

Adjuvant Weekly Paclitaxel and Trastuzumab for HER2-Positive Early-Stage Breast Cancer with Preserved Baseline LVEF: Incidence of Cardiotoxicity and Feasibility of Simplified Cardiac Surveillance

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Purpose: The incidence of trastuzumab-related cardiotoxicity is low among patients receiving regimens that do not include anthracyclines. We aimed to examine whether cardiac monitoring during paclitaxel and trastuzumab therapy can be simplified in a strictly defined low-risk population.

Patients and Methods: We both retrospectively and prospectively assessed the cardiotoxicity incidence among patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer treated with adjuvant paclitaxel and trastuzumab, excluding those with major cardiotoxicity risk factors such as a low baseline left ventricular ejection fraction (LVEF). First, records of patients with HER2-positive early-stage breast cancer treated during 2015–2021 were retrospectively reviewed. Eligibility criteria were as follows: (1) weekly paclitaxel and trastuzumab followed by trastuzumab; and (2) a baseline LVEF $\geq 55\%$. Second, patients considered suitable for simplified monitoring were prospectively enrolled. Inclusion criteria were a baseline LVEF $\geq 60\%$, age ≤ 65 years, and body mass index < 30 kg/m². Cardiac function was evaluated every 3 months by using global longitudinal strain (GLS), cardiac biomarkers, and the LVEF.

Results: Sixty-six patients were included in the retrospective study. No patients developed symptomatic cardiotoxicity (95% confidence interval [CI], 0%–5.5%). Three patients (4.5%; 95% CI, 1.5%–12.5%) had an asymptomatic LVEF decline, and all 66 completed the treatment. In the prospective pilot cohort, 9 patients completed therapy, and none developed cardiotoxicity (95% CI, 0%–29.9%). The median change in the LVEF at 12 months was -5% (range, -12% to -3%), and that in GLS was $+2.15\%$ (-5.5% to $+8.3\%$). No changes in the LVEF or GLS that required treatment interruption occurred, and cardiac biomarkers remained normal.

Conclusion: Among patients with HER2-positive early-stage breast cancer who received paclitaxel and trastuzumab, had a preserved baseline LVEF, and had no anthracycline exposure, the cardiotoxicity incidence was low, suggesting that cardiac monitoring may be simplified in this population.

Keywords: risk factor, low-risk, cardiac monitoring, anthracycline, global longitudinal strain

Introduction

As adjuvant therapy for human epidermal growth factor receptor 2 (HER2)-positive primary breast cancer, major trials suggest and practice guidelines recommend anthracycline- and taxane-based chemotherapy combined with anti-HER2 agents such as trastuzumab and pertuzumab.^{1–6} Anthracycline-containing treatment regimens are reportedly associated

with an 8%–10% incidence of an asymptomatic left ventricular (LV) ejection fraction (LVEF) decline.² Consequently, anthracycline-free regimens have become more common in clinical practice. In the Adjuvant Paclitaxel and Trastuzumab (APT) study, which supported the use of adjuvant weekly paclitaxel and trastuzumab for HER2-positive, lymph node-negative breast cancer, the incidence of cardiotoxicity was 3.2%, lower than that observed with anthracycline-containing regimens.⁷ Exploratory analyses in that study identified a baseline LVEF $\leq 55\%$ as a risk factor for cardiotoxicity.⁷ The incidence of cardiotoxicity during paclitaxel and trastuzumab therapy is expected to be very low among patients with normal baseline LVEF. Dang et al suggested that cardiac monitoring may be simplified in patients without cardiotoxicity risk factors.⁷

In addition, the final 10-year analysis of the APT trial confirmed the long-term efficacy of adjuvant paclitaxel plus trastuzumab for small, node-negative, HER2-positive breast cancer, further supporting the clinical relevance of this de-escalated regimen in appropriately selected patients.⁸ Current cardio-oncology recommendations of the European Society of Cardiology (ESC), American Society of Clinical Oncology (ASCO), and European Society for Medical Oncology (ESMO) emphasize baseline cardiac risk assessment and surveillance when potentially cardiotoxic therapy is provided; however, the optimal surveillance intensity for low-risk patients receiving non-anthracycline HER2-targeted regimens has not been sufficiently validated.^{9–11}

In this study, we aimed to examine whether cardiac monitoring during paclitaxel and trastuzumab therapy can be simplified in a strictly defined low-risk population. In the context of this study, a “low risk” was explicitly defined as having a preserved baseline LVEF and no prior anthracycline exposure, independent of general cardiovascular comorbidities such as hypertension or dyslipidemia.

Materials and Methods

Study Design

We explored the possibility of simplifying cardiac monitoring in two steps. First, we retrospectively analyzed the incidence of cardiotoxicity by using real-world data of patients with HER2-positive early-stage breast cancer treated with weekly paclitaxel and trastuzumab at our institution, excluding those with a low baseline LVEF, a risk factor identified by Dang et al.⁷

Second, we designed a pilot study based on our retrospective findings. In previous studies, paclitaxel and trastuzumab therapy-related cardiotoxicity was primarily assessed via clinical symptoms and LVEF changes. To address this limitation, we incorporated global longitudinal strain (GLS), cardiac biomarkers, and cardiology support in addition to LVEF in our pilot study, to more comprehensively evaluate patients' cardiac function and to assess the feasibility of simplified monitoring.

This study was conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. The Institutional Review Board of Mie University Hospital approved the study protocol (approval no.: H2021-097), and informed consent was obtained from all participants.

Retrospective Study

We reviewed medical records of patients treated for HER2-positive, lymph node-negative breast cancer at our institution from February 2015 to April 2021. Inclusion criteria were as follows: (1) weekly paclitaxel (80 mg/m²) and trastuzumab (4 mg/kg loading dose, followed by 2 mg/kg) for 12 weeks, followed by 9 months of trastuzumab monotherapy (6 mg/kg every 3 weeks); (2) echocardiography performed at baseline, during treatment (3–6 months), and at completion; and (3) baseline LVEF $\geq 55\%$.

We evaluated cardiotoxicity (symptomatic congestive heart failure [CHF] and an asymptomatic LVEF decline), changes in LVEF, and treatment completion. Cardiotoxicity was reassessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Grade 3 LV systolic dysfunction (LVSD) was defined as symptomatic CHF responsive to intervention, whereas grade 4 LVSD was defined as refractory CHF. Consistent with the APT study, a symptomatic LVEF decline was defined as an absolute LVEF decrease $\geq 10\%$ to $< 50\%$, or $\geq 16\%$ from baseline.⁵

Pilot Study

Based on the results of the retrospective review, we conducted a prospective pilot study among patients estimated to have low cardiotoxicity risk (Figure 1). Eligibility criteria were a baseline LVEF $\geq 60\%$, age ≤ 65 years, and body mass index (BMI) $< 30 \text{ kg/m}^2$. Although we included patients with an LVEF $\geq 55\%$ for the retrospective cohort, we adopted the stricter LVEF cutoff of $\geq 60\%$ for the prospective pilot to maximize safety in evaluating the feasibility of simplified monitoring. Echocardiography with GLS was performed and myocardial biomarkers (high-sensitivity troponin I [hs-TnI] and brain natriuretic peptide [BNP] levels) were measured every 3 months. Although the monitoring protocol was initially designed in 2021 based on prevailing cardio-oncology consensuses, we retrospectively applied the contemporary ESC 2022 guideline definitions for the final data analysis and reporting.¹¹ Cancer therapy-related cardiac dysfunction (CTRCD) was defined as an LVEF decrease $\geq 10\%$ to $< 50\%$ or $\geq 16\%$ from baseline.^{5,11} In accordance with the ESC 2022 guidelines, a relative decrease in GLS of $> 15\%$ from baseline was considered a clinically meaningful deterioration.¹¹ The incorporation of GLS and cardiac biomarkers was informed by a prior study showing that early changes in longitudinal strain and troponin levels may precede an overt LVEF decline and help identify patients at an increased risk of treatment-related cardiotoxicity.¹²

All echocardiographic images were obtained using a Philips Epiq 7C ultrasound scanner (Philips Healthcare, Seattle, USA). Standard M-mode, two-dimensional, and Doppler measurements were acquired according to American Society of Echocardiography (ASE) guidelines.¹³ Tissue Doppler-derived peak systolic, early diastolic, and late diastolic velocities of the septal mitral annulus were recorded. LV end-systolic and end-diastolic volumes were measured in the apical four- and two-chamber views, and the LVEF was calculated using the Simpson biplane method. Online two-dimensional speckle-tracking echocardiography (STE) was performed with electrocardiographic gating in the three standard apical views (four-, two-, and three-chamber views) by using automated cardiac motion quantification in the Q-Lab software installed on the Epiq 7C system. The software automatically tracked myocardial motion, and the operator manually adjusted myocardial boundaries when automated tracking was inaccurate. STE generated regional longitudinal strain

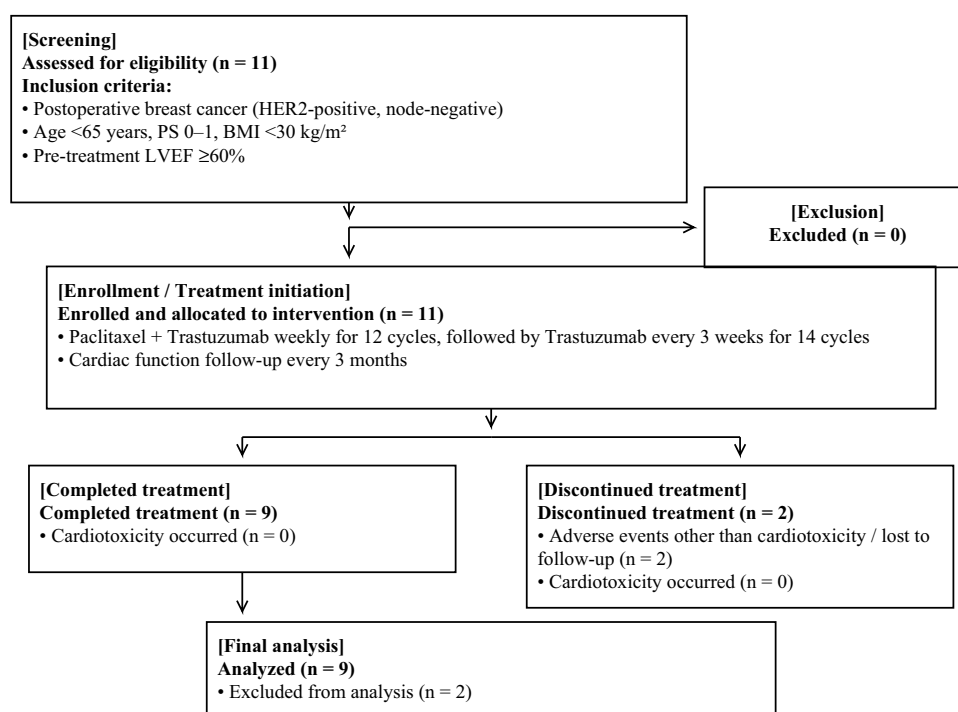


Figure 1 Study flow diagram. CTRCD was defined as a decrease in LVEF of $\geq 10\%$ to a value $< 50\%$ or a decrease of $\geq 16\%$ from the baseline value.

Abbreviations: BMI, body mass index; CTRCD, cancer therapy-related cardiac dysfunction; HER2, human epidermal growth factor receptor 2; LVEF, left ventricular ejection fraction; PS, Eastern Cooperative Oncology Group performance status.

values for the 17 standard LV myocardial segments defined by the ASE; these were recorded and averaged to produce the GLS. Poorly tracked segments were excluded from the GLS analysis after necessary manual adjustments.

BNP and TnI levels were measured using the Architect or Alinity systems (Abbott Laboratories, Abbott Park, IL), the platform routinely used at our institution for plasma biomarker quantification and widely considered a reference method. These measurements were performed using the hospital’s routine clinical laboratory assays. Biomarker results were interpreted using assay-specific institutional reference limits and the 99th-percentile upper reference limit for the hs-TnI assay.

Descriptive statistics were used to summarize patient characteristics and clinical outcomes for both the retrospective and prospective cohorts. Continuous variables are presented as medians and ranges, and categorical variables are expressed as frequencies and percentages. To quantify statistical uncertainty, 95% confidence intervals (CIs) for the incidence of cardiotoxicity were calculated using the Wilson score interval method for small samples in both studies. For the retrospective study, the sample size was determined by the number of eligible patients treated at our institution during the study period. Because the prospective pilot study was exploratory and hypothesis-generating in nature, a formal power-based sample size calculation was not performed. All statistical analyses were considered descriptive.

Results
Retrospective Study
Baseline Characteristics

Sixty-six patients met the eligibility criteria. Their baseline characteristics are summarized in Table 1. The median age was 56.5 years (range, 35–78 years), and all patients were female. Most patients (n = 61, 92.4%) had tumors ≤2 cm, while five patients (7.6%) had tumors >2 cm but ≤3 cm in size. Thirty-two patients (48.5%) had estrogen receptor (ER)-positive tumors, and 34 (51.5%) had ER-negative tumors. Comorbidities included hypertension (n = 14), dyslipidemia (n

Table 1 Baseline Characteristics

Characteristics	Number of Patients
	N = 66, n (%)
Age, years, median (range)	56.5 (32–78)
<50	17 (26)
50–59	21 (32)
60–69	19 (29)
≥70	9 (14)
Sex	
Female	66 (100)
Male	0 (0)
Tumor size	
≤2 cm	61 (92)
>2 cm to ≤3 cm	5 (8)
Estrogen receptor status	
Positive	32 (48)
Negative	34 (52)

(Continued)

Table 1 (Continued).

Characteristics	Number of Patients
	N = 66, n (%)
Radiation therapy	
Yes	12 (18)
No	54 (82)
Comorbidities	
Hypertension	14 (21)
Lipid disorder	13 (20)
Diabetes	2 (3)
BMI, kg/m ² , median (range)	21.7 (15.7–29.8)
Baseline LVEF, %, median (range)	70 (59–77)

Abbreviations: BMI, body mass index; LVEF, left ventricular ejection fraction.

= 13), and diabetes mellitus (n = 2). Nine patients with hypertension were receiving a calcium channel or angiotensin II receptor blocker. The median BMI was 21.7 kg/m² (range, 15.7–29.8 kg/m²), and the median baseline LVEF was 70% (range, 59%–77%).

Cardiac Outcomes

Changes in the LVEF are summarized in Table 2. By 3–6 months after initiating adjuvant chemotherapy, the median LVEF had decreased to 66% (range, 50%–77%), and at the end of treatment it was 67.5% (range, 56%–75%). A year after treatment, 9/66 patients (13.6%) were lost to follow-up owing to their transfer to another hospital. Among the remaining 57 patients, no heart failure or other major cardiac events were observed.

Incidence of LVEF Decline

An asymptomatic LVEF decline occurred in three patients (4.5%; 95% CI, 1.5%–12.5%), and no symptomatic cardiotoxicity was observed (0%; 95% CI, 0%–5.5%). The affected patients were aged 46, 51, and 74 years. The maximum reductions in their LVEF from baseline were 19%, 19%, and 16%, respectively. None of these patients had hypertension, diabetes, dyslipidemia, or a history of left-sided chest irradiation. One patient (aged 51 years) had a smoking history (5 cigarettes per day for 13 years beginning at age 20 years). Two patients (aged 46 and 51 years)

Table 2 Summary of LVEF Specified Time Points and Changes from Baseline Values

	Baseline		3–6 Months		12 Months	
	N = 66		N = 66	%	N = 66	%
LVEF reduction from baseline						
<10%			59	89.4	59	89.4
10–15%			6	9.1	5	7.6
≥16%			1	1.5	2	3.0
LVEF, %, median (range)	70	(59–77)	66	(50–77)	67.5	(56–75)

Abbreviations, LVEF, left ventricular ejection fraction.

had developed an asymptomatic LVEF decline by the final trastuzumab administration (1 year after treatment initiation), while the 74-year-old patient developed a decline during trastuzumab therapy. In all three cases, the nadir LVEF remained $\geq 50\%$, and no additional clinical or imaging findings suggestive of cardiotoxicity were identified. All three patients completed trastuzumab therapy at the discretion of their attending physicians.

Pilot Study

Baseline Characteristics

Eleven patients were enrolled as of the data cutoff date (October 2021 to October 2024). Two were excluded from the analysis owing to grade 3 transaminase elevation ($n = 1$) and patient withdrawal ($n = 1$), leaving nine evaluable for cardiotoxicity. Their baseline characteristics are summarized in Table 3. The median age was 55 years (range, 38–64 years), and all patients were female. Two patients (22.2%) had tumors > 2 cm in diameter, and seven patients (77.8%) had tumors measuring 0.5–2.0 cm. Seven patients (77.8%) had ER-positive tumors. Two (22.2%) had lipid disorders. Three (33.3%) were former smokers and one (11.1%) was a current smoker. One patient (11.1%) had received left-sided chest radiation. The median BMI was 20.7 kg/m² (range, 17.3–26.1 kg/m²), and the median baseline LVEF was 72% (range, 68%–76%).

Cardiac Outcomes

BNP and TnI levels were within normal limits in all patients at baseline. All patients completed adjuvant chemotherapy (100%). No cardiac events occurred (0%). GLS could not be measured in one patient; therefore, GLS analyses were conducted in eight patients.

As shown in Table 4A, the baseline LVEF ranged from 68% to 76%. At 12 months, all patients exhibited decreases from baseline, with a median decline of 5% (range, –12% to –3%). Temporal LVEF trends are shown in Figure 2A. The median LVEF declined progressively through 9 months and slightly recovered at 12 months. None of the patients met the criteria for a CTRCD, defined as a decrease in LVEF $\geq 10\%$ to $< 50\%$ or a decrease of $\geq 16\%$ from baseline (0%; 95% CI, 0%–29.9%).

GLS changes from baseline to 12 months varied, with a median change of +2.15% (range, –5.5% to 8.3%). As shown in Table 4B, five patients (patients 2, 3, 5, 6 and 8) showed worsening GLS values (less negative), whereas three (patients 4, 7 and 9) showed improvements. Figure 2B shows that the median GLS had worsened by 3 months, improved

Table 3 Patient Characteristics in the Prospective Study

Patient no.	Age, Years	BMI, kg/m ²	RT	Rt/Lt	HTN	DM	Smoking Status	BNP	TnI
1	55	18.9	–	Rt	–	–	Never	28	10.4
2	44	17.3	–	Rt	–	–	Former	6.8	< 10.0
3	57	17.6	+	Lt	–	–	Never	11	< 10.0
4	58	21.0	–	Rt	–	–	Former	8.3	< 10.0
5	64	20.7	–	Rt	–	–	Never	< 5.8	< 10.0
6	63	19.3	–	Rt	–	–	Never	53	< 10.0
7	52	22.5	–	Rt	–	–	Former	< 5.8	< 10.0
8	51	26.1	–	Lt	–	–	Never	< 5.8	< 10.0
9	38	23.6	–	Lt	–	–	Current	< 5.8	< 10.0

Notes. The upper reference limit (URL)/upper limit of normal (ULN) for each biomarker was defined according to the institutional laboratory reference range for the assay used during the study period (BNP, 18.4 pg/mL; TnI, 15.6 pg/mL). Biomarker elevation was defined as a value above the assay-specific ULN/URL.

Abbreviations: BMI, body mass index; RT, radiotherapy; Rt/Lt, right/left; HTN, hypertension; DM, diabetes mellitus; BNP, brain natriuretic peptide (pg/mL); TnI, troponin I (pg/mL); +, positive/present; –, negative/absent.

Table 4 Summary of Clinical Findings in Nine Patients

Patient no.	LVEF (%)					
	Baseline	3 M	6 M	9 M	12 M	1 year –Baseline
A LVEF						
1	74	74	75	69	66	–8
2	71	67	66	65	67	–4
3	72	70	72	62	68	–4
4	73	65	69	64	70	–3
5	73	73	71	69	68	–5
6	72	72	67	67	64	–8
7	70	67	69	61	66	–4
8	76	65	64	64	64	–12
9	68	63	60	63	63	–5
B GLS						
1	NE	NE	NE	NE	NE	NE
2	–16.3	–17.7	–21.0	–16.2	–16.3	7.6
3	–22.5	–21.9	–21.5	–17.4	–14.2	8.3
4	–18.1	–12.1	–13.1	–18.7	–20.7	–2.6
5	–22.6	–23.9	–22.9	–22.6	–19.5	3.1
6	–21.4	–17.4	–20.6	–13.3	–17.0	4.4
7	–13.1	–20.5	–22.9	–18.6	–18.6	–5.5
8	–17.2	–15.0	–16.0	–19.0	–16.0	1.2
9	–18.0	–18.0	–19.0	–19.0	–20	–2.0

Notes. Clinically meaningful GLS deterioration was defined as a decrease >15% from baseline (ESC 2022). None of the evaluable patients met this criterion. Values in the “1 year – baseline” column represent absolute differences (percentage points).

Abbreviations. LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; NE, not evaluated; M, months.

transiently by 6 months, and worsened again by 9 and 12 months. BNP and TnI levels remained within normal limits throughout the study.

Discussion

The treatment outcomes for patients with HER2-positive early-stage breast cancer have improved substantially with the introduction of perioperative combination therapies, which include trastuzumab, anthracyclines, and taxanes.^{1,3,6,8,14,15} However, the risk of trastuzumab-induced cardiotoxicity necessitates careful monitoring, which prompted extensive investigations into its mechanisms, incidence, and risk factors.^{7,15,16} Several studies have demonstrated that anthracycline-free regimens reduce the risk of cardiotoxicity.^{7,16} Notably, the APT trial suggested that cardiac monitoring may be simplified in selected patients.⁷

In our retrospective study of patients receiving adjuvant trastuzumab and paclitaxel, no symptomatic LVSD occurred, although three patients (4.5%) experienced an asymptomatic LVEF decline. All 66 patients completed therapy without interruptions or the need for medical intervention. In two previous trials, the same regimen was used: the reported

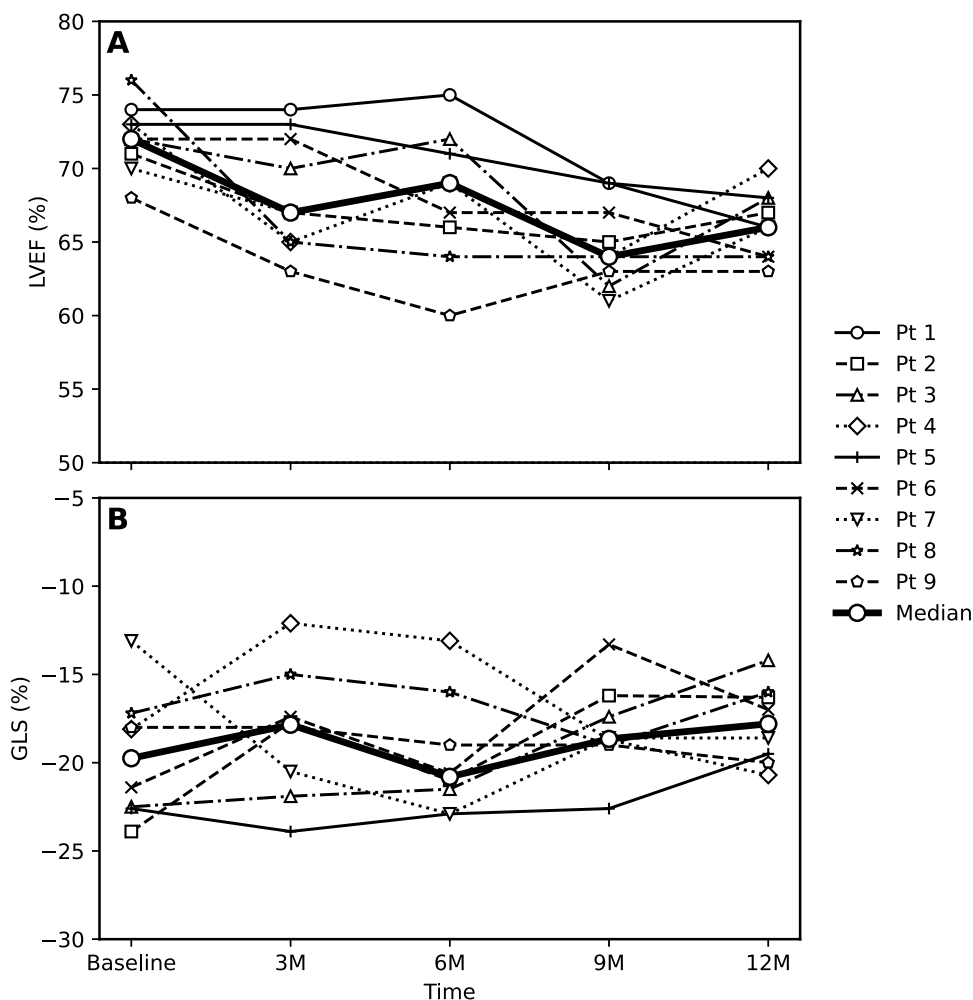


Figure 2 Time course of parameters in patients treated with trastuzumab. **(A)** LVEF and **(B)** GLS over the 12-month follow-up period. The thick solid line with large circles represents the median value at each time point. Individual patient trajectories are indicated by distinct line and marker styles to allow tracking between the two graphs. Note, Pt. 1 was not included in the GLS analysis.

Abbreviations: LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; PT, patient; M, months.

incidences of symptomatic LVSD and an asymptomatic LVEF decline were 0.5% and 3.2%, respectively, in the APT trial (11/13 patients completed treatment), and 1.8% and 5.3%, respectively, in the ATEMPT trial (5/6 patients completed treatment).^{7,17} The absence of symptomatic LVSD in our cohort may reflect the exclusion of patients with a low baseline LVEF—identified as a risk factor in the APT trial—and those with obesity, which was present in 34% of ATEMPT participants.^{7,17} More recently, the final 10-year analysis of the APT trial confirmed the long-term efficacy of adjuvant paclitaxel plus trastuzumab in this stage I population, and updated long-term results of the ATEMPT trial have expanded the evidence base for de-escalation strategies in patients with HER2-positive early-stage breast cancer.^{8,18}

A challenge in evaluating CTRCD is the variability in definitions across studies. For our retrospective analysis, we used the definition applied in the APT trial. Although three patients showed an LVEF decline $\geq 16\%$, none had an LVEF $< 50\%$. In contrast, according to the 2022 European Society of Cardiology (ESC) definition, the incidence of asymptomatic LVEF decline was 0%.¹¹ Although we also used the APT definition for our pilot study, we will additionally apply the ESC 2022 criteria for our final analyses.

In parallel with the ESC recommendations, ESMO and ASCO cardio-oncology guidelines also underscore the importance of risk stratification and cardiac monitoring during cancer therapy, while acknowledging limitations in the evidence base for surveillance schedules in lower-risk populations.^{9,10} Further highlighting this evidence gap, the results of a randomized trial in which 3-monthly and 4-monthly cardiac monitoring during trastuzumab-based therapy was

compared suggested that less frequent surveillance may be feasible in selected patients, and a contemporary review has highlighted substantial variation in monitoring practices and the need for risk-adapted strategies in HER2-positive breast cancer.^{19,20}

Enrollment in our pilot study began in 2021. To recruit a population expected to have an incidence of cardiotoxicity near 0%, we included patients aged ≤ 65 years with a baseline LVEF $\geq 60\%$ and BMI < 30 kg/m², informed by our retrospective findings. BNP and TnI were added as myocardial biomarkers, as age, BMI, and biomarker abnormalities are cited as risk factors for anti-HER2-related cardiotoxicity in the ESC 2022 guidelines.¹¹ Thus, the pilot population reflects a “low risk” cohort. Among nine evaluable patients, slight decreases in the LVEF and GLS were observed at 9–12 months, but none of the patients met the criteria for cardiotoxicity, and BNP and TnI levels remained normal. Although the sample was small, these findings suggest that cardiac monitoring may be simplified when patients are appropriately selected.

The ESC 2022 guidelines recommend echocardiographic assessment of LVEF and GLS every 3 months during anti-HER2 therapy, with a follow-up echocardiogram 1 year after treatment discontinuation.¹¹ Currently, even low-risk patients are advised to follow the same schedule as high-risk patients who receive anthracycline-containing regimens, although the guidelines acknowledge that surveillance protocols have not been fully validated in low-risk populations. Our pilot study, in which we uniquely combined real-world retrospective data with a prospective evaluation of GLS in a specific low-risk APT population, supports the simplification of cardiac monitoring. However, to validate these findings and establish definitive clinical guidelines, future randomized controlled trials in which standard echocardiographic surveillance is compared with risk-adapted, simplified monitoring strategies are warranted.

The identification of patients who are eligible for reduced monitoring is particularly valuable in scenarios in which healthcare delivery is impaired, such as during natural disasters or pandemics. During the coronavirus disease 2019 pandemic, professional societies recommended that hospital visits are minimized; for example, the ESMO suggested the postponement of cardiac evaluation of patients with asymptomatic early-stage breast cancer.²¹ Although the low-risk population is relatively small, its identification would enable efficient resource allocation and maintenance of care continuity, which is especially relevant in countries prone to natural disasters such as earthquakes.

This study has certain limitations, including its small sample size and single-institution design, which necessitate cautious interpretation of the findings. Furthermore, our follow-up period was limited to 12 months. Therefore, our conclusions primarily pertain to early treatment outcomes and the feasibility of monitoring de-escalation rather than addressing the long-term cardiac risk. Recruitment for the pilot study was slow owing to the stringent eligibility criteria. Furthermore, in real-world clinical practice, some patients who meet the eligibility criteria for the APT regimen are judged to be at a high risk of recurrence and instead receive neoadjuvant chemotherapy, further limiting the pool of eligible candidates. Nevertheless, enrollment will continue as additional cases become available.

Conclusion

We used real-world data to evaluate the incidence of cardiotoxicity among patients with HER2-positive early-stage breast cancer who received postoperative paclitaxel and trastuzumab. In the pilot study, we prospectively monitored the cardiac function of patients without major known risk factors (eg, a low baseline LVEF) via GLS and myocardial biomarkers. Trastuzumab-related cardiotoxicity was very low in this carefully selected population, supporting the feasibility of a risk-adapted de-escalation strategy for cardiac surveillance. In terms of future research, randomized controlled trials in which standard echocardiographic surveillance is compared with this risk-adapted de-escalation strategy are needed to validate our findings before broad implementation in clinical practice.

Abbreviations

APT, Adjuvant Paclitaxel and Trastuzumab; ASCO, American Society of Clinical Oncology; ASE, American Society of Echocardiography; BMI, body mass index; BNP, brain natriuretic peptide; CHF, congestive heart failure; CI, confidence interval; CTRCD, cancer therapy-related cardiac dysfunction; ER, estrogen receptor; ESC, European Society of Cardiology; ESMO, European Society for Medical Oncology; GLS, global longitudinal strain; HER2, human epidermal

growth factor receptor 2; hs, high sensitivity; LV, left ventricle; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; STE, speckle-tracking echocardiography; TnI, troponin I.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

This study was conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. The institutional review board of Mie University Hospital approved the study protocol (H2021-097). Informed consent was obtained from all participants.

Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Dr Toshiro Mizuno reports other from Astrazeneca, other from Daiichi Sankyo, other from Gilead, other from MSD, outside the submitted work. The authors report no conflicts of interest in this work.

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