The Importance of Monitoring Cardiac Function by Echocardiography to Detect Real-World Breast-Cancer-Therapy-Related Cardiotoxicity

Naotaka UCHIDA1), Tetsuro OHTA2), Seiji OKADA2), Kimiko HIROE2),
Yasuki MATSUI3) and Takeshi NOTSU1)

1) Department of Breast, Endocrine, Vascular and Thoracic Surgery, Matsue City Hospital
2) Department of Cardiology, Matsue City Hospital

Background: Breast cancer treatments carry the risk of cardiac problems that may impact the patient’s overall outcome. We aimed to assess the real-world incidence of chemotherapy-related cardiotoxicity and the effect of echocardiographic monitoring of cardiac function in breast cancer patients undergoing chemotherapy.

Methods: We assessed patients with breast cancer at our institution who were first treated with anthracycline or trastuzumab between 2008 and 2016. Cardiotoxicity was defined as follows: 1) symptomatic congestive heart failure (CHF); 2) asymptomatic cardiac dysfunction, as determined by any of the following findings: a) brain natriuretic peptide (BNP) ≥ 100 pg/mL, b) decrease from baseline ≥ 10% of the left ventricular ejection fraction (LVEF), or c) LVEF < 50%. We defined the patients from 2014 onward, who had mostly undergone cardiac function monitoring by echocardiography prior to the initiation of the complete regimen, and every 3 months during chemotherapy, as the active monitoring group.

Results: After a median follow-up of 4 years, 11 of 118 (9.3%) patients developed cardiotoxicity. Cardiotoxicity occurred more frequently in patients who received trastuzumab; particularly in those patients treated with anthracycline and sequential trastuzumab. Asymptomatic cardiotoxicity was detected first in all cases. Two (1.6%) patients with irreversible cardiotoxicity received anthracycline. Forty-two of 118 patients (36%) underwent active monitoring. Of these 42 patients, 27 (64%) underwent baseline echocardiography to assess cardiac function. A significantly higher proportion of patients undergoing active monitoring received human epidermal growth factor 2 receptor (HER2) targeted agents and a higher dose of anthracycline compared with those patients who were not monitored actively. Cardiotoxicity was identified significantly earlier (median: 1.5 year vs. 5.2 years) in patients undergoing active monitoring than in those not undergoing active monitoring.

Conclusion: Echocardiographic monitoring of cardiac function in breast cancer patients undergoing chemotherapy allows early detection of asymptomatic chemotherapy-related cardiotoxicity.

Key words: breast cancer, chemotherapy, anthracyclines, trastuzumab, cardiotoxicity

Original Article

Received: October 6, 2017  Accepted: December 6, 2017

Introduction

Improved chemotherapy and targeted therapeutic agents for breast cancer have provided patients with better outcomes. As a consequence, attention has focused on not only acute but also late-occurring cancer-therapy-related cardiotoxicity in breast cancer survivors. Cardiovascular disease is the predominant cause of mortality in women with breast cancer who are older than 65 years, and reducing the risk of cardiovascular disease after the diagnosis and treatment of breast cancer in these patients is essential for their long-term care1).

Anthracycline and trastuzumab have been key therapeutic agents for breast cancer. However, they can cause cardiotoxicity that is likely to have major effects on patient outcomes. A recent meta-analysis found that after a median follow-up of 9 years, 6% and 18% of patients developed overt and subclinical cardiotoxicities, respectively, due to anthracyclines2). The respective symptomatic and asymptomatic rates of cardiotoxicity range from 2% to 4% and 10.4% to 18.6%, when anthracycline is administered before trastuzumab3-4). Clinical trials have investigated the cardiotoxicity induced by chemotherapy or trastuzumab. However, the effects of cardiotoxicity in patients with various backgrounds have not been well documented. Furthermore, it is practically difficult to perform cardiac function monitoring by echocardiography in all cases because the human resources are limited.

We aimed to assess the real-world incidence of chemotherapy-related cardiotoxicity and the effect of echocardiographic monitoring of cardiac function in breast cancer patients receiving chemotherapy.
Factors that increased the risk of cardiotoxicity included: trastuzumab used for tumors overexpressing human epidermal growth factor 2 receptor (HER2) targeted agents were initiated, because differentiating whether or not they were induced by chemotherapy and/or HER2 targeted agents was difficult.

Treatments
Treatments were determined by the treating physician, based on disease stage, histological and biological evaluations, risk factors for recurrence, and patient preference. Informed consent was obtained from all individual participants included in the study. The chemotherapy regimen that included anthracycline was FEC (epirubicin 60~100 mg/m², cyclophosphamide 500 mg/m², fluorouracil 500 mg/m² every 3 weeks for 4 courses in most patients, but up to 6 courses). The trastuzumab-containing regimens used for tumors overexpressing human epidermal growth factor 2 receptor (HER2) included the following: trastuzumab alone, trastuzumab plus chemotherapy included docetaxel or eribulin, or trastuzumab plus pertuzumab plus chemotherapy. Except for 1 patient receiving weekly trastuzumab regimen, trastuzumab was initially administered intravenously at a dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks. Trastuzumab used as adjuvant therapy was administered for 1 year.

Endpoint and definition of cardiotoxicity
The endpoint was the first event related to cardiotoxicity. Cardiotoxicity was defined as follows: 1) symptomatic congestive heart failure (CHF); 2) asymptomatic CHF with any of the following measured parameters: a) brain natriuretic peptide (BNP) ≥ 100 pg/mL, b) ≥ 10% decrease in LVEF from baseline, or c) LVEF < 50%.

Monitoring of cardiac function
We compared patients who first received anthracycline or trastuzumab before December 31th, 2013 (n = 76), with the patients who first received anthracycline or trastuzumab after January 1st, 2014 (n = 42), to assess the effects of monitoring of cardiac function. Previously, echocardiographic monitoring of cardiac function in breast cancer patients was performed before the initiation of trastuzumab therapy and/or if the patients developed signs and symptoms suggestive of cardiac problems. The assessment was performed by cardiologists after consulting with a breast cancer specialist. However, the breast specialist with knowledge of cardio-oncology arrived at our institutional post in 2014 and subsequently aggressive monitoring of cardiac function by echocardiography before and during chemotherapy was implemented. Furthermore, cardiologists also have started to be aware and very interested in cardio-oncology and have begun to follow breast cancer patients before, during, and, based on circumstances, after chemotherapy. We defined the patients from 2014 onward, who has mostly undergone cardiac function monitoring by echocardiography before the initiation of the entire regimen and every 3 months during chemotherapy, active monitoring group. LVEF was measured by echocardiography performed by a cardiologist or medical technologist certified as a medical sonographer by the Japan Society of Ultrasonics in Medicine. LVEF was measured by the modified Simpson method. The schedule for cardiac-monitoring was mainly decided by the cardiologist. No interventions such as administration of cardioprotective agents to prevent worsening cardiac problems were performed.

Statistics
The Mann-Whitney U test was used for comparisons of continuous outcomes, and the chi-square test was used for comparisons of categorical variables. The time to cardiotoxicity was defined as the interval between the date of first anthracycline or trastuzumab treatment and the date of the first confirmation of cardiotoxicity. The times to cardiac events were assessed using the Kaplan-Meier method and compared using the log-rank test. Differences were considered significant for \( p < 0.05 \).

Results
Patient characteristics
Table 1 shows characteristics of the 118 patients included in this study. After a median follow-up of 4 years, cardiotoxicity developed in 11 (9.3%) patients. History of trastuzumab use, particularly in those patients treated with anthracycline and sequential trastuzumab, was significantly greater in the cardiotoxicity group. The difference in body mass index (BMI), cardiovascular comorbidities and anthracycline accumulation between the patients developing cardiotoxicity and those who did not were not significant. The difference in baseline values for LVEF and BNP between the patients developing cardiotoxicity
and those who did not were not significant.

**Characteristics of patients with cardiotoxicity**

Table 2 shows the characteristics of patients with cardiotoxicity. Asymptomatic cardiotoxicity was first detected in all the cases. The patient (case A) first manifested asymptomatic cardiotoxicity (LVEF ≥ 10% decrease from baseline and LVEF < 50%), and continued receiving adjuvant trastuzumab. However, she developed symptomatic New York Heart Association (NYHA) II CHF 4 months later, and trastuzumab was discontinued. She then improved, and 1.5 years later her LVEF was 63%. Six of 11 patients (55%) developed cardiotoxicity while receiving adjuvant trastuzumab. In patients who underwent FEC therapy, cardiotoxicity developed both at the late phase when they were receiving hormone therapy, as well as at the acute phase just after finishing FEC therapy. The 2 patients showing irreversible cardiotoxicity had received FEC therapy. The patient (case E), who had locally advanced breast cancer of the right breast, received a neoadjuvant FEC regimen of 4 cycles at 39 years of age followed by triweekly docetaxel, and underwent

### Table 1 Patients characteristics according to whether or not they developed cardiotoxicity

|                        | Cardiotoxicity | p  |
|------------------------|---------------|----|
|                        | Yes (n = 11)  | No (n = 107) |
| Age, years; Median (range) | 55 (39–68) | 57 (32–82) | 0.6905 |
| BMI, Median (range)     | 21.7 (18.3–26.5) | 22.6 (16.1–32.8) | 0.5081 |
| Cardiovascular comorbidities |           |    |
| Yes                    | 5 (45%) | 42 (39%) | 0.6891 |
| Hypertension           | 2 (19%) | 26 (24%) | 0.5966 |
| Dyslipidemia           | 4 (36%) | 21 (20%) |
| Diabetes               | 0 (0%) | 7 (7%) |
| Heart disease          | 1 (9%) | 5 (5%) |
| Stroke                 | 0 (0%) | 4 (4%) |
| No                     | 6 (55%) | 65 (61%) |
| Laterality             |           |    |
| Left                   | 6 (55%) | 49 (46%) | 0.8057 |
| Right                  | 4 (36%) | 50 (47%) |
| Bilateral              | 1 (9%) | 8 (7%) |
| Anthracycline          |           |    |
| Yes                    | 6 (55%) | 87 (81%) | 0.0386 |
| No                     | 5 (45%) | 20 (19%) |
| Chemotherapy other than anthracycline |       |    |
| Yes                    | 11 (100%) | 82 (77%) | 0.0709 |
| No                     | 0 (0%) | 25 (23%) |
| Anthracyline accumulation, mg/m² | 370 (240–398) | 328 (58–621) | 0.3020 |
| Yes                    | 8 (73%) | 29 (27%) | 0.0019 |
| No                     | 3 (27%) | 78 (73%) |
| HER2-targeted agents other than trastuzumab |       |    |
| Yes                    | 0 (0%) | 3 (3%) | 0.5737 |
| No                     | 11 (100%) | 104 (97%) |
| Anthracyline and sequential trastuzumab |       |    |
| Yes                    | 3 (27%) | 9 (8%) | 0.0487 |
| No                     | 8 (73%) | 98 (92%) |
| Endocrine therapy      |           |    |
| Yes                    | 8 (73%) | 65 (61%) | 0.4360 |
| No                     | 3 (27%) | 42 (39%) |
| Baseline LVEF, %; Median (range) Assessment |       |    |
| Yes                    | 61 (50–67) | 59 (50–70) | 0.5141 |
| No                     | 10 (91%) | 47 (44%) |
| Baseline BNP, pg/mL; Median (range) Assessment |       |    |
| Yes                    | 13.5 (5.8–21.8) | 19.9 (5.8–71.1) | 0.1869 |
| No                     | 8 (73%) | 26 (24%) | 0.0007 |
mastectomy and radiation therapy before the onset of cardiotoxicity. Her total anthracycline dose was 396 mg/m$^2$. Two years after the first date of FEC regimen, her LVEF increased to 50%, an improvement of <10% from the nadir value of 46% and remained >−5% from baseline. At cardiotoxicity, her LVEF was decreased compared with baseline, but her BNP level was <100 pg/mL.

**Effect after active monitoring of cardiac function**

Table 3 shows characteristics of patients stratified by actively monitoring for cardiac function. Forty-two of 118 patients (36%) underwent active monitoring. Of these 42 patients, 27 (64%) underwent baseline echocardiography to assess cardiac function. A significantly higher proportion of patients undergoing active monitoring received HER2-targeted agents and a higher dose of anthracycline than patients not undergoing active monitoring. Many more elderly people were among the patients undergoing active monitoring received HER2-targeted agents and a higher dose of anthracycline than patients not undergoing active monitoring. Many more elderly people were among the patients undergoing active monitoring received HER2-targeted agents and a higher dose of anthracycline than patients not undergoing active monitoring.

**Discussion**

The types of chemotherapy-related cardiotoxicities have been classified into 2 groups, type I (myocardial damage) and type II (myocardial dysfunction). Anthracyclines cause type I cardiotoxicity, which is dose related and irreversible. Anthracycline-related toxicity is related to the free radicals and oxidative stress induced by the agent. Trastuzumab causes type II toxicity, which is not dose related and is reversible except for 20% of cases. In our study, epirubicin, which is less cardiotoxic than doxorubicin, was used at a cumulative dose <900 mg/m$^2$, the cumulative dose that incidence of heart failure rises significantly above. Consequently, a history of anthracycline use could not be the major cause of cardiotoxicity.

The methods for detecting cardiotoxicity have varied. BNP serum levels are insensitive measures of early subclinical cardiac damage, but they are often used for cardiac function evaluation before, during and after cancer therapy because of wide availability, easy repeatability, and versatility. Global longitudinal myocardial strain (GLS) as detected by echocardiography and serum troponin levels are believed to be sensitive measures for early cardiotoxicity. In our study, asymptomatic cardiotoxicity was identified significantly earlier in active monitoring group than non-active monitoring group. The results suggest that echocardiography has been an effective and key method for evaluating subclinical cardiotoxicity. Meanwhile, none of our study patients with cardiotoxicity showed elevated serum levels of BNP when cardiotoxicity was observed, and suggests that BNP measurements may not be useful for detecting early cardiotoxicity.

Global longitudinal myocardial strain (GLS) as detected by echocardiography and serum troponin levels are believed to be sensitive measures for early cardiotoxicity. GLS is known to be more sensitive measure than LVEF. Therefore, we recently have begun to measure GLS and
serum troponin levels, and further direction of our study will provide evidence for them.

There are not established schedule for monitoring cardiac function based on randomized clinical trials. Plana et al. has proposed performing monitoring baseline and every 3 months during trastuzumab therapy\(^8\). Concerning anthracycline, performing monitoring baseline, just after and 6 months after finishing chemotherapy has been proposed\(^9\). Meanwhile, chemotherapy induced cardiac dysfunction has been shown to be irreversible unless it is found in 6 months\(^10,\,^{11}\). In our study, asymptomatic cardiotoxicity were identified during therapy with adjuvant trastuzumab. Patients received anthracycline showed cardiotoxicity at just after finishing FEC therapy or during adjuvant hormone therapy, late phase. Therefore, monitoring cardiac function every 3 months during tras-

### Table 3: Patient characteristics according to whether or not they underwent active monitoring for cardiac function

|                          | Active monitoring  | Non-active monitoring | \(p\)  |
|--------------------------|--------------------|-----------------------|--------|
| Age, years; Median (range)| 61 (33–82)         | 54 (32–73)            | 0.0236 |
| BMI; Median (range)       | 22.4 (16.1–30.9)   | 22.3 (16.4–32.8)      | 0.5271 |
| Cardiovascular comorbidities |                  |                       |        |
| Yes                      | 18 (43%)           | 29 (38%)              | 0.6176 |
| Hypertension             | 12 (29%)           | 16 (21%)              | 0.9002 |
| Dyslipidemia             | 8 (19%)            | 17 (22%)              |        |
| Diabetes                 | 3 (7%)             | 4 (5%)                |        |
| Heart disease            | 2 (5%)             | 4 (5%)                |        |
| Stroke                   | 1 (2%)             | 3 (4%)                |        |
| No                       | 24 (57%)           | 47 (62%)              |        |
| Laterality               |                    |                       | 0.056  |
| Left                     | 25 (60%)           | 30 (39%)              |        |
| Right                    | 13 (31%)           | 41 (54%)              |        |
| Bilateral                | 4 (9%)             | 5 (7%)                |        |
| Anthracycline            |                    |                       | 0.3227 |
| Yes                      | 31 (74%)           | 62 (82%)              |        |
| No                       | 11 (26%)           | 14 (18%)              |        |
| Chemotherapy other than anthracycline |         |                       | 0.0666 |
| Yes                      | 37 (88%)           | 56 (74%)              |        |
| No                       | 5 (12%)            | 20 (26%)              |        |
| Anthracycline accumulation, mg/m\(^2\) | 370 (159–592)     | 312 (58–421)          | 0.0437 |
| Trastuzumab              |                    |                       | 0.0012 |
| Yes                      | 21 (50%)           | 16 (21%)              |        |
| No                       | 21 (50%)           | 60 (79%)              |        |
| HER2-targeted agents other than trastuzumab |         |                       | 0.0183 |
| Yes                      | 3 (7%)             | 0 (0%)                |        |
| No                       | 39 (93%)           | 76 (100%)             |        |
| Anthracycline and sequential trastuzumab |         |                       | 0.0826 |
| Yes                      | 7 (17%)            | 5 (7%)                |        |
| No                       | 35 (83%)           | 71 (93%)              |        |
| Endocrine therapy        |                    |                       | 0.6972 |
| Yes                      | 25 (60%)           | 48 (63%)              |        |
| No                       | 17 (40%)           | 28 (37%)              |        |
| Baseline LVEF, %; Median (range) | 59 (53–69)    | 61 (50–70)            | 0.3203 |
| Assessment               |                    |                       |        |
| Yes                      | 27 (64%)           | 30 (39%)              | 0.0098 |
| No                       | 15 (36%)           | 46 (61%)              |        |
| Baseline BNP, pg/mL; Median (range) | 17.4 (7.3–71.1)  | 11.1 (5.8–27.0)       | 0.0495 |
| Assessment               |                    |                       | < 0.0001|
| Yes                      | 22 (52%)           | 12 (19%)              |        |
| No                       | 20 (48%)           | 64 (84%)              |        |
| Cardiotoxicity           |                    |                       | 0.0008 |
| Yes                      | 9 (21%)            | 2 (2%)                |        |
| No                       | 33 (79%)           | 74 (98%)              |        |
undergoing active monitoring. A history of trastuzumab in patients undergoing active monitoring than in those not cardiotoxicity. They were also measured more frequently in patients with cardiotoxicity than in patients without nature. LVEF and BNP were measured more frequently in the patients with cardiotoxicity. In the addition to the damage due to anthracycline and/or trastuzumab, occurred significantly more frequently in the patients with cardiotoxicity. In the patients undergoing active monitoring, a greater population of those patients received HER2-targeted agents and a higher dose of anthracycline; and that group contained more elderly people and showed higher BNP levels. These characteristics could lead the treating physicians to consider implementing aggressive monitoring of cardiac function. Because of these findings and that this was a retrospective study, selection bias could have affected our findings. Furthermore, because of the short follow-up period, we did not demonstrate that early detection of cardiotoxicity by active monitoring could improve the outcome of breast cancer patient. However, to our knowledge, the availability of real-world data, especially data from a local community with higher population aging rate has been limited. Since the elderly tend to develop cardiovascular disease and heart failure, chemotherapy-related cardiotoxicity will continue to be an important issue.

In conclusion, echocardiographic monitoring of cardiac function in breast cancer patients receiving chemotherapy allows early detection of asymptomatic chemotherapy-related cardiotoxicity.

Conflicts of Interest

Naotaka Uchida, Tetsuro Ohta, Seiji Okada, Kimiko Hiroe, Yasuki Matsui and Takeshi Notsu have no conflicts of interest.

References

1) Patnaik JL, Byers T, DiGuiseppi C, Dabelea D, Denberg TD. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. Breast Cancer Res 2013; 15: R64.

2) Lotriente M, Biondi-Zoccai G, Abbate A, Lanzetta G, D’Ascenzo F, Malavasi V, and et al. Review and meta-analysis of incidence and clinical predictors of anthracycline cardiotoxicity. Am J Cardiol 2013; 112: 1980–1984.

3) Khouri MG, Douglas PS, Mackey JR, Martin M, Scott JM, Scherrer-Crosbie M, and et al. Cancer therapy-induced cardiac toxicity in early breast cancer: addressing the unresolved issues. Circulation 2012; 126: 2749–2763.

4) Tan-Chiu E, Yothers G, Romond E, Geyer CE Jr, Ewer M, Keefe D, and et al. 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 2005; 23: 7811–7819.

5) Perez EA, Suman VJ, Davidson NE, Sledge GW, Kaufman PA, Hudis CA, and et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. J Clin Oncol 2008; 26: 1231–1238.

6) Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, and et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 2011; 365: 1273–1283.

7) Okada A, Tanabe M, Ito Y, Takahashi S, Oguchi M, Hori R, and et al. Cardiac Safety in Patients with Human Epidermal Growth Factor Receptor-Related 2-Overexpressing Operable Breast Cancer Receiving Neoadjuvant or Adjuvant Chemotherapy Combined with Taxane and Trastuzumab. Jpn J Breast Cancer 2013; 28: 313–321.

8) Plana JC, Galderisi M, Barac A, Ewer MS, Ky B,
Scherrer-Crosbie M, and et al. 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. *Eur Heart J Cardiovasc Imaging* 2014; 15: 1063–1093.

9) Ewer MS, Lippman SM. Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. *J Clin Oncol*. 2005; 23: 2900–2902.

10) Cardinale D, Colombo A, Lamantia G, Colombo N, Civelli M, De Giacomi G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. *J Am Coll Cardiol* 2010; 55: 213–220.

11) Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiaro R, Galderisi M, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur Heart J* 2016; 37(36): 2768–2801.

12) Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-esophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; 376: 687–697.

13) Mann DL, Bristow MR. Mechanisms and models in heart failure: the biomechanical model and beyond. *Circulation* 2005; 111: 2837–2849.