	TRC $N=27$	No TRC $N=133$	P value
LAD, mm	34.5 ± 6.0	33.1 ± 4.8	34.7 ± 6.2	0.27
LAVI	29.1 ± 8.5	30.3 ± 10.7	29.0 ± 8.3	0.66
S′	7.4 ± 1.5	6.4 ± 1.3	7.5 ± 1.5	0.0022
E/*A*	1.1 ± 0.4	1.1 ± 0.5	1.0 ± 0.4	0.86
E′	7.3 ± 2.2	7.3 ± 2.6	7.3 ± 2.2	0.96
E/*E′*	10.2 ± 3.3	9.7 ± 3.8	10.3 ± 3.2	0.50

Data are presented as number (%) of patients, mean ± SD, or median (quartiles 1–3)

HER2, human epidermal growth factor receptor type2; LVDd, left ventricular diameter diastole; LVDs, left ventricular diameter systole; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; LAVI, left atrial volume index

Table 3 Multivariate logistic model for the development of TRC

Variable	OR	CI	P value
Age at diagnosis, year	1.00	0.96–1.05	0.84
Body mass index	1.02	0.90–1.15	0.77
Doxorubicin equivalent dose, mg/m^2	1.00	0.99–1.01	0.16
LVEF before trastuzumab, %	1.30	1.16–1.48	0.0001

OR, odds ratio; CI, per 1 unit change of continuous variable; LVEF, left ventricular ejection fraction

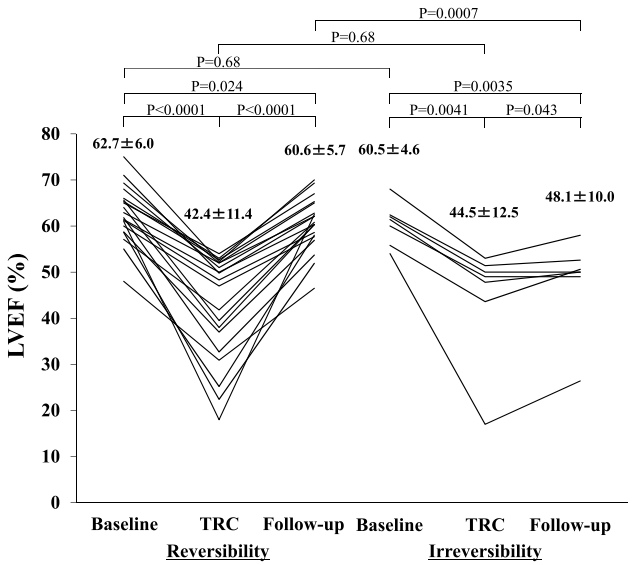

Fig. 2 Left ventricular ejection fraction for the individual patient with TRC who showed reversibility or irreversibility of LV systolic dysfunction at baseline, lowest LVEF, and last follow-up

population reported symptomatic HF in 0–6.7% of patients, and total TRC in 11.4–43.6% of patients [8]. Our data were almost comparable to these previous reports.

TRC occurred relatively early after the initiation of trastuzumab at the median time of 4 months, which was also consistent with previous reports [3, 17, 21]. Importantly, the incidence of all TRC was confined to the period during trastuzumab treatment and did not increase after completion of treatment, which was consistent with long-term follow-up RCT data [22]. These features are distinct from anthracycline-related cardiotoxicity which usually manifest following to treatment [23, 24].

The value of LVEF measured before trastuzumab therapy was independently associated with the development of TRC, which was in line with a large clinical study [25]. This observation suggests the double-hit phenomenon in patients with cardiomyocyte made vulnerable by the preceding anthracycline therapy and susceptible to further cardiac insults by trastuzumab [26]. In our study, 76.4% of patients received preceding anthracycline therapy and a 5.8% decrease in LVEF at the completion of anthracycline therapy was detected in patients developing subsequent TRC. Anthracyclines and trastuzumab act synergistically to develop cardiotoxicity. When anthracycline causes subclinical LV dysfunction, the ability of cardiomyocytes to repair the damage might be impaired by following administration of trastuzumab by interfering HER2/Neuregulin signaling pathways essential for cardiomyocyte survival and protection against cardiac injury [27]. This hypothesis is supported by the fact that the incidence of TRC had an inverse correlation with the time from last anthracycline administration to trastuzumab initiation [12]. Recent studies reported that cardiac troponins and systolic deformation indices measured by longitudinal strain echocardiography after the completion of anthracycline therapy predicted subsequent development of TRC [14, 28] and cumulative anthracycline dose increased the risk of TRC [29]. The present study failed to observe anthracycline dose as an independent predictor of TRC and the lack of association might be the result of the lower dose of anthracyclines administered compared with the prior studies. Large-scale cohort studies showed that the cumulative incidence of symptomatic HF or asymptomatic decline of LVEF was higher in patients treated with trastuzumab in combination

Table 4 Characteristics of patients with reversibility of LV dysfunction

Characteristics	Reversibility $N=20$	Irreversibility $N=7$	P value
Demographics			
Age at diagnosis, year	52 ± 12	51 ± 11	0.63
Body mass index	22.7 ± 5.3	19.1 ± 2.5	0.094
Breast cancer stage			0.62
Early	10 (50.0)	3 (42.9)	
Advanced	6 (30.0)	1 (14.3)	
Metastatic	4 (20.0)	3 (42.9)	
Affected breast			> 0.99
Right	8 (0.0)	3 (42.9)	
Left	12 (60.0)	4 (57.1)	
Tumor grade			
Estrogen receptor+	12 (60.0)	5 (71.4)	0.68
Progesterone receptor+	8 (40.0)	4 (57.1)	0.66
HER2+	20 (100)	7 (100)	1.00
Left radiation therapy	4 (20.0)	2 (28.6)	0.63
Prior chemotherapy			0.31
Anthracycline chemotherapy	16 (81.0)	7 (100)	0.55
Cumulative doxorubicin equivalent dose, mg/m^2	199 ± 36	240 ± 55	0.032
Concomitant anti-cancer agent			
Microtubule-targeting agent	15 (75.0)	7 (100)	0.28
Antimetabolites	8 (40.0)	6 (85.7)	0.077
Alkylating agent	15 (75.0)	6 (85.7)	> 0.99
Selective estrogen-receptor modulators	2 (10.0)	3 (42.9)	0.091
Cardiovascular risk factors			
Hypertension	3 (15.0)	0 (0)	0.55
Diabetes	1 (5.0)	0 (0)	> 0.99
Hypercholesterolemia	2 (10.0)	0 (0)	> 0.99
Smoker	2 (10.0)	2 (28.6)	0.27
Cardiac disease	1 (5.0)	0 (0)	> 0.99
TRC			0.74
I	7 (35.0)	3 (42.9)	
II	7 (35.0)	3 (42.9)	
III	6 (30.0)	1 (14.3)	
Time from last anthracycline administration to trastuzumab initiation, days	34 (24–67)	54 (38–128)	0.23
Time from trastuzumab initiation to TRC, months	4.0 (2.0–6.3)	6.0 (4.0–6.0)	0.50
Medication			
HF treatment (renin–angiotensin inhibitors and/or β-blocker)	13 (65.0)	1 (14.3)	0.033
Statin	2 (10.0)	0 (0)	> 0.99
Echocardiographic data before trastuzumab therapy			
LVDd, mm	46.5 ± 4.3	45.0 ± 4.0	0.47
LVDs, mm	30.9 ± 4.7	30.0 ± 3.7	0.65
LVEDVI, mL/m^2	67.8 ± 17.3	64.3 ± 14.8	0.70
LVESVI, mL/m^2	25.7 ± 9.0	25.2 ± 7.0	0.78
LVEF, %	63.8 ± 9.6	60.7 ± 6.8	0.59
LAD, mm	33.2 ± 4.2	28.7 ± 4.6	0.051
S'	6.2 ± 1.0	7.2 ± 1.8	0.10
E/A	1.0 ± 0.5	1.1 ± 0.5	0.78
E'	6.9 ± 2.8	8.5 ± 1.6	0.48
E/E'	9.9 ± 4.2	7.6 ± 1.0	0.18

Table 4 (continued)

Characteristics	Reversibility $N=20$	Irreversibility $N=7$	P value
Echocardiographic data at TRC			
LVDd, mm	49.7 ± 5.8	47.7 ± 3.8	0.60
LVDs, mm	37.4 ± 6.8	33.1 ± 2.2	0.15
LVEDVI, mL/m^2	78.4 ± 24.2	72.4 ± 13.4	0.67
LVESVI, mL/m^2	40.2 ± 18.2	32.5 ± 6.2	0.33
LVEF, %	50.3 ± 7.8	53.8 ± 5.0	0.68
LAD, mm	35.0 ± 5.7	31.3 ± 6.3	0.15
S′	5.9 ± 1.4	6.4 ± 0.8	0.26
E/A	1.2 ± 0.5	1.2 ± 0.3	0.79
E′	7.0 ± 3.2	8.4 ± 0.9	0.36
E/E′	11.9 ± 6.5	8.6 ± 1.6	0.21
Lowest LVEF	42.2 ± 11.8	43.9 ± 15.7	0.68
Maximal LVEF decline, %	20.6 ± 9.3	17.4 ± 12.1	0.28

Data are presented as number (%) of patients, mean ± SD, or median (quartiles 1–3)

HER2, human epidermal growth factor receptor type2; LVDd, left ventricular diameter diastole; LVDs, left ventricular diameter systole; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; LAD, left atrial diameter

Table 5 Multivariate logistic model for reversibility of LV dysfunction

Variable	OR	CI	P value
Doxorubicin equivalent dose, mg/m^2	1.03	1.01–1.07	0.020
HF treatment (renin–angiotensin inhibitors and/or β-blocker)	19.0	1.00–592.2	0.034
Body mass index	1.43	0.85–2.38	0.14
Lowest LVEF, %	1.06	0.92–1.25	0.36

LVEF, left ventricular ejection fraction; OR, odds ratio; CI, per 1 unit change of continuous variable

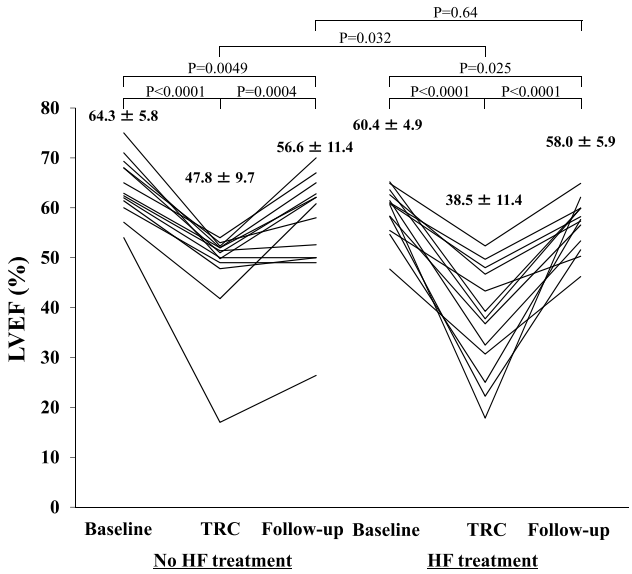

Fig. 3 Left ventricular ejection fraction for the individual patient with TRC who received HF treatment or not before chemotherapy, lowest LVEF, and last follow-up

with anthracyclines than those that received trastuzumab in monotherapy [30, 31]. In RCTs, 2–8% of patients were excluded from candidates for trastuzumab therapy due to LV dysfunction after the conclusion of anthracycline-based therapy [21, 32]. These findings underline the essential role of anthracyclines in the development of TRC and emphasize the importance of cardiac assessment before the initiation of trastuzumab, especially after anthracycline treatment.

Although the risk of symptomatic HF by trastuzumab was relatively low, the development of TRC during chemotherapy has several potential consequences including premature trastuzumab discontinuation. In clinical practice, discontinuation of trastuzumab is recommended when LVEF declines ≥ 16% from baseline value or when it decreases lower than normal level and ≥ 10% from baseline value. Following these instructions, asymptomatic or symptomatic TRC led to discontinuation or permanent cessation of trastuzumab among 70.4% of TRC patients in our study. Furthermore, 53.3% of patients who later received trastuzumab therapy after LVEF recovery suffered further LVEF decline, resulting in the second discontinuation of trastuzumab therapy. Recent studies suggest that early discontinuation of trastuzumab may elevate major adverse cardiac events and cancer recurrence, leading to poor survival [33]. Additionally, shorter duration of trastuzumab therapy failed to show non-inferiority compared to standard therapy [34, 35].

Ewer and Lippman proposed to classify cardiotoxicity as type I and II based on the structural abnormalities and the potential reversibility of cardiac dysfunction [12]. Type I cardiotoxicity, defined as irreversible cardiac damage which is accompanied by ultrastructural change, is caused by anthracyclines. Type II cardiotoxicity induced by trastuzumab has long been considered reversible after the discontinuation of therapy and characterized as myocardial stunning without structural myocardial change. However, subsequent analyses showed that the decrease in LVEF seen in patients treated with anthracyclines and trastuzumab did not reverse to baseline values despite its discontinuation [14, 15, 36]. Our results also support these findings, and 25.9% of patients with TRC had a sustained decrease in LVEF even after trastuzumab discontinuation. Additionally, the LVEF of those with reversibility did not fully recover to the pre-chemotherapy baseline level. Multivariate analysis in our study revealed that the cumulative anthracycline dose was an independent predictor of irreversible decline in LVEF. The previous study showed that the reversibility of cardiac dysfunction occurred less frequently in troponin-positive patients who were exposed to prior anthracyclines [14]. These findings suggest that a synergistic effect of anthracyclines and trastuzumab exists to develop TRC as well as irreversibility of LV dysfunction. On the other hand, preclinical studies showed that trastuzumab itself induced apoptosis of cardiomyocyte thus leading to the irreversible change observed by electron microscopy [11, 37]. The persistent decline in LVEF following trastuzumab administration without anthracyclines has been reported [38]. Large clinical studies revealed that cumulative incidence of heart failure continued to increase with time in patients who underwent trastuzumab in monotherapy or in combination with anthracyclines [31, 39]. These findings suggest that trastuzumab may cause long-lasting effects on the myocardium and the cardiac damage associated with anthracyclines or trastuzumab show considerable overlap. In the clinical settings, anthracyclines and trastuzumab are usually sequentially administered and the final manifestation of cardiac dysfunction results from a synergic or combined effect of both agents. Consequently, it is difficult to distinguish cardiac damages caused by anthracyclines from those by trastuzumab in patients that received their combination. Long-term follow-up data showed that subclinical LV dysfunction persisted for several years after the conclusion of chemotherapy [21, 32]. Therefore, strategies to detect and minimize TRC should be investigated to prevent sustained LV dysfunction.

The reversibility of LV systolic dysfunction was associated with the support of renin–angiotensin inhibitors and β-blockers. Even granting that spontaneous reversibility of cardiac dysfunction had occurred by cessation of trastuzumab, the rate of reversibility was greater in patients treated with renin–angiotensin inhibitors and β-blockers than those without them (92.9% vs 53.8%, $P=0.033$). These findings were in agreement with the retrospective studies and the recent RCT [17, 40–42]. The prophylactic administration of renin–angiotensin inhibitors and β-blockers to prevent cardiotoxicity is the subject of recent clinical research. However, there have been conflicting results about which HF treatment provides the best benefit. The Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy (PRADA) trial showed the modest benefit of candesartan, but not metoprolol, in preventing the decline in LVEF [42]. Another RCT failed to reproduce the beneficial effects of candesartan [43]. The MANTICORE-101 (Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research) trial showed the modest benefit of bisoprolol compared to perindopril in preventing the decline in LVEF [41]. However, all these clinical trials are limited by their small sample size, different chemotherapy regimens, and different timing of prophylactic administration. Furthermore, the endpoints of asymptomatic LV dysfunction or heart failure were not evaluated. Therefore, there is currently insufficient data to identify which HF treatment is superior. A re-challenge with trastuzumab after recovery of LVEF following discontinuation of trastuzumab or HF treatment has been well tolerated [44]. However, our study demonstrated that recurrent decline of LVEF was observed among 53.3% of patients. The discrepancy can be explained by all the patients who underwent a second interruption of trastuzumab therapy did not receive HF treatment. These findings suggest that even if LVEF recovers after discontinuation of trastuzumab, cardiac damage may render the myocardium susceptible to subsequent insults and need to be protected by HF treatment. In support of this hypothesis, HF treatment induced reversibility after the discontinuation of trastuzumab [44]. Formulated guidelines for the treatment of TRC are not yet available, HF treatment needs to be considered for patients who developed TRC [45]. In contrast, the mechanisms underlying its beneficial effect on LVEF reversibility have not been studied. A recent study showed that HF treatment did not prevent LV remodeling [41]. Further studies are warranted to investigate its incremental benefit.

Study limitations

Our study was limited by the retrospective nature of the available data at a single institution and the potential for selection bias. The sample size was small and the duration of follow-up was not long. The timing of echocardiograms was not uniform in each patient. Cardiac MRI which has the potential to detect early cardiotoxicity was not performed in this study. Consequently, the incidences of TRC and cardiac recovery were likely underestimated or overestimated. It is

possible that further reversibility would be observed with additional long-term follow-up.

Conclusions

TRC was a relatively frequent side effect that leads to discontinuation of life-saving trastuzumab therapies in breast cancer patients particularly with reduced LVEF before treatment. Cardiac dysfunction was reversible in 74.1% of patients and the lack of HF treatment might fail to recover from TRC. Early identification of patients who may develop TRC and appropriate HF treatment might enhance cardiac reversibility.

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Compliance with ethical standards

Conflict of interest Dr. Tsutsui has received the research grant from Actelion, Daichii-Sankyo, and Astellas, and lecture fees from Astellas, Otsuka, Takeda, Daichii-Sankyo, Mitsubishi Tanabe, Boehringer Ingelheim, Novartis, Bayer, and Bristol-Myers Squibb.

References

1. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL (1987) Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 235(4785):177–182
2. Gabos Z, Sinha R, Hanson J, Chauhan N, Hugh J, Mackey JR, Abdulkarim B (2006) Prognostic significance of human epidermal growth factor receptor positivity for the development of brain metastasis after newly diagnosed breast cancer. J Clin Oncol 24(36):5658–5663. https://doi.org/10.1200/JCO.2006.07.0250
3. Smith I, Procter M, Gelber RD, Guillaume S, Feyereislova A, Dowsett M, Goldhirsch A, Untch M, Mariani G, Baselga J, Kaufmann M, Cameron D, Bell R, Bergh J, Coleman R, Wardley A, Harbeck N, Lopez RI, Mallmann P, Gelmon K, Wilcken N, Wist E, Sanchez Rovira P, Piccart-Gebhart MJ, team Hs (2007) 2-Year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet 369(9555):29–36. https://doi.org/10.1016/S0140-6736(07)60028-2
4. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J, Norton L (2001) Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 344(11):783–792. https://doi.org/10.1056/NEJM200103153441101
5. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, Gianni L, Baselga J, Bell R, Jackisch C, Cameron D, Dowsett M, Barrios CH, Steger G, Huang CS, Andersson M, Inbar M, Lichinitser M, Lang I, Nitz U, Iwata H, Thomssen C, Lohrisch C, Suter TM, Ruschoff J, Suto T, Greatorex V, Ward C, Straehle C, McFadden E, Dolci MS, Gelber RD, Herceptin Adjuvant Trial Study T (2005) Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 353(16):1659–1672. https://doi.org/10.1056/NEJMoa052306
6. Marty M, Cognetti F, Maraninchi D, Snyder R, Mauriac L, Tubiana-Hulin M, Chan S, Grimes D, Anton A, Lluch A, Kennedy J, O'Byrne K, Conte P, Green M, Ward C, Mayne K, Extra JM (2005) Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol 23(19):4265–4274. https://doi.org/10.1200/JCO.2005.04.173
7. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, Tan-Chiu E, Martino S, Paik S, Kaufman PA, Swain SM, Pisansky TM, Fehrenbacher L, Kutteh LA, Vogel VG, Visscher DW, Yothers G, Jenkins RB, Brown AM, Dakhil SR, Mamounas EP, Lingle WL, Klein PM, Ingle JN, Wolmark N (2005) Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 353(16):1673–1684. https://doi.org/10.1056/NEJMoa052122
8. Onitilo AA, Engel JM, Stankowski RV (2014) Cardiovascular toxicity associated with adjuvant trastuzumab therapy: prevalence, patient characteristics, and risk factors. Ther Adv Drug Saf 5(4):154–166. https://doi.org/10.1177/2042098614529603
9. De Keulenaer GW, Doggen K, Lemmens K (2010) The vulnerability of the heart as a pluricellular paracrine organ: lessons from unexpected triggers of heart failure in targeted ErbB2 anticancer therapy. Circ Res 106(1):35–46. https://doi.org/10.1161/CIRCRESAHA.109.205906
10. Mohan N, Shen Y, Endo Y, ElZarrad MK, Wu WJ (2016) Trastuzumab, but not pertuzumab, dysregulates HER2 signaling to mediate inhibition of autophagy and increase in reactive oxygen species production in human cardiomyocytes. Mol Cancer Ther 15(6):1321–1331. https://doi.org/10.1158/1535-7163.MCT-15-0741
11. Gordon LI, Burke MA, Singh AT, Prachand S, Lieberman ED, Sun L, Naik TJ, Prasad SV, Ardehali H (2009) Blockade of the erbB2 receptor induces cardiomyocyte death through mitochondrial and reactive oxygen species-dependent pathways. J Biol Chem 284(4):2080–2087. https://doi.org/10.1074/jbc.M804570200
12. Ewer MS, Lippman SM (2005) Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. J Clin Oncol 23(13):2900–2902. https://doi.org/10.1200/JCO.2005.05.827
13. Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, D'Amico R (2012) Trastuzumab containing regimens for early breast cancer. Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.CD006243.pub2
14. Cardinale D, Colombo A, Torrisi R, Sandri MT, Civelli M, Salvatici M, Lamantia G, Colombo N, Cortinovis S, Dessanai MA, Nole F, Veglia F, Cipolla CM (2010) Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. J Clin Oncol 28(25):3910–3916. https://doi.org/10.1200/JCO.2009.27.3615
15. Telli ML, Hunt SA, Carlson RW, Guardino AE (2007) Trastuzumab-related cardiotoxicity: calling into question the concept of reversibility. J Clin Oncol 25(23):3525–3533. https://doi.org/10.1200/JCO.2007.11.0106
16. Procter M, Suter TM, de Azambuja E, Dafni U, van Dooren V, Muehlbauer S, Climent MA, Rechberger E, Liu WT, Toi M, Coombes RC, Dodwell D, Pagani O, Madrid J, Hall M,

Chen SC, Focan C, Muschol M, van Veldhuisen DJ, Piccart-Gebhart MJ (2010) Longer-term assessment of trastuzumab-related cardiac adverse events in the herceptin adjuvant (HERA) trial. J Clin Oncol 28(21):3422–3428. https://doi.org/10.1200/JCO.2009.26.0463

17. Guarneri V, Lenihan DJ, Valero V, Durand JB, Broglio K, Hess KR, Michaud LB, Gonzalez-Angulo AM, Hortobagyi GN, Esteva FJ (2006) Long-term cardiac tolerability of trastuzumab in metastatic breast cancer: the M.D. Anderson Cancer Center experience. J Clin Oncol 24(25):4107–4115. https://doi.org/10.1200/JCO.2005.04.9551
18. Kalam K, Marwick TH (2013) Role of cardioprotective therapy for prevention of cardiotoxicity with chemotherapy: a systematic review and meta-analysis. Eur J Cancer 49(13):2900–2909. https://doi.org/10.1016/j.ejca.2013.04.030
19. Ohtani K, Fujino T, Ide T, Funakoshi K, Sakamoto I, Hiasa KI, Higo T, Kamezaki K, Akashi K, Tsutsui H (2018) Recovery from left ventricular dysfunction was associated with the early introduction of heart failure medical treatment in cancer patients with anthracycline-induced cardiotoxicity. Clin Res Cardiol. https://doi.org/10.1007/s00392-018-1386-0
20. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, Ganame J, Sebag IA, Agler DA, Badano LP, Banchs J, Cardinale D, Carver J, Cerqueira M, DeCara JM, Edvardsen T, Flamm SD, Force T, Griffin BP, Jerusalem G, Liu JE, Magalhaes A, Marwick T, Sanchez LY, Sicari R, Villarraga HR, Lancellotti P (2014) Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 27(9):911–939. https://doi.org/10.1016/j.echo.2014.07.012
21. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, Mackey J, Glaspy J, Chan A, Pawlicki M, Pinter T, Valero V, Liu MC, Sauter G, von Minckwitz G, Visco F, Bee V, Buyse M, Bendahmane B, Tabah-Fisch I, Lindsay MA, Riva A, Crown J, Breast Cancer International Research G (2011) Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 365(14):1273–1283. https://doi.org/10.1056/NEJMoa0910383
22. de Azambuja E, Procter MJ, van Veldhuisen DJ, Agbor-Tarh D, Metzger-Filho O, Steinseifer J, Untch M, Smith IE, Gianni L, Baselga J, Jackisch C, Cameron DA, Bell R, Leyland-Jones B, Dowsett M, Gelber RD, Piccart-Gebhart MJ, Suter TM (2014) Trastuzumab-associated cardiac events at 8 years of median follow-up in the herceptin adjuvant trial (BIG 1-01). J Clin Oncol 32(20):2159–2165. https://doi.org/10.1200/JCO.2013.53.9288
23. Singal PK, Iliskovic N (1998) Doxorubicin-induced cardiomyopathy. N Engl J Med 339(13):900–905. https://doi.org/10.1056/NEJM199809243391307
24. Pinder MC, Duan Z, Goodwin JS, Hortobagyi GN, Giordano SH (2007) Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. J Clin Oncol 25(25):3808–3815. https://doi.org/10.1200/JCO.2006.10.4976
25. Tan-Chiu E, Yothers G, Romond E, Geyer CE Jr, Ewer M, Keefe D, Shannon RP, Swain SM, Brown A, Fehrenbacher L, Vogel VG, Seay TE, Rastogi P, Mamounas EP, Wolmark N, Bryant J (2005) Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol 23(31):7811–7819. https://doi.org/10.1200/JCO.2005.02.4091
26. Jones LW, Haykowsky MJ, Swartz JJ, Douglas PS, Mackey JR (2007) Early breast cancer therapy and cardiovascular injury. J Am Coll Cardiol 50(15):1435–1441. https://doi.org/10.1016/j.jacc.2007.06.037
27. Bersell K, Arab S, Haring B, Kuhn B (2009) Neuregulin1/ErbB4 signaling induces cardiomyocyte proliferation and repair of heart injury. Cell 138(2):257–270. https://doi.org/10.1016/j.cell.2009.04.060
28. Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Tan TC, Cohen V, Banchs J, Carver JR, Wiegers SE, Martin RP, Picard MH, Gerszten RE, Halpern EF, Passeri J, Kuter I, Scherrer-Crosbie M (2012) Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab. Circ Cardiovasc Imaging 5(5):596–603. https://doi.org/10.1161/CIRCIMAGING.112.973321
29. Farolfi A, Melegari E, Aquilina M, Scarpi E, Ibrahim T, Maltoni R, Sarti S, Cecconetto L, Pietri E, Ferrario C, Fedeli A, Faedi M, Nanni O, Frassineti GL, Amadori D, Rocca A (2013) Trastuzumab-induced cardiotoxicity in early breast cancer patients: a retrospective study of possible risk and protective factors. Heart 99(9):634–639. https://doi.org/10.1136/heartjnl-2012-303151
30. Thavendiranathan P, Abdel-Qadir H, Fischer HD, Camacho X, Amir E, Austin PC, Lee DS (2016) Breast cancer therapy-related cardiac dysfunction in adult women treated in routine clinical practice: a population-based cohort study. J Clin Oncol 34(19):2239–2246. https://doi.org/10.1200/JCO.2015.65.1505
31. Chen J, Long JB, Hurria A, Owusu C, Steingart RM, Gross CP (2012) Incidence of heart failure or cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. J Am Coll Cardiol 60(24):2504–2512. https://doi.org/10.1016/j.jacc.2012.07.068
32. Romond EH, Jeong JH, Rastogi P, Swain SM, Geyer CE Jr, Ewer MS, Rathi V, Fehrenbacher L, Brufsky A, Azar CA, Flynn PJ, Zapas JL, Polikoff J, Gross HM, Biggs DD, Atkins JN, Tan-Chiu E, Zheng P, Yothers G, Mamounas EP, Wolmark N (2012) Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol 30(31):3792–3799. https://doi.org/10.1200/JCO.2011.40.0010
33. Gong IY, Verma S, Yan AT, Ko DT, Earle CC, Tomlinson GA, Trudeau ME, Krahn MD, Krzyzanowska MK, Brezden-Masley CB, Gavura S, Peacock S, Chan KK (2016) Long-term cardiovascular outcomes and overall survival of early-stage breast cancer patients with early discontinuation of trastuzumab: a population-based study. Breast Cancer Res Treat 157(3):535–544. https://doi.org/10.1007/s10549-016-3823-y
34. Pivot X, Romieu G, Debled M, Pierga JY, Kerbrat P, Bachelot T, Lortholary A, Espie M, Fumoleau P, Serin D, Jacquin JP, Jouannaud C, Rios M, Abadie-Lacourtoisie S, Tubiana-Mathieu N, Cany L, Catala S, Khayat D, Pauporte I, Kramar A, Investigators Pt (2013) 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. Lancet Oncol 14(8):741–748. https://doi.org/10.1016/S1470-2045(13)70225-0
35. Mavroudis D, Saloustros E, Malamos N, Kakolyris S, Boukovinas I, Papakotoulas P, Kentepozidis N, Ziras N, Georgoulias V, Breast Cancer Investigators of Hellenic Oncology Research Group AG (2015) Six versus 12 months of adjuvant trastuzumab in combination with dose-dense chemotherapy for women with HER2-positive breast cancer: a multicenter randomized study by the Hellenic Oncology Research Group (HORG). Ann Oncol 26(7):1333–1340. https://doi.org/10.1093/annonc/mdv213
36. Narayan HK, Finkelman B, French B, Plappert T, Hyman D, Smith AM, Margulies KB, Ky B (2017) Detailed echocardiographic phenotyping in breast cancer patients: associations with ejection fraction decline, recovery, and heart failure symptoms over 3 years of follow-up. Circulation 135(15):1397–1412. https://doi.org/10.1161/CIRCULATIONAHA.116.023463

37. Riccio G, Esposito G, Leoncini E, Contu R, Condorelli G, Chiariello M, Laccetti P, Hrelia S, D'Alessio G, De Lorenzo C (2009) Cardiotoxic effects, or lack thereof, of anti-ErbB2 immunoagents. FASEB J 23(9):3171–3178. https://doi.org/10.1096/fj.09-131383
38. Dang C, Guo H, Najita J, Yardley D, Marcom K, Albain K, Rugo H, Miller K, Ellis M, Shapira I, Wolff AC, Carey LA, Moy B, Groarke J, Moslehi J, Krop I, Burstein HJ, Hudis C, Winer EP, Tolaney SM (2016) Cardiac outcomes of patients receiving adjuvant weekly paclitaxel and trastuzumab for node-negative, ERBB2-positive breast cancer. JAMA Oncol 2(1):29–36. https://doi.org/10.1001/jamaoncol.2015.3709
39. Goldhar HA, Yan AT, Ko DT, Earle CC, Tomlinson GA, Trudeau ME, Krahn MD, Krzyzanowska MK, Pal RS, Brezden-Masley C, Gavura S, Lien K, Chan KK (2016) The temporal risk of heart failure associated with adjuvant trastuzumab in breast cancer patients: a population study. J Natl Cancer Inst. https://doi.org/10.1093/jnci/djv301
40. Seicean S, Seicean A, Alan N, Plana JC, Budd GT, Marwick TH (2013) Cardioprotective effect of beta-adrenoceptor blockade in patients with breast cancer undergoing chemotherapy: follow-up study of heart failure. Circ Heart Fail 6(3):420–426. https://doi.org/10.1161/CIRCHEARTFAILURE.112.000055
41. Pituskin E, Mackey JR, Koshman S, Jassal D, Pitz M, Haykowsky MJ, Pagano JJ, Chow K, Thompson RB, Vos LJ, Ghosh S, Oudit GY, Ezekowitz JA, Paterson DI (2017) Multidisciplinary approach to novel therapies in cardio-oncology research (MANTICORE 101-Breast): a randomized trial for the prevention of trastuzumab-associated cardiotoxicity. J Clin Oncol 35(8):870–877. https://doi.org/10.1200/JCO.2016.68.7830
42. Gulati G, Heck SL, Ree AH, Hoffmann P, Schulz-Menger J, Fagerland MW, Gravdehaug B, von Knobelsdorff-Brenkenhoff F, Bratland A, Storas TH, Hagve TA, Rosjo H, Steine K, Geisler J, Omland T (2016) Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 × 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. Eur Heart J 37(21):1671–1680. https://doi.org/10.1093/eurheartj/ehw022
43. Boekhout AH, Gietema JA, Milojkovic Kerklaan B, van Werkhoven ED, Altena R, Honkoop A, Los M, Smit WM, Nieboer P, Smorenburg CH, Mandigers CM, van der Wouw AJ, Kessels L, van der Velden AW, Ottevanger PB, Smilde T, de Boer J, van Veldhuisen DJ, Kema IP, de Vries EG, Schellens JH (2016) Angiotensin II-receptor inhibition with candesartan to prevent trastuzumab-related cardiotoxic effects in patients with early breast cancer: a randomized clinical trial. JAMA Oncol 2(8):1030–1037. https://doi.org/10.1001/jamaoncol.2016.1726
44. Ewer MS, Vooletich MT, Durand JB, Woods ML, Davis JR, Valero V, Lenihan DJ (2005) Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. J Clin Oncol 23(31):7820–7826. https://doi.org/10.1200/JCO.2005.13.300
45. Tilemann LM, Heckmann MB, Katus HA, Lehmann LH, Muller OJ (2018) Cardio-oncology: conflicting priorities of anticancer treatment and cardiovascular outcome. Clin Res Cardiol 107(4):271–280. https://doi.org/10.1007/s00392-018-1202-x