Effectiveness of Surveillance by Echocardiography for Cancer Therapeutics-Related Cardiac Dysfunction of Patients with Breast Cancer

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ABSTRACT

Background: Cancer therapeutics-related cardiac dysfunction (CTRCD) affect the prognosis of patients with breast cancer. Echocardiographic surveillance of patients treated with anti-HER2 antibodies has been recommended, but few reports have provided evidence on patients with breast cancer only. We aimed to evaluate the effectiveness of echocardiographic surveillance for breast cancer patients.

Methods: We identified 250 patients with breast cancer who were treated with anti-HER2 antibodies from July 2007 to September 2021. We divided 48 patients with echocardiographic surveillance every 3 months into the surveillance group and 202 patients without echocardiographic surveillance into the non-surveillance group. In the surveillance group, patients with a considerable reduction in GLS of 15% were considered for the initiation of cardioprotective drugs. The composite outcome of CTRCD and acute heart failure was the study endpoint.

Results: The mean age was 59 ± 12 years. During the follow-up period of 15 months (12-17 months), 12 patients reached the endpoint. The surveillance group had significantly lower incidence of the composite outcome (2.1% vs. 5.5%, adjusted odds ratio: 0.28, 95% confidential intervals: 0.09–0.94; p=0.039) and higher rates of prescriptions of cardioprotective drugs than the non-surveillance group.

Conclusions: The incidence of cardiac complications was significantly lower in the surveillance group than the non-surveillance group, which supports the effectiveness of echocardiographic surveillance in patients with breast cancer.

Key Words: heart failure; cardio oncology; cardiotoxic drugs; echocardiography surveillance

Abbreviations list

CTRCD: cancer therapeutics-related cardiac dysfunction

ACEi: angiotensin-converting enzyme inhibitor

ARB: angiotensin receptor blocker

GLS: global longitudinal strain

LVEF: left ventricular ejection fraction

Introduction

The prognosis of cancer patients has improved owing to advances in the early detection and treatment of cardiotoxicity caused by anticancer drugs. However, the major cardiotoxic effects of anticancer drugs have been reported more frequently. [1, 2] Anthracyclines and anti-HER2 (human epidermal growth factor receptor type 2) antibody, which is commonly used in the treatment of breast cancer patients, often cause CTRCD and heart failure. [3-5] Among cancers, breast cancer develops at a relatively young age and complications of CTRCD and heart failure strongly affect the patient's prognosis and quality of life. [6, 7] Echocardiographic surveillance is recommended by the American Society of Echocardiography and the European Society of Cardiology with the initiation of these anticancer drugs. [8 9] The diagnosis of cardiotoxicity has long been based on echocardiographic measurements of the left ventricular ejection fraction (LVEF). Global longitudinal strain (GLS) is a technique of echocardiography for the measurement of global long-axis function by myocardial strain and is a more sensitive and reproducible marker for detecting potential myocardial damage than LVEF. [10] Therefore, guidelines recommend follow-up echocardiographic examination using LVEF and GLS, every three months, to detect myocardial damage. [8, 9, 11] The SUCCOUR trial is the only prospective randomized controlled trial on CTRCD and GLS-guided cardio-protection. [12-14] These studies reported that the incidence of CTRCD was significantly lower for GLS-guided than for EF-guided., although the change in LVEF was comparable between GLS-guided and EF-guided. However, these study included diseases other than breast cancers and the association with the incidence of heart failure was unclear. We hypothesized that echocardiographic

surveillance could better prevent the development of CTRCD and heart failure, even in patients with breast cancer. This study aimed to assess the impact of periodic echocardiographic surveillance in breast cancer therapy utilizing chemotherapy with cardiotoxicity.

Methods

Study population. This is a retrospective cohort study using data of Tokushima University Hospital. We enrolled 264 patients with breast cancer who were treated with anti-HER2 antibody, including in combination with anthracyclines, for the first time from July 2007 to September 2021 at Tokushima University Hospital (**Figure 1**). Patients who had previously used anthracyclines or anti-HER2 antibody were not enrolled. We excluded four patients who were lost to follow-up and ten patients who did not undergo baseline LVEF or GLS measurements before chemotherapy. All patients in the surveillance group underwent at least three echocardiographic examinations (baseline and two follow-up examinations). This study followed the Declaration of Helsinki and was approved by the Institutional Review Board of the Tokushima University Hospital (no. 3186-2), and written informed consents were obtained from the patients. Neither patients nor the public were involved in the design, conduct, reporting, or dissemination of our research.

Echocardiography. LVEF was calculated using biplane method of disks. We calculated the average GLS using three apical views. All GLS measurements were performed using a commercially available echocardiographic system (Vivid E9 and E95; GE Medical, Milwaukee, WI, USA). [15]

Clinical Outcomes. The main outcome was the composite outcome of CTRCD with a symptom and acute heart failure. Subclinical left ventricular dysfunction was evaluated as the secondary outcomes. The follow-up period was from the initiation to the end of chemotherapy or the incidence of the outcome. Outcomes were evaluated until March 2022 or the end of the follow-up period. CTRCD was diagnosed when LVEF fell more than 10% below the baseline and below the lower limit of normal LVEF. We defined the lower limit of normal LVEF as 50%, which is similar to the Japanese Society of Echocardiography. [10] Subclinical left ventricular dysfunction was defined as GLS decreased by more than 15% compared to baseline after anticancer therapy. [8, 9] We defined acute heart failure as the presence of either BNP levels greater than 200 pg/mL or evidence of congestion on X-ray/echocardiography, with the need for diuretic therapy.

Surveillance. **Figure 2** shows the surveillance flow chart. Patients who had echocardiographic surveillance of LVEF and GLS at up to every three months after start of chemotherapy were assigned to the surveillance group. Patients who had not undergone periodic echocardiography were assigned to the non-surveillance group. Surveillance was continued until the end of chemotherapy or the development of the composite outcome. Most patients who started treatment after July 2018 were classified into the surveillance group, with the exception of a few patients who were not referred for echocardiographic surveillance. With the diagnosis of CTRCD or acute heart failure at follow-up, the surveillance was terminated, and patients were considered for discontinuation of chemotherapy and initiation of cardioprotective drugs. When subclinical left ventricular dysfunction occurred, patients were considered for the initiation of cardioprotective drugs

or shortening the follow-up period. **Figure 3** shows representative cases of the surveillance group treated with cardioprotective drugs.

Statistical analysis. Continuous variables are expressed as mean ± standard deviation (SD) or median (interquartile range; IQR), and categorical variables as proportion (%). Baseline characteristics were compared between the 2 groups by using an unpaired Student's t-test or Fisher exact test as appropriate. The prescription rates of drugs between the 2 groups was compared by using an unpaired Student's t-test. The propensity score (PS) was estimated using a logistic regression model, with surveillance as the dependent variable, and the following five clinically relevant covariates: age, body mass index (BMI), stage of cancer, treatment with anthracyclines and radiation therapy. Stage of cancer was selected as a covariate because of significant differences between the two groups, age and BMI as risk factors for CTRCD and acute heart failure, and anthracyclines and radiation therapy as both. [8, 16-18] We used inverse probability treatment weighting with a logistic regression model adjusted for the follow-up period and estimated the odds ratio (OR) and 95% confidence interval (CI) with surveillance for the incidence of the composite outcome. We assigned patients in the surveillance group a weight of 1÷PS and patients in the non-surveillance group a weight of 1÷ (1−PS). All statistical tests were two-sided and p values less than 0.05 were considered statistically significant. Statistical analysis was performed using JMP 14.0 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics. Among all patients (n=250), 99.6% (n=249) were female (**Table 1**). The mean age was 59 ± 12 years and the follow-up period 15 months (12-17months). There were 48 and 202 patients in the surveillance and non-surveillance groups, respectively. Compared to the non-surveillance group, the surveillance group had significantly a higher number of stage 1-2 cancer, a shorter follow-up period, more chemotherapy with anthracyclines, and less radiation therapy. The distribution of age, sex, BMI, smoking, comorbidities, baseline LVEF, cardioprotective drugs at baseline and anthracycline equivalence dose was similar between the two groups. Of all patients, 29.6% had hypertension. As antihypertensive drugs, a total of 17.6% were taking angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), and 3.6% were using beta-blockers at baseline.

Surveillance and cardioprotective drugs. The changes in left ventricular function in the surveillance group are shown in **Table 2**. During the follow-up period of the surveillance, the median decline in LVEF from baseline was 4% and the median relative decline in GLS from baseline was 10.7%.

The prescription rates of cardioprotective drugs before and after chemotherapy are shown in **Table 3**. In the surveillance group, 19 (39.6%) patients developed subclinical left ventricular dysfunction. For these patients, ACEi, ARB and beta-blockers were prescribed at the physician's discretion. The results showed that eleven (57.9%) were prescribed cardioprotective drugs; six patients (31.6%) were prescribed only ACEi, ARB or beta-blockers and five patients (26.3%) were prescribed the two-drug combination. Some

patients in the non-surveillance group were also prescribed these drugs for hypertension and palpitations. After chemotherapy, significantly more patients in the surveillance group were treated with cardioprotective drugs than in the non-surveillance group (34.0% vs. 18.9%, p=0.024), especially beta-blockers only (8.5% vs. 1.0%, p=0.004) and combination therapy (12.8% vs. 4.2%, p=0.025).

Outcomes. The composite outcome occurred in twelve patients (4.8%) overall (**Table 4**). Their mean age was 61 years, six (50%) had cancer stage 1-2, six (50%) were treated with anthracycline, nine (75%) with radiation therapy, and the median time to outcomes onset was about 13 months. In the surveillance group, one patient had CTRCD with shortness of breath at the first follow-up 3 months after the start of chemotherapy. In the non-surveillance group, two patients developed CTRCD with shortness of breath, eight patients developed CTRCD with acute heart failure and one patient developed acute heart failure only. After adjusting for inverse probability treatment weighting and follow-up period, the surveillance group had a significantly lower incidence of the composite outcome than the non-surveillance group (2.1% vs. 5.5%, OR:0.28, 95% CI:0.09–0.94; p=0.039). Of the twelve patients, five patients were hospitalized for acute heart failure and two patients did not improve EF above 50%, all in the non-surveillance group. Six patients were not restarted on chemotherapy, and they were either.

Discussion

The main findings of this study were 1) the composite outcome of CTRCD and acute heart failure was present in 4.8% of the patients with breast cancer receiving chemotherapy; 2)

The surveillance group had a lower composite outcome and a higher rate of prescriptions for cardioprotective drugs than the non-surveillance group; 3) 39.6% of patients in the surveillance group developed subclinical left ventricular dysfunction, and half of the patients with subclinical left ventricular dysfunction were prescribed cardioprotective drugs.

To the best of our knowledge, this study is the first to report that echocardiographic surveillance reduces the composite outcome of cardiotoxicity in a study of breast cancer patients only.

Impact of surveillance. This study showed that the surveillance group had a significantly lower incidence of composite outcomes than the non-surveillance group. Early detection of cardiac dysfunction by echocardiographic surveillance and initiation of cardioprotective drugs prevent a decrease in LVEF. [19, 20] In addition, it has been reported that GLS-guided initiation of cardioprotective drugs can reduce the progression of myocardial dysfunction better than LVEF-guided initiation. This is because a decrease in GLS precedes a decrease in LVEF, [21, 22] and GLS-guidance allows for early onset of treatment of cardiac dysfunction. [13] In this study, six patients who developed the composite outcome were unable to resume chemotherapy, and two of them did not recover LVEF above 50%. Since these factors affect prognosis, preventing heart failure and LVEF decline through surveillance may improve long-term prognosis.

Nine of the eleven patients with the composite outcome in the non-surveillance group had heart failure and were started on diuretic therapy, but one patient with the composite

outcome in the surveillance group had no congestion and did not require diuretics. Surveillance leads to early detection and treatment of CTRCD before symptoms of heart failure appear, which promotes recovery of LVEF and reduces cardiac events. [19] One patient developed CTRCD three months after the initiation of trastuzumab therapy. Cardiac damage has been reported to occur early after the initiation of trastuzumab treatment. [23] In addition to the surveillance protocol of the guidelines, we shorted the follow-up period interval for patients at high risk for CTRCD and those with reduced GLS. Adjusting the follow-up period to suit individual patients may further reduce the incidence of CTRCD.

Cardioprotective drugs. Patients with cardiac damage due to chemotherapy are likely to benefit from ACEi or ARB and beta-blocker treatment. [24] Combination therapy may be more effective than either therapy alone. [4, 19] However, the initiation rate of cardioprotective agents was low in our study. This could be due to two reasons: The risk of CTRCD after chemotherapy is lower than that during chemotherapy; this is demonstrated in the case of the patient who developed subclinical left ventricular dysfunction at the end of chemotherapy. Second, overall, breast cancer patients tend to be younger than patients with other types of cancer and have lower blood pressures and pulse rates. ACEi and ARB tend to lower blood pressure, and beta-blockers tend to lower the pulse rate. Therefore, cardioprotective agents should be tailored to individual patients.

Prophylactic administration of cardioprotective drugs at the initiation of anticancer therapy may be beneficial for reducing the incidence of CTRCD. However, the reported incidence of CTRCD is not high in patients with breast cancer, and it is necessary to identify patients

who would benefit from prophylactic administration in terms of health care economics and complications.

Perspectives. Although the cardio-oncology field has evolved, the importance of CTRCD surveillance is still poorly recognized. In many institutions, chemotherapy for breast cancer patients is administered by breast surgeons or oncologists, not cardiologists, and systems and protocols have not yet been established for CTRCD surveillance. Close collaboration between cardiologists and managing physicians may promote echocardiographic surveillance, which may improve prognosis and maintain the quality of life of patients with breast cancer. We believe that this study will support the effectiveness of surveillance and raise awareness regarding its necessity. Further research is needed on the effectiveness of tailoring surveillance and prophylactic cardioprotective therapy according to individual cardiovascular risk.

Limitations. First, the potential differences between the two groups were adjusted using inverse probability treatment weighting but never completely. The number of covariates was limited because of the small number of incidence of outcomes. Therefore, it was not possible to adjust for all risk factors for CTRCD and acute heart failure. This nonrandomized observational prospective study could also be affected by hidden bias due to unknown unadjusted differences. The non-surveillance group included one male patient and tended to have a higher stage of cancer. The hidden biases may have remained in these patients. Second, this was a single-center retrospective study, and may have been biased. Third, cardioprotective drugs for subclinical left ventricular dysfunction were administered

at the cardiologist's discretion. Forth, the incidence of CTRCD in the surveillance group in this study was lower than those reported in other studies. Fifth, in the non-surveillance group, the incidence of subclinical left ventricular dysfunction could not be assessed accurately because echocardiography was performed irregularly and only at the physician's discretion. Therefore, it was not possible to compare the incidence of subclinical left ventricular dysfunction between the two groups. Sixth, since this study included long-term patients from 2007 to 2019, there may have been differences in anticancer treatment protocols and in pharmacological and surgical therapies between patients.

Conclusions: The incidence of the composite outcome of CTRCD with a symptom and acute heart failure was significantly lower in the surveillance group than in the non-surveillance group. According to new guidelines, it was mentioned that early detection of CTRCD allows clinicians to incorporate cardioprotective therapy before LVEF is significantly reduced, and also decreases the risk of interruption of cancer treatment affecting patient survival. [25] This study supports the effectiveness of echocardiographic surveillance and that statement of new guideline.

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Conflicts of Interest: None

Contributors: H Yamada conceived the idea for this study. Y Okushi conducted data analyses. The initial draft of the manuscript was produced by K Kusunose and Y Okushi. All the authors were involved in interpreting the results and writing the manuscript. All authors have read and approved the final manuscript.

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Figure Title

Figure 1: Flowchart of the study. We enrolled 264 patients with breast cancer who received anti-HER2 antibodies for the first time from July 2007 to September 2021 at Tokushima University Hospital. After excluding patients who were lost to follow-up and did not undergo baseline left ventricular ejection fraction or global longitudinal strain measurement before chemotherapy, 250 patients were included. There were 48 patients in the surveillance group and 202 patients in the non-surveillance group.

Figure 2: Surveillance protocol of this study. In the surveillance group, 48 patients underwent follow-up echocardiographic examinations every one to three months after baseline, and left ventricular ejection fraction and global longitudinal strain were measured each time. When subclinical left ventricular dysfunction occurred, the patients were considered for initiation of cardioprotective drugs or shortening of the follow-up period.

Figure 3. Representative cases of the surveillance group with cardioprotective drugs. The global longitudinal strain (GLS) bull's-eye diagram, follow-up echocardiographic measurements, and cardioprotective drugs from baseline to the sixth follow-up. Red letters are used when GLS was lower than normal (-16% to -19%) or when ΔGLS was higher Δ15%.

Table. 1 Baseline characteristics with and without surveillance

	All Patients (n=250)	Surveillance (n=48)	Non-Surveillance (n=202)	p
Follow-up period (months)	15 (12-17)	13 (8-16)	15 (13-18)	0.005
Age (years)	59±12	57±12	60±12	0.141
Female (%)	99.6	100.0	99.5	0.625
BMI	23.3±4.5	23.5±4.8	23.3±4.6	0.962
Stage 1-2 (%)	68.4	91.7	62.9	<0.001
Smoking (%)	15.2	16.7	14.9	0.753
Hypertension (%)	29.6	27.1	30.2	0.671
Diabetes mellitus (%)	7.2	2.1	8.4	0.127
Hyperlipidaemia (%)	11.2	12.5	10.9	0.751
Chronic heart failure (%)	0.8	0.0	1.0	0.489
Myocardial infarction (%)	0.8	0.0	1.0	0.489
Baseline LVEF (%)	65.1±4.0	65.1±3.2	65.1±4.1	0.992
Pre ACEi/ARB (%)	17.6	18.8	17.3	0.816
Pre Beta blocker (%)	3.6	6.3	3.0	0.273
Anthracycline (%)	52.4	68.8	48.5	0.015
Anthracycline equivalence dose (mg/m^2)	190±47	197±39	188±49	0.303
Radiation (%)	46.8	33.3	50.0	0.038

Data are presented as percentage of patients or median (interquartile range). Abbreviations: BMI, body mass index; LVEF, left ventricular ejection fraction; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table. 2 The changes in left ventricular function in the surveillance group

	Baseline (%)	Post (%)	ΔLVEF (%)	Δ%GLS (%)
LVEF	65±3	60±4	4 (1-7)	
GLS	-19.9±2.5	-17.6±2.5		10.7 (0.0-20.6)

Data of the incidence of outcomes are presented as number (proportion). Abbreviations: LVEF, left ventricular ejection fraction; GLS, global longitudinal strain.

Table. 3 The prescription rates of drugs before and after chemotherapy

	Before chemotherapy			***After chemotherapy***		
Treatment	Surveillance (n=48)	Non-surveillance (n=202)	p	Surveillance (n=47)	Non-surveillance (n=191)	p
All (%)	10 (20.8)	36 (17.8)	0.628	16 (34.0)	36 (18.9)	0.024
Only ACEi/ARB (%)	7 (14.6)	30 (14.9)	0.963	6 (12.8)	26 (13.6)	0.879
Only Beta blocker (%)	1 (2.1)	1 (0.5)	0.267	4 (8.5)	2 (1.0)	0.004
Combination (%)	2 (4.2)	5 (2.5)	0.523	6 (12.8)	8 (4.2)	0.025

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LV, left ventricular.

Table. 4 The incidence and odds ratio of the composite outcome

	All Patients (n=250)	Surveillance (n=48)	Non-Surveillance (n=202)	*Adjusted OR (95% CI)	p
Composite Outcome (%)	12 (4.8)	1 (2.1)	11 (5.5)	0.28 (0.09-0.94)	0.039

Data are presented as number (proportion). Abbreviations: OR, odds ratio; CI, confidence interval.

* OR was adjusted for inverse probability treatment weighting and follow-up period.