# Adjuvant Weekly Paclitaxel and Trastuzumab for HER2-Positive Breast Cancer without Risk Factors of Cardiotoxicity. Possibility of Omitting Cardiac Monitoring during Treatment.

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**Research**

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# Abstract

**Background:** Although weekly paclitaxel and trastuzumab is generally considered to be less cardiotoxic than an anthracycline regimen, low baseline left ventricular ejection fraction (LVEF) of ≤55%, hypertension, and high body mass index (BMI) have been reported as risk factors for cardiotoxicity. Without these risk factors, the incidence of cardiotoxicity is expected to be minimal.

**Method:** We retrospectively reviewed the medical records of 86 patients with HER2-positive, node-negative breast cancer between February 2012 and December 2018. Patients were selected for this study according to the following criteria: (1) patients were administered weekly treatment with paclitaxel and trastuzumab for 12 weeks, followed by trastuzumab; (2) baseline LVEF was 60% or more; (3) echocardiography was performed before, during, and at the end of treatment; (4) no hypertension or well-controlled with medication; and (5) BMI was < 30. We investigated the occurrence of cardiotoxicity. A decline in LVEF was defined as a decrease of 15% or more from baseline, or < 50% decrease in LVEF.

**Results:** A total of 40 patients fulfilled the eligibility criteria. The median age was 55.5 (35 to 72) and median baseline LVEF was 68% (60 to 77). The median number of echocardiograms was five (3-7). Out of 40, trastuzumab were completed in 39. Among the 39 patients, no symptomatic congestive heart failure or asymptomatic LVEF decline was observed.

**Conclusion:** In our study, no cardiotoxicity was observed in paclitaxel and trastuzumab. Assessment of cardiac function during treatment may be simplified in patients without risk factors for cardiotoxicity.


# Introduction

In adjuvant therapy for HER2-positive primary breast cancer, major guidelines recommend a combination of chemotherapy anthracyclines and taxanes with anti-HER2 therapy such as trastuzumab and pertuzumab. During treatment with anti-HER2 therapy, management of cardiotoxicity is important.

Previous studies have reported that the risk factors for the development of cardiotoxicity in anti-HER2 therapy include anthracycline exposure, age (50 years and older), obesity, hypertension, and low baseline left ventricular ejection fraction (LVEF)[1-4]. In the regimen containing anthracycline, the incidence of asymptomatic LVEF decline is reported to be 8% to 10%[1]. Therefore, the regimen not containing anthracycline has become widespread in clinical practice.

In the Adjuvant Paclitaxel and Trastuzumab (APT) study, which reported the usefulness of adjuvant weekly paclitaxel and trastuzumab for HER2-positive, node-negative breast cancer, the incidence of cardiotoxicity was 3.2%, which was lower than that of anthracycline-containing regimens[5]. Exploratory studies in the APT study found that low baseline LVEF of £ 55%, hypertension, and high body mass index (BMI) were risk factors for developing cardiotoxicity[6]. If patients do not have these risk factors, the incidence of cardiotoxicity during weekly paclitaxel and trastuzumab is expected to be extremely low.

We retrospectively examined the incidence of cardiotoxicity in patients with no risk factors for cardiotoxicity in HER2-positive early breast cancer treated with weekly paclitaxel and trastuzumab.

## Material And Methods

We retrospectively reviewed the medical records of 86 patients with HER2- positive, lymph node-negative breast cancer between February 2012 and December 2018 at our institute. Patients were selected for this study according to the following criteria: (1) patients were administered weekly treatment with paclitaxel (80 mg/$m^2$) and trastuzumab (4mg/kg followed by 2 mg/kg) for 12 weeks, followed by 9 months of trastuzumab monotherapy (6 mg/kg every 3 weeks); (2) LVEF at baseline was 60% or more; (3) echocardiography was performed before, during, and at the end of treatment; (4) no hypertension or well-controlled with medication; and (5) BMI was < 30. We investigated the occurrence of cardiotoxicity (symptomatic congestive heart failure, asymptomatic decline in LVEF) changes in LVEF and treatment completion rate during trastuzumab therapy.

Cardiotoxicity during treatment was reassessed by the National Cancer Institute Common Toxicity Criteria Adverse Events version 3.0. Grade 3 left ventricular systolic dysfunction (LVSD) is symptomatic congestive heart failure (CHF) responsive to intervention and grade 4 LVSD is refractory CHF. Asymptomatic decline in LVEF was defined by a decrease of 15 or more percentage points from baseline, or < 50% decrease in LVEF.

## Results

# Baseline characteristics

A total of 40 patients fulfilled the eligibility criteria for this study (Study Flow Diagrams). The baseline characteristics of the 40 patients are shown in Table 1. The median age was 55.5 years (range 35 to 72 years). All patients were female. Thirty-four patients had tumors that measured 2 cm or less and six had tumors that measured between 2 and 3 cm. Eighteen patients had estrogen receptor-positive tumor and 22 were negative. Patients also had hypertension (n = 8), lipid disorder (n = 3), and diabetes mellitus (n = 1). Eight patients with hypertension had received a calcium channel blocker or angiotensin II receptor blocker. Median BMI was 21.8 (range 17.2 to 29.1) and median LVEF at baseline was 68% (range 60 to 77).

# Cardiac Outcomes

The median number of echocardiograms during treatment was five (range 3-7). Out of 40 patients, weekly paclitaxel and trastuzumab followed by trastuzumab monotherapy was completed in 39 patients. One patient discontinued trastuzumab monotherapy after eight courses because of the patient's request.

Among the 39 patients who completed trastuzumab, no symptomatic CHF or asymptomatic LVEF decline was observed during treatment (Table 2).

The changes in LVEF are shown in Table 3. The changes in LVEF were compared at three points: baseline, after the completion of 12 weeks of treatment with trastuzumab, and at the end of trastuzumab (within 2 months before and after the final administration). Compared with baseline LVEF, the LVEF level decreased slightly after the start of trastuzumab. By age group, there was no difference in the LVEF changes during treatment between the less than 55 years and 55 years or older groups.

Analysis of 21 patients with echocardiography performed every 3 months during treatment showed that most patients had a decrease in LVEF of less than 10% (Table 4).

# Discussion

Adjuvant weekly paclitaxel and trastuzumab for HER2-positive, node-negative breast cancer is considered standard of care due to its excellent outcome and favorable tolerability. The notable feature of this regimen is its low cardiotoxicity, which is attributed to the absence of anthracycline.

In our study, we also investigated the frequency of cardiotoxicity by excluding cases with other risk factors, low baseline LVEF, and high BMI. As a result, no case of treatment discontinuation due to cardiotoxicity was observed.

Of the three risk factors identified in sub-analysis of the APT trial, our analysis included eight patients with hypertension, but no symptomatic CHF or asymptomatic LVEF reduction was observed in these eight. The reason why cardiac events could be avoided in these eight patients may be related to the absence of other risk factors such as low baseline LVEF and high BMI. Without these risk factors, well-controlled hypertension with anti-hypertensive medication may not be a risk factor in this regimen. However, our study was a small retrospective study, and the number and timing of echocardiograms vary during treatment, so the results need to be interpreted carefully.

Based on the results of previous clinical studies, regular echocardiographic follow-up of cardiac function has been recommended during administration of anti-HER2 therapeutic agents[7, 8]. However, if patients without these risk factors receive adjuvant paclitaxel and trastuzumab, it may simplify routine cardiac function monitoring. Omission of echocardiograms may lead to improvement of patient QOL and reduction of medical costs.

Under the COVID-19 pandemic, the necessity of simplifying cardiac monitoring is increasingly important. In cancer treatment under the COVID-19 pandemic, there is a demand for a treatment that is different from routine medical treatment such as avoiding chemotherapy with high risk of febrile neutropenia and selecting regimens with few hospital visits. According to ESMO guidelines in the COVID-19 era, cardiac function assessment during treatment for early-stage breast cancer should be postponed in the absence of symptoms[9]. Even in anti-HER2 therapy for HER2-positive patients, echocardiography is of medium

priority in the guidelines. Thus, it is important to identify targets that can simplify cardiac function monitoring. Currently, we are planning a prospective study to test the hypothesis that HER2-positive early breast cancer patients without risk factors for cardiotoxicity can omit regular echocardiography during treatment.

In conclusion, no cardiotoxicity was observed in adjuvant weekly paclitaxel and trastuzumab for HER2-positive early breast cancer without cardiotoxicity risk factors. Assessment of cardiac function during treatment may be simplified in patients without risk factors for cardiotoxicity.

## Abbreviations

LVEF, left ventricular ejection fraction; BMI, body mass index; LVSD, left ventricular systolic dysfunction; CHF, symptomatic congestive heart failure

## Declarations

# Acknowledgements

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# Authors’ contributions

Toshiro Mizuno wrote the initial draft of the manuscript and contributed to interpretation of data. Akira Tsunoda, Mikiya Ishihara and Kanako Saito contributed to analysis and interpretation of data. All authors critically reviewed the manuscript and approved the final version of the manuscript.

# Ethical approval

The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization and Good Clinical Practice guidelines. The study protocol was approved by the Institutional Review Board of Mie University Hospital.

# Consent for publication

Not Applicable

# Competing interests

The authors declare that they have no competing interests.

# Declaration of competing interest

All authors indicate no financial relationships.

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# Availability of data and materials

The dataset analyzed during the current study are available from the corresponding author upon reasonable request.

## References

1. Perez EA, Suman VJ, Davidson NE, Sledge GW, Kaufman PA, Hudis CA, 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(8):1231-8.
2. Ewer SM, Ewer MS. Cardiotoxicity profile of trastuzumab. Drug Saf. 2008; 31(6):459-67.
3. Romond EH, Jeong JH, Rastogi P, Swain SM, Geyer CE Jr, Ewer MS, et al. Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol. 2012; 30(31):3792-9.
4. Guenancia C, Lefebvre A, Cardinale D, Yu AF, Ladoire S, Ghiringhelli F, Zeller M,, et al. Obesity As a Risk Factor for Anthracyclines and Trastuzumab Cardiotoxicity in Breast Cancer: A Systematic Review and Meta-Analysis. J Clin Oncol. 2016; 34(26):3157-65.
5. Tolaney SM, Barry WT, Dang CT, Yardley DA, Moy B, Marcom PK, et al. Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-positive Breast Cancer. N Engl J Med. 2015 Jan 8; 372(2):134-41.
6. Dang C, Guo H, Najita J, Yardley D, Marcom K, Albain K, et al. Cardiac Outcomes of Patients on Adjuvant Weekly Paclitaxel and Trastuzumab for Node Negative, HER2 Positive Breast Cancer. JAMA Oncol. 2016 January; 2(1): 29–36.
7. Curigliano G, Lenihan D, Fradley M, Ganatra S, Barac A, Blaes A, et al. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. Ann Oncol. 2020 Feb; 31(2):171-190.

8. Armenian SH, Lacchetti C, Barac A, Carver J, Constine LS, Denduluri N, et al. Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2017 Mar 10;35(8):893-911
9. de Azambuja E, Trapani D, Loibl S, Delaloge S, Senkus E, Criscitiello C, et al. ESMO Management and Treatment Adapted Recommendations in the COVID-19 Era: Breast Cancer. ESMO Open 2020 May; 5(Suppl 3): e000793. doi: 10.1136/esmoopen-2020-000793

# Tables

**Table 1. Baseline characteristics**

| Characteristics | Patients (n=40) |
|---|---|
| Age, median | 55.5 (range 32-72) |
| < 50 | 13 (32%) |
| 50-60 | 11 (27%) |
| 60-70 | 11 (27%) |
| 70 ³ | 5 (12%) |
| Sex | |
| Female | 40 (100%) |
| Male | 0 (0%) |
| Tumor size | |
| £ 2 cm | 34 (85%) |
| > 2 cm to £ 3 cm | 6 (15%) |
| Estrogen-receptor status | |
| Positive | 18 (45%) |
| Negative | 22 (55%) |
| Radiation therapy | |
| Yes | 8 (20%) |
| No | 32 (80%) |
| Commodity | |
| Hypertension | 8 (20%) |
| Lipid disorder | 3 (0.7%) |
| Diabetes | 1 (0.2%) |
| Body mass index | 21.8 (range 17.2-29.1) |
| Baseline LVEF | 68% (range 60-77) |

LVEF; left ventricular ejection fraction

**Table 2. Cardiac Outcomes**

| | N=39* |
|---|---|
| Median number of echocardiography assessments | 5 (range 3-7) |
| Cardiac events | |
| Symptomatic CHF | 0 (0%) |
| Asymptomatic LVEF decline | 0 (0%) |

*Patients who completed weekly paclitaxel and trastuzumab followed by trastuzumab monotherapy

CHF; congestive heart failure, LVEF; left ventricular ejection fraction

**Table 3. Changes in Left Ventricular Ejection Fraction by Age**

| LVEF | All patients (n=39) | Age <55 (n=18) | Age 55³ (n=21) |
|---|---|---|---|
| Baseline | 68% (60-77) | 68% (61-74) | 68% (60-77) |
| 3 months # | 66% (57-74) | 63.5% (57-71) | 68% (59-74) |
| 12 months * | 66.6% (50-75) | 64.5% (50-71) | 67% (60-75) |

#,* Echocardiography at 3 months and at 12 months were defined as performed after administration of paclitaxel and trastuzumab, and within 2 months before and after the final administration of trastuzumab, respectively.

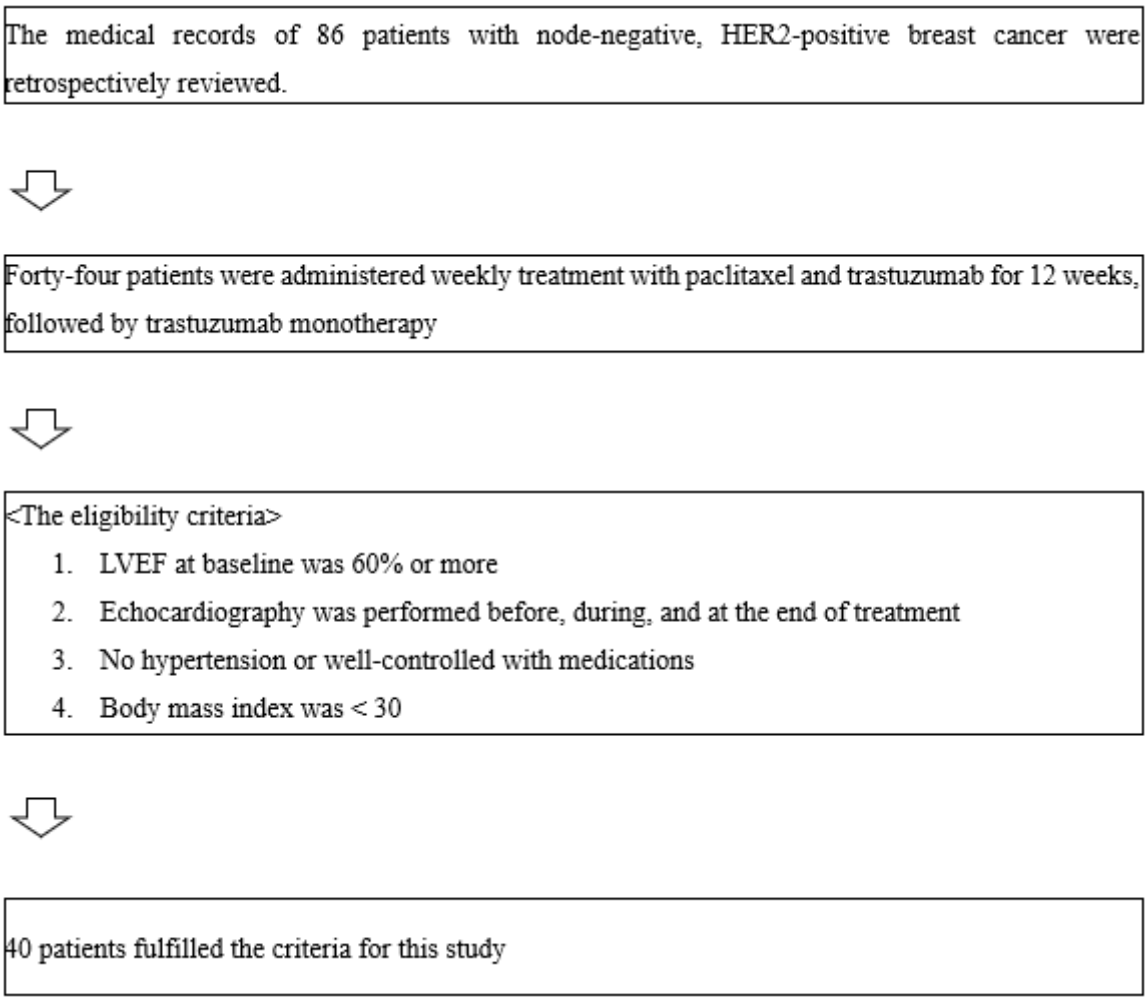
LVEF; left ventricular ejection fraction

**Table 4. Changes in Left Ventricular Ejection Fraction every 3 Months**

| | Baseline (N=21) | 3 months | 6 months | 9 months | 12 months |
|---|---|---|---|---|---|
| LVEF reduction from baseline | | | | | |
| < 10% | | 18 (85%) | 20 (95%) | 20 (95%) | 18 (85%) |
| 10-14% | | 3 (15%) | 1 (5%) | 1 (5%) | 3 (15%) |
| ³ 15% | | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| LVEF | | | | | |
| Median(range) | 68% (61-77) | 67.5% (57-74) | 68% (59-74) | 65% (52-77) | 67.5% (50-74) |

LVEF; left ventricular ejection fraction

# Figures



## Figure 1

Study flow diagrams