Safety survey on infusion reaction and cardiac dysfunction when switching from reference trastuzumab (HERCEPTIN®) to biosimilar trastuzumab (Trastuzumab-NK) in the treatment of HER2-positive breast cancer

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Abstract. The present study is a safety survey of patients with human epidermal growth factor receptor type 2-positive, chemotherapy-naive breast cancer treated with trastuzumab plus paclitaxel at the Saitama Cancer Center (Saitama, Japan) between April 2018 and March 2022. The expression of infusion reaction (IR) and the effect on cardiac function were investigated in patients who switched from reference trastuzumab (HERCEPTIN®) to biosimilar trastuzumab (Trastuzumab-NK) and continued treatment (switching group). The two groups (reference vs. biosimilar trastuzumab) had no significant difference in the expression of IR (P>0.999). In the switching group, IR associated with switching did not occur in all nine eligible patients. Left ventricular ejection fraction (LVEF) was used to assess cardiac function, and no patient in either group experienced a significant decrease in LVEF with treatment, meaning that there was no effect of switching on the decrease in LVEF. These results suggested that switching from reference to biosimilar trastuzumab may not have a significant effect on the frequency of IR expression or the occurrence of cardiac dysfunction.

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Abbreviations: IR, infusion reaction; HER2, human epidermal growth factor receptor type 2; PTX, paclitaxel; LVEF, left ventricular ejection fraction; CTCAE, Common Terminology Criteria for Adverse Events; PER, pertuzumab

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Key words: trastuzumab, biosimilar, infusion reaction, LVEF

Introduction

Recently, the use of biosimilars has been promoted from the perspective of medical cost optimization. Biosimilar trastuzumab, indicated for human epidermal growth factor receptor type 2 (HER2)-positive breast cancer, was launched in 2018. Clinically, biosimilar trastuzumab is used less frequently than HERCEPTIN® (reference trastuzumab), but new research (1-4) now recognizes it as a viable treatment option along with reference trastuzumab. However, although its equivalence/identity has been confirmed, a biosimilar is not exactly the same compound as its biotech predecessor, and thus monitoring for adverse events is important regardless of the history of use of the reference biopharmaceutical. Trastuzumab, for example, requires a particularly careful response to infusion reactions (IR) (5) and monitoring for cardiac dysfunction (6-8). Clinically, it is assumed that there will be cases of i) treatment with reference trastuzumab, ii) treatment with biosimilar trastuzumab, and iii) switching from reference trastuzumab to trastuzumab biosimilar. However, there is an extreme lack of information on IR and cardiac dysfunction, especially in cases of treatment switching.

Among the many regimens, since we assessed IR and cardiac dysfunction, we focused on patients without concomitant use of potentially IR-inducing biopharmaceutical pertuzumab (PER) and without prior treatment with a potentially cardiac-inducing anthracycline regimen. Considering this background, we decided to focus on the patients who selected adjuvant therapy with paclitaxel (PTX) plus trastuzumab as initial therapy.

In this study, we aimed to gain further insight into the safety of biosimilar trastuzumab by evaluating the incidence of IR and changes in cardiac function after switching from reference to biosimilar trastuzumab in the first treatment PTX + trastuzumab regimen.

Materials and methods

Patients and study design. The medical records of patients who were given PTX + trastuzumab regimen receiving their

first treatment as adjuvant therapy at the Saitama Cancer Center (Saitama, Japan) between April 2018 and March 2022 were retrospectively reviewed. The reference trastuzumab was HERCEPTIN® (Chugai Pharmaceutical Co., Ltd.), while the biosimilar trastuzumab was Trastuzumab BS for I.V Infusion 60/150 mg 'NK': Trastuzumab-NK (Nippon Kayaku Co., Ltd.) was used. We switched from reference trastuzumab to trastuzumab-NK on August 19, 2020 (Fig. 1). Patients were divided into three groups: a reference trastuzumab-only group (reference trastuzumab group), a group that switched from reference trastuzumab to trastuzumab-NK and continued treatment (switching group), and a trastuzumab-NK-only group (trastuzumab-NK group). Eligible patients were excluded if they had previously received chemotherapy or were receiving PTX and anticancer drugs other than trastuzumab. Patients were not excluded based on the presence or absence of ER/PR, stage classification, or radiation therapy.

Treatment. The PTX + trastuzumab regimen consisted of trastuzumab at 8 mg/kg in 90 min for the first dose, 6 mg/kg in 30 min for the second and subsequent doses, PTX at 80 mg/m^2 for 1 h, trastuzumab administered triweekly, and PTX administered weekly. Dexamethasone 9.9 mg, d-Chlorpheniramine Maleate 5 mg, and famotidine 20 mg were administered as premedication. This sequence of administration of drugs is standard in our hospital.

Survey items. Baseline patient characteristics were recorded, such as age, weight, BMI, HER2 score, left ventricular ejection fraction (LVEF), trastuzumab dose per body weight, dosing time, and IR expression status. For IR, the presence of Grade 1 or higher was evaluated based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Cardiac function was assessed based on the Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (JCS 2017/JHFS 2017), and changes were evaluated based on LVEF test results before and at any point after treatment initiation.

Statistical analysis. Statistical analysis was performed using JMP 14 (SAS Institute, Cary, NC, USA). IR expression in the reference trastuzumab group and the trastuzumab-NK group were compared using the Fisher's exact test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Baseline clinical characteristics. There were 37 patients, including 21 in the reference trastuzumab group, 9 in the switching group, and 7 in the trastuzumab-NK group (Table I). There were no changes in premedication.

IR expression. IR of Grade 1 or higher developed in 5 patients (24%) in the reference trastuzumab group, 3 patients (33%) in the switching group, and 2 patients (29%) in the trastuzumab-NK group (Table II). Notably 3 patients in the switching group developed IR at the first dose of reference trastuzumab. There was no significant difference in IR expression between the reference trastuzumab group and trastuzumab-NK group ($P>0.999$). IR was characterized by the presence of fever, chills, erythema, skin rash, pruritus, and flushing. The time of onset was the day of or the day after the start of treatment in 7 out of 9 patients (Table III).

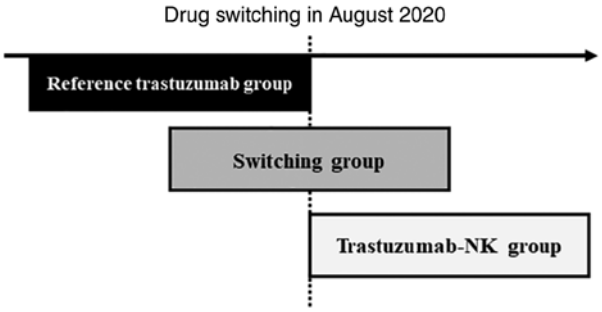

Figure 1. Study design. The study was from April 1, 2018, to March 31, 2022. The switch date from reference trastuzumab to Trastuzumab-NK was in August, 2020.

Cardiac function assessment. All patients had an LVEF of at least 60% before the start of treatment and no patients had heart failure (Table I). LVEF was measured after the start of treatment in 20 patients (reference trastuzumab group: 12 patients, switching group: 4 patients, trastuzumab-NK group: 4 patients), and no patient discontinued treatment due to a decrease in LVEF caused by treatment (Fig. 2).

Discussion

Trastuzumab is an anti-HER2 humanized monoclonal antibody biopharmaceutical indicated for the treatment of HER2-positive breast cancer and advanced or recurrent unresectable gastric cancer (9). Since breast cancers with confirmed HER2 overexpression account for approximately 20% of all breast cancer patients (10), it is extremely important to accumulate safety information on trastuzumab biosimilars, a key drug in the treatment of breast cancer. Although this is a different trastuzumab biosimilar from the product used in the present study, the safety information associated with this biosimilar is reported in a study (11).

The result of this study showed no significant difference in the frequency of IR expression between reference trastuzumab and trastuzumab-NK (Table II), which is similar to a previous study (12,13). Based on these results, we confirmed IR in the switching group and found that IR did not occur with switching, but rather only with reference trastuzumab administration. The authors initially expected IR to occur when switching from reference trastuzumab to trastuzumab-NK and continuing treatment (i.e., at the first dose of trastuzumab-NK), although IR did not occur during the switch in all 9 patients (Table II). We believe there are two reasons for this. First is the difference between the initial reference trastuzumab dose and the trastuzumab-NK dose at the time of switching. One of the risk factors for IR with trastuzumab is a high dose per body weight (14). Especially for the loading dose, an 8 mg/kg triweekly dose is reported to have a higher incidence of IR than a 4 mg/kg weekly dose and 6 mg/kg biweekly dose (14). The initial dose of trastuzumab in the reference trastuzumab group and the biosimilar group was 8 mg/kg, whereas the dose of trastuzumab-NK in the switching group was 6 mg/kg. This

Table I. Baseline patient characteristics.

Characteristic	Reference trastuzumab group (n=21)	Switching group (n=9)	Trastuzumab-NK group (n=7)
Age, years			
Mean (SD)	62.1 (10.6)	63.7 (10.9)	58.7 (13.4)
Median (range)	65.0 (43-76)	66.0 (47-79)	62.0 (38-73)
Weight, kg			
Mean (SD)	56.2 (9.2)	52.5 (8.7)	56.9 (7.9)
Median (range)	54.6 (45.5-79.1)	48.9 (41.8-63.0)	54.0 (48.8-69.0)
BMI, kg/m^2			
Mean (SD)	23.0 (3.78)	21.5 (2.88)	23.6 (3.24)
Median (range)	22.1 (17.5-30.6)	22.5 (17.6-25.5)	22.6 (20.0-28.2)
HER2 score			
+2	4	0	0
+3	17	9	7
Stage			
IA	13	8	7
IIA	8	0	0
IIIB	0	1	0
+Radiation therapy	6	2	0
LVEF result, %			
Mean (SD)	68.3 (3.6)	67.7 (3.9)	66.0 (3.3)
Median (range)	67.5 (63.0-79.0)	69.0 (60.0-72.0)	66.0 (62.0-71.0)

Data are presented as mean (SD), median (range) or n. Parameters of age, weight, BMI and LVEF at the start of trastuzumab treatments. LVEF, left ventricular ejection fraction.

Table II. Incidence of infusion reactions.

Expression of infusion reaction	Reference trastuzumab group (n=21)[a]	Switching group (n=9)	Trastuzumab-NK group (n=7)[a]	P-value[a]
Yes	5 (24%)	3 (33%)	2 (29%)	>0.999
No	16 (76%)	6 (67%)	5 (71%)	

[a]Fisher's exact test.

is a lower dose than in the other two groups, which may have been one reason why IR was not induced. Second, the dose of trastuzumab-NK in the switching group corresponds to a maintenance dose. In general, it is known that the frequency of IR expression is not increased with maintenance dosing of trastuzumab compared to the initial dose, even at higher maintenance doses (e.g., 6 mg/kg) during triweekly and shorter durations such as 30 min (15,16). Due to these considerations, IR did not occur even after 30 min of administration. On the other hand, since the frequency of IR expression in trastuzumab-NK is about 11%, IR may still occur during the switch (12). However, the results of this study suggest that IR may be less likely to occur at the time of switching, even at the maintenance dose (e.g., 6 mg/kg). In addition, this study found that IR was less likely to occur even if the maintenance dosing time (30 min) was used, providing meaningful information on dosing conditions when switching. Although dosage and administration at the time of switching should be carefully considered, the results of this study suggest that switching to trastuzumab-NK in patients who have previously received reference trastuzumab may be less likely to cause IR.

Cardiac function was then assessed using LVEF based on the JCS 2017/JHFS 2017 guidelines. One patient in the reference trastuzumab group exhibited a decrease in LVEF of more than 10 points before and after treatment, but LVEF was still within normal limits, and continued treatment after the decrease in LVEF. The normal range of LVEF in Japanese women is 64±5% (17), and heart failure below 50% is often considered a criterion for discontinuation of treatment. A decrease in LVEF can be influenced by multiple factors other

Table III. Details of infusion reaction.

Group	Patient number	Adverse events	Drugs	Days from start of treatment until adverse even
Reference trastuzumab Group	1	Pruritic	Reference trastuzumab	2
	2	Chill	Reference trastuzumab	1
	3	Fever	Reference trastuzumab	2
	4	Pruritic	Reference trastuzumab	1
	5	Eczema	Reference trastuzumab	141
Switching group	6	Rash	Reference trastuzumab	294
	7	Eczema	Reference trastuzumab	1
	8	Stomachache	Reference trastuzumab	1
Trastuzumab-NK group	9	Flushed face	Trastuzumab-NK	2
	10	Fever	Trastuzumab-NK	1

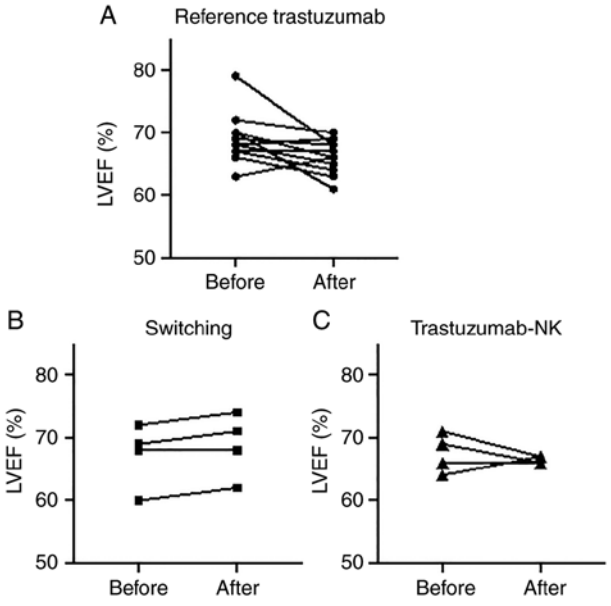

Figure 2. Changes in LVEF before and after trastuzumab treatment in the (A) reference trastuzumab group, (B) switching group and (C) trastuzumab-NK group. LVEF, left ventricular ejection fraction.

than trastuzumab, including a history of cardiac disease, age, known risk factors for trastuzumab-related cardiac dysfunction (e.g., history of anthracycline use), and low baseline LVEF (6,18). We believe that the inclusion of patients on the first-line PTX + trastuzumab regimen and the assessment of cardiac function before the initiation of therapy in this study allowed us to exclude the influence of these risk factors for cardiac dysfunction and to evaluate the impact of trastuzumab. Considering that none of the patients in any group had a decrease in LVEF below 50%, the results suggest that switching from reference trastuzumab to trastuzumab-NK and continuing treatment is not significantly different than in the other two groups. Currently, periodic post-treatment LVEF testing is not performed on all the patients at our hospital because it is not a required part of the regimen. However, a certain percentage of patients may experience a decline in cardiac function during trastuzumab therapy, and thus monitoring is still necessary.

This study has some limitations. First, this is a retrospective observational study with a small sample size in a single center. Furthermore, the effect of PTX on cardiotoxicity cannot be eliminated. PTX has a small number of cardiotoxic effects; however, compared to the cardiotoxicity of trastuzumab, these effects are negligible and unlikely to be of concern in the clinical settings (19). Therefore, in this study, which aims to evaluate the safety of switching from reference trastuzumab to biosimilars, the results will not be affected by PTX because the effect of PTX on cardiac function is comparable in all the three groups of patients without prior treatment. However, we believe that one of the strengths of this study is that we were able to secure patients without concomitant use of the biopharmaceutical PER, as well as without prior treatment with an anthracycline regimen, which can induce IR and cardiac dysfunction, respectively. In particular, PER is often used in combination with trastuzumab, and in the case of combination regimens, it is difficult to identify which IR is caused by which drug. In addition, prior treatment with an anthracycline is associated with an increased risk of cardiac dysfunction (6-8), and the effect of the prior treatment cannot be excluded, since the effect of trastuzumab on cardiac function cannot be adequately assessed. The fact that we were able to evaluate the impact of switching to trastuzumab under these conditions is significant, although further studies including a larger sample size is needed to validate our findings.

In summary, this study suggests that switching from reference trastuzumab to trastuzumab biosimilar may not have a significant effect on the frequency of IR expression or the occurrence of cardiac dysfunction.

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Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Authors' contributions

TA conceived the study. TA, AS and DO designed the experiments. TA, AS, DO and KM analyzed the data. TA and AS wrote the paper. All authors confirm the authenticity of all the raw data, and provided intellectual input, and are responsible for the contents of the paper, including the data, analysis, and interpretation. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Saitama Cancer Center (approval no. 1296). As this was a retrospective observational study, consent was not obtained from individual patients. An information disclosure document about this study was created and published for the study patient, guaranteeing the opportunity for the study patient to refuse.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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