Usefulness of Global Longitudinal Strain-Guided Management in Preventing Human Epidermal Growth Factor Receptor 2 (HER2) Inhibitor-Induced Myocardial Damage

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Background: Trastuzumab, an anti-human epidermal growth factor receptor 2 (HER2) monoclonal antibody, is a specific first-line treatment for patients with HER2-positive cancers. Cardiac dysfunction is among the most problematic adverse events associated with trastuzumab. Although regular echocardiographic screening is recommended for early detection of cardiac damage, few reports have investigated the validity of echocardiographic screening in chemotherapy. Therefore, the aim of this study was to determine whether a GLS-guided management approach could reduce cardiotoxicity and discontinuation of trastuzumab chemotherapy.

Methods and Results: To evaluate the usefulness of global longitudinal strain (GLS)-guided cardioprotective interventions, we retrospectively analyzed 67 patients treated with trastuzumab who underwent structured echocardiographic assessments before and after 1, 3, and 6 courses of trastuzumab administration. If a >15% relative decrease in GLS was identified, cardioprotective agents were administered. Thirty (44.8%) patients had breast cancer; the remaining patients had salivary gland cancer. The median observation period for the intervention group was 304 days from the initial evaluation. Nineteen (28.4%) patients exhibited a >15% relative decrease in GLS, and consequently received cardioprotective agents. The incidence of trastuzumab discontinuation for cardiogenic reasons was significantly lower among patients receiving GLS-guided interventions than among those not receiving the intervention (2.4% vs. 24.0%; P=0.009). The incidence of a subsequent decline in left ventricular ejection fraction was lower among patients receiving the intervention than among those not receiving the intervention (4.8% vs. 24.0%; P=0.04).

Conclusions: GLS-guided cardioprotective intervention significantly decreased the incidence of trastuzumab discontinuation.

Key Words: Cardio-oncology; Echocardiography; Global longitudinal strain; Heart failure; Trastuzumab

Trastuzumab is an anti-human epidermal growth factor receptor 2 (HER2) monoclonal antibody used to treat HER2-positive breast and salivary gland cancers. It is the first-line treatment for patients with HER2-positive breast cancer. However, cardiac dysfunction is the most problematic adverse event associated with the use of trastuzumab. The incidence of trastuzumab-associated cardiac dysfunction is 7.0–18.6% and that of trastuzumab-associated congestive heart failure is 0.4–2.2%. In addition, discontinuation of trastuzumab chemotherapy is associated with cardiovascular events and an increased risk of all-cause death. Therefore, further studies on optimal follow-up methods to complete chemotherapy without discontinuation for cardiogenic reasons are warranted.

Prescribing cardioprotective drugs in advance to all patients scheduled for anticancer treatment is a viable method to prevent chemotherapy discontinuation. The MANTICORE 101–Breast trial was a placebo-controlled randomized trial into the prevention of trastuzumab-related cardiotoxicity. In that trial, compared with placebo, treatment with angiotensin-converting enzyme (ACE) inhibitors or β-blockers prior to trastuzumab administration did not significantly reduce the risk of cancer therapy-related cardiac dysfunction (CTRCD). Another method to prevent chemotherapy discontinuation is to prescribe cardioprotective drugs only in those patients who develop...
subclinical cardiotoxicity, characterized by an increase in troponin levels and a decline in global longitudinal strain (GLS). A decline in GLS, a measurement of left ventricular longitudinal shortening, in response to anticancer drugs precedes a decline in left ventricular ejection fraction (LVEF). In the SUCCOUR trial, anthracycline-treated patients were randomized to either a GLS- or LVEF-guided arm, in which ACE inhibitors and β-blockers were initiated when GLS and LVEF decreased, respectively. There was a lower incidence of CTRCD in the GLS-guided arm than in the LVEF-guided arm.

Consequently, a uniform approach of administering cardioprotective agents before chemotherapy may not work; instead, GLS-guided risk assessment may be useful in preventing CTRCD. However, evidence regarding the usefulness of GLS-guided intervention methods in trastuzumab chemotherapy is limited. Therefore, the aim of this study was to determine whether a GLS-guided management approach reduced LVEF-based cardiotoxicity (LVEF-CTRCD) and discontinuation of trastuzumab chemotherapy.

Methods

Patient Cohort
The present single-center retrospective cohort study identified patients who visited the cardio-oncology unit at the International University of Health and Welfare Mita Hospital between April 1, 2017 and August 31, 2020 before receiving trastuzumab for HER2-positive breast cancer or salivary gland cancer. At the International University of Health and Welfare Mita Hospital, patients receiving trastuzumab chemotherapy underwent the standardized follow-up “cardioprotective protocol” (see below). Patients who discontinued trastuzumab before the sixth course of trastuzumab administration or 3 months after the first administration for non-cardiogenic reasons were excluded from analysis.

Patients who visited the cardio-oncology unit from April 2017 to August 2020 (n=84)

Exclusion
- Not administer trastuzumab (n=11)
- Never visit follow-up by cardio-oncology unit (n=5)

Patients who underwent trastuzumab administration (n=68)

Exclusion
- Discontinue trastuzumab before the sixth course of trastuzumab administration or 3 months after the first administration for non-cardiogenic reasons (n=1)

Study population (n=67)

Cardioprotective Protocol group (n=42)

Control group (n=25)

Figure 1. Study flow diagram. In all, 84 patients were referred to the cardio-oncology unit prior to trastuzumab administration. We excluded 11 patients, and enrolled the remaining 67 patients in the analysis. Among these 67 patients, the 42 (62.7%) who underwent the global longitudinal strain (GLS)-guided protocol were classified as the cardioprotective protocol group, and the remaining 25 (37.3%), who did not receive the GLS-guided protocol, were classified as the control group.
courses of trastuzumab. If cardiotoxicity was not observed by the sixth-course follow-up, the scheduled follow-ups were terminated. If cardiotoxicity was recognized, patients continued to be followed up every 3 months.

GLS was measured using automated function imaging with 3 apical views. GLS-based cardiotoxicity (GLS-CTRCD) was defined as a reduction in GLS of >15% compared with baseline. LVEF was measured using the modified Simpson method. LVEF-CTRCD was defined as a reduction in LVEF of >10% compared to baseline, to a value <53%. According to our cardioprotective protocol, when patients met the criteria for GLS-CTRCD, they were prescribed ACE inhibitors or angiotensin II receptor blockers (ARBs) to prevent decreases in LVEF. In cases of prior administration of ACE inhibitors or ARBs, patients received a higher drug dose or additional β-blockers. Drug selection and dose adjustments were determined by physicians in the cardio-oncology unit.

Transthoracic echocardiography was performed by cardiac sonographers using an ultrasound system (Vivid E9; GE Healthcare, Wisconsin, MI, USA). All GLS and LVEF data in echocardiograms were validated as follows: all echocardiography was performed by a few well-trained sonographers, and all recorded images and analyses were evaluated and validated by both the sonographers and board-certified cardiologists. High-sensitivity troponin I levels were measured using an Abbott Architect analyzer.

Patients classified into the control group were those who skipped scheduled follow-ups, those for whom GLS data could not be technically obtained, those administered ACE inhibitors or β-blockers not on the basis of GLS-CTRCD criteria, and those not administered ACE inhibitors or β-blockers despite meeting the criteria for GLS-CTRCD.

The study sample size was calculated as follows: in the analysis of the BCIRG-006 (Breast Cancer International Research Group 006) study, trastuzumab cardiotoxicity was reported at 19%. In the present study, registration of 60 patients was deemed necessary to calculate the 95% confidence interval of the event rate at ±10% precision. This study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the International University of Health and Welfare (5-18-8). Owing to the retrospective nature of the study, patients’ consent was not required. Data were extracted from medical records.

**Outcomes**

The primary endpoint was defined as discontinuation of trastuzumab for cardiogenic reasons. The secondary endpoints were LVEF-CTRCD and symptomatic heart failure. Discontinuation of trastuzumab for cardiogenic reasons was defined as discontinuation of chemotherapy because of the occurrence of shortness of breath, edema, or pulmonary congestion due to reduced cardiac function. The observation period was from the time of the first visit to the cardio-oncology unit until August 31, 2021.

**Statistical Analysis**

Normally distributed continuous variables are expressed as the mean±SD, whereas continuous variables that were not normally distributed are presented as the median with interquartile range (IQR). Baseline characteristics were compared between the 2 groups using Student’s t-test when data were normally distributed and the Wilcoxon test when the data were not normally distributed. Fisher’s exact test was used for comparisons of primary and secondary endpoints between groups. Cumulative event rates were estimated using the Kaplan-Meier method for the primary endpoint and compared using log-rank tests. Descriptive statistics were performed for LVEF recovery 1 year after the onset of LVEF-CTRCD. All statistical analyses were performed using JMP 15.2.0 (SAS Institute Japan, Tokyo, Japan). Statistical significance was set at two-tailed P<0.05.

**Results**

In all, 84 consecutive patients who were referred to the cardio-oncology unit prior to trastuzumab administration were identified (Figure 2). Eleven patients who did not use
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of 67 patients, 39 (58.2%) were women; the mean (±SD) patient age was 63 ± 11 years. Twenty (29.9%) patients had a history of anthracycline use (median dose 400 mg/m²) and 9 (13.4%) patients had a history of chest irradiation. Of 67 patients, 42 (62.7%) who underwent the GLS-guided protocol were classified into the cardioprotective protocol group, and the remaining 25 trastuzumab thereafter were excluded, as was another patient who discontinued trastuzumab for non-cardiogenic reasons before the third follow-up. The remaining 67 patients were enrolled in the analysis.

The baseline characteristics of the study participants are presented in Table 1. Approximately half the patients had breast cancer (n=30; 44.8%) and the rest had salivary gland cancer (n=37; 55.2%). Of the 67 patients, 39 (58.2%) were women; the mean (±SD) patient age was 63±11 years. Twenty (29.9%) patients had a history of anthracycline use (median dose 400 mg/m²) and 9 (13.4%) patients had a history of chest irradiation. Of 67 patients, 42 (62.7%) who underwent the GLS-guided protocol were classified into the cardioprotective protocol group, and the remaining 25 patients were enrolled in the analysis.

Table 1. Baseline Characteristics of Patients

| Total (n=67) | Cardioprotective protocol (n=42; 62.7%) | Control (n=25; 37.3%) | P value |
|-------------|----------------------------------------|-----------------------|---------|
| Age (years) | 63±11                                  | 62±11                 | 63±11   | 0.7     |
| Male sex    |                                        | 28 (41.8)             | 17 (40.5) | 11 (44.0) | 0.8     |
| BMI (kg/m²) | 22.6±3.4                               | 22.9±3.4              | 22.2±3.4 | 0.4     |
| Smoking history | 20 (29.9)                             | 11 (26.2)             | 9 (36.0) | 0.4     |
| Hypertension | 24 (35.8)                              | 15 (35.7)             | 9 (36.0) | 1.0     |
| Diabetes    | 10 (14.9)                              | 7 (16.7)              | 3 (12.0) | 0.7     |
| Dyslipidemia | 10 (14.9)                              | 7 (16.7)              | 3 (12.0) | 0.7     |
| Cardiovascular disease | 0 (0.0)                               | 0 (0.0)               | 0 (0.0)  |         |
| Symptomatic heart failure | 0 (0.0)                           | 0 (0.0)               | 0 (0.0)  |         |
| Breast cancer patients | 30 (44.8)                         | 18 (42.9)             | 12 (48.0) | 0.8     |
| Cancer stage I | 4 (13.3)                               | 1 (5.6)               | 3 (25.0) |         |
| II | 11 (36.7)                              | 6 (33.3)              | 5 (41.7) |         |
| III | 3 (10.0)                              | 3 (16.7)              | 0 (0.0)  |         |
| IV | 12 (44.0)                              | 8 (44.4)              | 4 (33.3) |         |
| Salivary gland cancer patients | 37 (55.2)                         | 24 (57.1)             | 13 (52) | 0.8     |
| Cancer stage I | 0 (0.0)                               | 0 (0.0)               | 0 (0.0)  |         |
| II | 0 (0.0)                               | 0 (0.0)               | 0 (0.0)  |         |
| III | 3 (8.1)                              | 2 (8.3)               | 1 (7.7)  |         |
| IV | 34 (91.9)                             | 22 (91.7)             | 12 (92.3) |         |
| Anthracycline use | 20 (29.9)                         | 11 (26.2)             | 9 (36.0) | 0.4     |
| Anthracycline dose (mg/m²) | 400 [370–400]                         | 400 [320–400]         | 400 [380–400] | 0.6     |
| Left chest irradiation | 9 (13.4)                             | 4 (9.5)               | 5 (20.0) | 0.3     |
| LVEF (%) | 65.5±5.0                               | 65.3±4.5              | 65.7±5.9 | 0.8     |
| GLS (%) | −17.9±2.1                              | −17.8±1.9             | −18.0±2.6 | 0.9     |
| BNP (pg/mL) | 14 [7–25]                              | 14 [7–27]             | 15 [7–26] | 0.9     |
| TnI (pg/ mL) | 3 [1–6]                             | 3 [2–6]               | 4 [1–6]  | 1.0     |
| β-blockers | 0 (0.0)                               | 0 (0.0)               | 0 (0.0)  |         |
| ACE inhibitors/ARBs | 11 (16.4)                         | 6 (14.3)              | 5 (20.0) | 0.7     |

Unless indicated otherwise, data are expressed as the mean±SD, median [interquartile range], or n (%). Categorical data were analyzed using Chi-squared or Fisher’s exact tests, as appropriate. Continuous data were analyzed using unpaired t-tests or the Wilcoxon test, as appropriate. Statistical significance was set at P<0.05. Clinical characteristics, cancer, cancer therapy, cardiac imaging parameters, cardiac biomarkers, and cardioprotective drug use were compared between the cardioprotective protocol and control groups. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; GLS, global longitudinal strain determined using an echocardiogram; LVEF, left ventricular ejection fraction determined using an echocardiogram; TnI, troponin I.

Table 2. Primary and Secondary Endpoints and Clinical Events

| Total (n=67) | Cardioprotective protocol (n=42) | Control (n=25) | P value |
|-------------|----------------------------------|---------------|---------|
| Primary endpoint | 7 (10.4)                         | 1 (2.4)        | 6 (24.0) | 0.009  |
| Secondary endpoints |                                |               |         |
| LVEF-CTRCD | 8 (11.9)                         | 2 (4.8)        | 6 (24.0) | 0.04   |
| Symptomatic heart failure | 3 (4.5)                         | 1 (2.4)        | 2 (8.0)  | 0.6    |

Unless indicated otherwise, data shown (%). Categorical data were analyzed using the Chi-squared or Fisher’s exact tests, as appropriate. Statistical significance was set at P<0.05. The primary endpoint was discontinuation of trastuzumab for cardiogenic reasons. LVEF-CTRCD, left ventricular ejection fraction-based cancer-therapy related cardiotoxicity.
was significantly lower in the cardioprotective protocol than control group (2.4% vs. 24.0%; P=0.009). In addition, Kaplan-Meier analysis demonstrated that the incidence of primary endpoint-free survival was higher in the cardioprotective protocol than control group (Figure 3). Regarding the secondary endpoints, the occurrence of LVEF-CTRCD was significantly lower in the cardioprotective protocol than control group (n=2 [4.8%] vs. n=6 [24.0%]; P=0.04). The incidence of symptomatic heart failure was higher in the control than cardioprotective protocol group (P=0.6).

The drug types and doses in the cardioprotective protocol group are presented in the Supplementary Table. The type of drug was determined by the treating physician and the dose of each drug was administered at the maximum tolerated dose. GLS-CTRCD occurred in 19 patients (28.4%). Inspection of the timing of the GLS-CTRCDs revealed that it occurred by the sixth course of trastuzumab in 89.5% (n=17) of patients: GLS-CTRCD was documented in 4 (21.1%), 10 (52.6%), and 3 (15.8%) patients at the follow-up after the first, third and sixth courses of trastuzumab, respectively.

Finally, we examined the recovery of cardiac function 1 year after the onset of LVEF-CTRCD between the 2 groups after the occurrence of myocardial injury. In the cardioprotective protocol group, both patients with LVEF-CTRCD experienced a remarkable recovery in LVEF during the long follow-up period. In contrast, in the control group, 83% of patients with LVEF-CTRCD did not show LVEF recovery after a long period (Figure 4).

**Discussion**

**Prevention of Cardiac Damage and Trastuzumab Discontinuation**

The data from this study suggest that GLS-guided cardioprotective management is useful in preventing trastuzumab-related cardiac damage and trastuzumab discontinuation. First, the GLS-guided cardioprotective protocol group had a significantly lower incidence of trastuzumab discontinuation for cardiogenic reasons than the control group. Second, the incidence of LVEF-CTRCD was significantly lower in the cardioprotective protocol than control group (2.4% vs. 24.0%; P=0.009). In addition, Kaplan-Meier analysis demonstrated that the incidence of primary endpoint-free survival was higher in the cardioprotective protocol than control group (Figure 3). Regarding the secondary endpoints, the occurrence of LVEF-CTRCD was significantly lower in the cardioprotective protocol than control group (n=2 [4.8%] vs. n=6 [24.0%]; P=0.04). The incidence of symptomatic heart failure was higher in the control than cardioprotective protocol group (P=0.6).

To evaluate the significance of the GLS-guided cardioprotective protocol, we examined whether there were any differences in the endpoints between the 2 groups (Table 2). Importantly, the incidence of the primary endpoint (i.e., discontinuation of trastuzumab for cardiogenic reasons) was significantly lower in the cardioprotective protocol than control group (2.4% vs. 24.0%; P=0.009). In addition, Kaplan-Meier analysis demonstrated that the incidence of primary endpoint-free survival was higher in the cardioprotective protocol than control group (Figure 3). Regarding the secondary endpoints, the occurrence of LVEF-CTRCD was significantly lower in the cardioprotective protocol than control group (n=2 [4.8%] vs. n=6 [24.0%]; P=0.04). The incidence of symptomatic heart failure was higher in the control than cardioprotective protocol group (P=0.6).

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lower in the cardioprotective protocol than control group. Third, a beneficial effect on LVEF recovery was observed in the cardioprotective protocol group.

Although a few studies have been conducted on GLS-guided treatment for patients receiving trastuzumab chemotherapy, its usefulness has not been confirmed. A previous observational study by Santoro et al investigated the usefulness of GLS-guided treatment with a single-arm study. 10 That study included patients with breast cancer who were treated with anthracycline and trastuzumab. All patients were started on ACE inhibitors and β-blockers when GLS decreased by >15% from baseline. Of these patients, 3.4% developed LVEF-CTRCD, with an incidence ranging from 7% to 34%. The outcomes of that study suggest that GLS-guided therapy may be useful in preventing LVEF-CTRCD considering the reported frequency of myocardial injury. 10,11

The incidence of LVEF-CTRCD was similar in the present study, suggesting that the GLS-guided approach had a similar effect in our cohort. Importantly, we directly examined the usefulness of the GLS-guided approach in classical evaluations within the same cohort. That is, we showed that the frequent follow-up and GLS-guided approach could prevent trastuzumab discontinuation and LVEF-CTRCD compared with the classical approach within the same cohort. This supports the usefulness of GLS-guided cardioprotective management.

Further, our study provides valuable information regarding the appropriate frequency of follow-up. Although the frequency of echocardiography screening is not clearly defined in the guidelines, a 3-month follow-up has been commonly used. Díaz-Antón et al conducted a study on the optimal timing of echocardiography to detect GLS-CTRCD. 12 That study included patients with breast cancer who were treated with anthracycline and/or trastuzumab, and echocardiography tests were performed more frequently than in many other studies. Echocardiography was performed before starting chemotherapy, between the second and third courses of anthracycline, and 1, 3, 6, and 12 months after the end of anthracycline treatment. After 5 months of starting anthracycline, the incidence of LVEF-CTRCD differed significantly. However, approximately 3 months after the initial anthracycline administration, the incidence of GLS-CTRCD was significantly different between the groups. It was concluded that 3 months after anthracycline initiation was the optimal time to detect a decline in GLS. 12

In the present study, we reported that 89.5% of overall GLS-CTRCD was detected up to the sixth course of trastuzumab. GLS-CTRCD was detected in 21.1% and 73.7% of all patients after the first and third courses of trastuzumab, indicating that trastuzumab-associated GLS-CTRCD is frequently observed in the early phase of treatment. Therefore, intensive and frequent follow-up should be performed in the early phase of trastuzumab treatment to predict CTRCD using GLS.

Furthermore, we demonstrated the impact of the cardioprotective protocol on LVEF recovery. Patients in the cardioprotective protocol group had a greater tendency for LVEF recovery than those in the control group 1 year after the onset of LVEF-CTRCD. LVEF recovery after CTRCD could help patients restart and complete chemotherapy. 7 Patients following the cardioprotective protocol may also complete chemotherapy earlier than those not following the protocol because the protocol allows for early intervention before myocardial damage becomes irreversible.

Study Limitations
This study has several limitations. First, the analysis was conducted retrospectively, whereas our screening program was conducted with a prespecified prospective protocol for screening. Second, the study analyzed 2 types of cancers: breast and salivary gland cancers. These 2 cancers differ in terms of sex and the anthracycline pre-administration, hence the background factors may differ between patients. Third, although no significant differences were observed between the cardioprotective protocol and control groups regarding known risk factors for developing CTRCD at baseline, confounding or selection bias may have affected the results. To strengthen the present results, a randomized controlled trial is needed to determine the effect of GLS-guided treatment with the endpoint of trastuzumab chemotherapy completion.

Conclusions
In conclusion, our GLS-guided cardioprotective protocol significantly decreased the incidence of trastuzumab discontinuation. Frequent evaluations of GLS in the early treatment phases may be important for preventing CTRCD.

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Disclosures
The authors declare that they have no conflicts of interest.

Author Contributions
K.Y. was involved in the conceptualization, methodology, validation, formal analysis, investigation, writing the original draft, reviewing and editing subsequent drafts, and visualization. Yudai Tamura was involved in conception, methodology, validation, formal analysis, verification, and writing. H.T. was involved in investigation, reviewing and editing subsequent drafts, and validation. A.F. was involved in the investigation, J.I., H.Y., and A.K. were involved in reviewing and editing subsequent drafts. Yuichi Tamura was involved in supervision, conceptualization, validation, formal analysis, investigation, resources, data curation, writing the original draft, reviewing and editing subsequent drafts, visualization, and project administration.

IRB Information
This study was approved by the Ethics Committee of the International University of Health and Welfare (5-18-8).

Data Availability
The deidentified participant data will not be shared.

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Supplementary Files

Please find supplementary file(s):  
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