Safety Evaluation of Initial CT-P6 Administration for 30 min during the Switch from Reference Trastuzumab in Maintenance Infusion: A Multicenter Observational Study

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INTRODUCTION

Trastuzumab is a humanized, recombinant monoclonal antibody targeting the extracellular domain of the human epidermal growth factor receptor-2 (HER 2) protein, resulting in the inhibition of HER 2-mediated signaling and related tumor proliferation. Moreover, it induces anticancer effects via antibody-dependent cellular cytotoxicity. HER 2 overexpression has been confirmed in up to 30% of breast cancer cases and 20% of gastric cancer cases. It has become a mainstay of treatment in nearly all stages of HER 2-overexpressed breast cancer and has been suggested to be effective against HER 2-positive gastric cancer.

Biosimilars are defined as biological medicinal products that contain a version of the active substance of an already authorized original biological medicinal product (called the reference product). The use of biosimilars helps reduce treatment expense, as biological medicines are costly.

CT-P6 is a biosimilar to trastuzumab, with clinical data showing it to be bioequivalent to the reference drug. It has been approved for all administration methods as well as the reference in Japan in 2019.

Infusion-related reaction (IRR), which is also described as a hypersensitivity reaction, is one of the most frequent adverse effects caused by infused monoclonal antibodies. The mechanism underlying IRR associated with these antibodies is not fully understood, although it has been speculated that such antibodies may lead to cytokine release through interactions with their molecular targets in tumors or other circulating cells, leading to the induction of many symptoms such as fever, chills, rigors, hypotension, and dyspnea. Previous studies have suggested that IRR occurs in up to 40% of patients receiving trastuzumab, most frequently during or immediately after the first infusion. However, it is less common with subsequent maintenance infusions. It has also been reported that obesity and advanced disease stages are risk factors, whereas premedication including corticosteroids, antihistamines, and antipyretics is a preventive factor for trastuzumab-induced IRRs. In addition to IRRs, cardiac disorders, skin toxicity, or diarrhea are also uncommonly observed in trastuzumab-administered patients.

It is recommended that trastuzumab be administered at doses of 8 mg/kg over 90 min in the first loading infusion and 6 mg/kg for 30–90 min in subsequent maintenance infusions for IRR prevention. In general, a 30-min infusion is preferable in terms of bed control and patient charge in the maintenance phase. In practice, when a biosimilar is adopted in an institution, patients receiving treatment are switched from the reference to biosimilar in the middle of the treatment, as it is suitable to adopt either drug for adequate inventory control and risk management. A study reported that in four patients, a change from reference trastuzumab to CT-P6 during the maintenance period resulted in no IRRs or cardiac events, although the administration method was not detailed. Against this background, the information on the safety regarding initial administration time of CT-P6 during the switch from reference trastuzumab in maintenance infusion is needed. Here, we examined safety, especially focusing on IRR, in the adminis-
oration of CT-P6 at a dose of 6mg/kg for 30min as the first injection after the switch from reference trastuzumab during maintenance infusion.

MATERIALS AND METHODS

Study Design, Setting, and Patients In this retrospective, multicenter observational study, we enrolled 141 patients with breast or gastric cancer who received a switch from tri-weekly reference trastuzumab (6–8mg/kg) to CT-P6 in maintenance infusions from November 2019 to March 2020. All patients had sufficient renal and liver function and a performance status (PS) of 0 to 1. Patients who had experienced IRRs during the reference trastuzumab treatment were excluded. One patient was excluded owing to IRR following the reference trastuzumab treatment; finally, all remaining patients were enrolled in this study. The study was approved by the institutional review board of each participating institution (in case of Hokkaido University Hospital Approval No. 019-0015) and was conducted in accordance with the Declaration of Helsinki and STROBE statement. In view of the retrospective nature of the study, informed consent from the subjects was not mandated.

Treatment Methods CT-P6 (6mg/kg) was dissolved in saline (250mL) and administered intravenously for 30min. Premedication to prevent nausea and vomiting or hypersensitivity was administered prior to the co-administration of CT-P6 with an infusion of a cytotoxic agent (paclitaxel, docetaxel, gemcitabine, vinorelbine, eribulin, and oxaliplatin). The premedication drugs included 5-hydroxytryptamine 3 (5HT3) antagonists, dexamethasone, and histamine types 1 and 2 receptor antagonists, and they were dosed according to the current guideline and package insert of paclitaxel17,18) When CT-P6 was co-administered with pertuzumab or administered alone, premedication was not provided. In case of IRRs, supportive care medicines were administered in accordance with each institution’s guidelines.

Survey of Adverse Effects All required information was obtained from the patients’ medical records. The incidence of adverse effects during the first cycle of CT-P6 administration was evaluated. The severity of adverse effects was graded according to the Common Terminology Criteria for Adverse Events version 5.0.

The primary endpoint in this study was defined as the incidence of IRR. The secondary endpoint was the incidence of other adverse effects such as diarrhea and skin toxicity.

Statistical Analysis The differences in the adverse effects before and after the switch were assessed using the McNemar test. All analyses were conducted using the JMP version 14.0 statistical software (SAS Institute Japan, Tokyo, Japan). A p value <0.05 indicated a statistically significant difference.

RESULTS

Patient Characteristics The baseline patient characteristics are shown in Table 1. All patients had PS 0–1; 95.7% patients were diagnosed with breast cancer, and approximately 44% were in the advanced stage. The treatment at the switch included CT-P6 alone (17.9%) or with cytotoxic agents (23.6%), anti-hormonal drugs (25.7%), and pertuzumab (62.9%). The median administration time of trastuzumab at the switch to CT-P6 was 13 administrations (range, 2–140). Patients with liver dysfunction (grade 1 or higher aspartate transaminase, alanine aminotransferase, and total bilirubin elevation) accounted for 7.9% and those with renal dysfunction (grade 1 or higher serum creatinine elevation) accounted for 3.6%. Approximately 20% of the patients were administered

| Table 1. Patient Characteristics | Number (n = 140) |
|---------------------------------|-----------------|
| Sex (male/female)               | 6/134           |
| Age (years, median, range)      | 61 (33–92)      |
| Performance status              | 0–1 140         |
| Cancer types and staging        |                |
| Breast                          | 134             |
| I–III                           | 78              |
| IV/Recurrence                   | 55              |
| Unknown                         | 1               |
| Gastric                         | 6               |
| IV                             | 6               |
| Treatment setting               |                |
| Adjuvant                        | 71              |
| Neoadjuvant                     | 7               |
| Metastatic/Recurrence           | 62              |
| Prior treatment                 |                |
| 0                               | 51              |
| 1                               | 51              |
| 2                               | 25              |
| 3 or more                       | 13              |
| Treatment regimen               |                |
| CT-P6 + PER                     | 45              |
| CT-P6 alone                     | 25              |
| CT-P6 + PER + LET               | 11              |
| CT-P6 + LET                     | 10              |
| CT-P6 + PER + DOC               | 8               |
| CT-P6 + PER + ERI               | 6               |
| CT-P6 + TAM                     | 4               |
| CT-P6 + PER + TAM               | 4               |
| CT-P6 + PER + PTX               | 3               |
| CT-P6 + PER + VNR               | 3               |
| CT-P6 + CAPE                    | 3               |
| CT-P6 + PTX, CT-P6 + GEM, CT-P6 + DOC, CT-P6 + PER + TAM + LHRHa | 2 |
| Others                          | 10              |
| Median administration times of trastuzumab during the switch to CT-P6 | 13 (2–140) |
| Body weight (kg) (median, range)| 51.8 (37.6–89.2) |
| BMI (kg/m2) (median, range)     | 21.8 (15.5–32.6) |
| Liver dysfunction               | 11              |
| Renal dysfunction               | 5               |
| Regular administration of       |                |
| NSAIDs                          | 8               |
| Antihistamines                  | 20              |
| Corticosteroids                 | 1               |
| Premedication                   | 29              |

Liver dysfunction: grade 1 or higher aspartate transaminase, alanine aminotransferase, and total bilirubin elevation. Renal dysfunction: grade 1 or higher serum creatinine elevation. PER: pertuzumab; LET: letrozole; DOC: docetaxel; ERI: eribulin; TAM: tamoxifen; PTX: paclitaxel; VNR: vinorelbine; CAPE: capcitabine; GEM: gemcitabine; LHRHa: Luteinizing Hormone-Releasing Hormone analogue; BMI: body mass index; NSAIDs: non-steroidal anti-inflammatory drugs.
ever, such reactions have been reported at a lower frequency in the non-HER 2 blockade group. Moreover, Vogel et al. revealed that the rate of fatal adverse events in the reference trastuzumab group was not statistically different from that in a control group. The adverse effects commonly caused by trastuzumab use are IRRs, cardiac toxicity, diarrhea, and skin toxicity. However, a meta-analysis showed that the incidence of IRRs, cardiac toxicity, diarrhea, and skin toxicity was 6.4%, 7.1%, 5.0%, and 6.4%, respectively. Moreover, a new incidence of diarrhea was reported in one patient following the switch at her thirteenth trastuzumab administration. The frequency of skin toxicity in the reference trastuzumab and CT-P6 groups was 6.4% and 6.4%, respectively. CT-P6 treatment did not result in a new incidence of skin toxicity. These toxicities were evaluated to be of grade 1. The incidence of these toxicities was 12.9 and 11.4% in the reference trastuzumab and CT-P6 groups, respectively, without significant differences.

**DISCUSSION**

Drug development is associated with high costs, and the increase in the number of cancer patients and the prices of new drugs place an enormous burden on the public medical insurance systems. The adoption of generic medicines or biosimilars into routine practice is one of the most effective approaches to economize medical expenses. In clinical practice, it is essential to ensure a simple and safe switch from the original drugs to alternatives/generics. The adverse effects commonly caused by trastuzumab use are IRRs, cardiac toxicity, diarrhea, and skin toxicity. However, a meta-analysis revealed that the rate of fatal adverse events in the reference trastuzumab group was not statistically different from that in a non-HER 2 blockade group. Moreover, Vogel et al. reported that the infusion duration and/or peak serum concentrations of the monoclonal antibody affect the incidence of IRRs. However, such reactions have been reported at a lower frequency following subsequent maintenance infusion. It is unclear how to administer biosimilars when switching from the reference medicines, especially the duration of infusion in case of trastuzumab. In addition, the number of patients in outpatient chemotherapy centers is increasing; thus, it is desirable to reduce the treatment time per person and achieve efficient bed control. For these reasons, we decided to observe the effect of initial CT-P6 administration for 30 min during the switch from the reference trastuzumab in maintenance infusion and then evaluated its safety, particularly focusing on IRRs. This is the first report to evaluate the safety of the switch method from a reference drug to biosimilar during chemotherapeutic treatment.

As a result, IRR was noted in one patient (0.7%; n = 140) following CT-P6 administration. The patient experienced a grade 3 IRR following the first CT-P6 administration, which corresponded to the sixth trastuzumab administration. Moreover, the patient did not present any symptoms without premedication or extension of administration time following second and subsequent CT-P6 administrations. Ring et al. reported that trastuzumab-induced IRR incidence was 3.5% and that of grade 3 IRR was 1.2% during maintenance infusion. Thompson et al. reported this incidence to be 1.5% with no severe symptoms, consistent with our study findings. Therefore, it is acceptable to use this administration method during the switch from the reference trastuzumab in maintenance infusion. However, it is unknown whether IRR occurred due to the switch, as the patient was in an adjuvant setting and her BMI was 23.4 kg/m², which did not correspond to the suggested risk factors. Therefore, we propose that all patients should be carefully monitored during the first CT-P6 administration. In addition, CT-P6 should be administered as 8-mg/kg and 90-min infusions when the injection interval is more than 28 d.

It has been reported that obesity and advanced disease stage are the risk factors for trastuzumab-induced IRR. In contrast, trastuzumab is frequently co-administered with cytotoxic drugs, especially with taxanes. Moreover, corticosteroids and/or antihistamines are administered as anti-emetic or anti-hypersensitivity premedication in such cases. It has been reported that they are effective in trastuzumab-induced IRR prevention. Therefore, it is possible to speculate that the incidence of IRR is lower when it is co-administered with other cytotoxic medicines; however, the currently available data to justify the use of premedication in patients receiving trastuzumab alone are still insufficient. Unnecessary premedication can induce adverse effects, such as insomnia, increased blood sugar following corticosteroid use, and sedation following antihistamine use, which could affect patient QOL and treatment efficiency. Further studies are needed to elucidate the necessity of premedication and its administration method, especially in trastuzumab monotherapy.

We also evaluated the incidence of early adverse effects caused by the switch. Diarrhea and skin toxicity incidences were similar between the reference trastuzumab and CT-P6 treatments, although one patient experienced a new incidence of diarrhea following the switch. These results also suggest that the administration method does not affect the profile of early adverse effects.

There are some limitations to our study on the safety of the alternative method. First, this study was retrospectively evaluated without a control group. Second, we evaluated only

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**Table 2. Incidence of IRRs, Diarrhea, and Skin Toxicity Following Trastuzumab Treatments**

| Toxicity        | Reference trastuzumab | CT-P6 | p-Value | New incidence of the toxicity |
|-----------------|-----------------------|-------|---------|-----------------------------|
| IRR             | 0%                    | 0.7%  | —       | 0.7%                        |
| Diarrhea        | 7.1%                  | 6.4%  | 0.32    | 0.7%                        |
| Skin toxicity   | 6.4%                  | 5.0%  | 0.16    | 0%                          |
| Total           | 12.9%                 | 11.4% | 0.56    | 1.4%                        |

A new incidence of toxicity was defined as an adverse effect that was first observed after the initial CT-P6 administration. IRR; infusion-related reaction.
early adverse effects such as IRRs, diarrhea, and skin toxicity. It is necessary to assess long-term adverse effects such as pulmonary and cardiac toxicities. Third, it is also important to evaluate the effect of changes in anti-tumor efficacy, in addition to safety.

In conclusion, we demonstrated that an initial CT-P6 administration at a dose of 6 mg/kg for 30 min at the time of the switch from the reference trastuzumab during maintenance infusion is an acceptable administration method. These outcomes may be useful for the administration of other biosimilars.

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