Safety study on switching from intravenous to fixed-dose subcutaneous formulation of pertuzumab and trastuzumab

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Abstract. To the best of our knowledge, there have been no reports from clinical settings regarding safety information on a fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection (PHESGO®) when switched from the intravenous formulation of pertuzumab and trastuzumab in Japan. The lack of information on switching from the intravenous formulation to PHESGO in clinical settings may contribute to hesitation in making the switch. The present study analyzed the safety of 51 patients with breast or colorectal cancer treated with PHESGO. The focus was on evaluating infusion reactions (IRs), and skin and subcutaneous tissue disorders. The study included patients who received PHESGO at the Saitama Cancer Center between January 1, 2024 and March 31, 2024. The group using it as initial induction therapy was compared with the group that switched from the intravenous formulation. IRs were assessed using the Common Terminology Criteria for Adverse Events version 5.0. Patients with grade 1 or higher symptoms on the day of administration or the following day were considered to have IRs. IRs occurred in 4 of 16 patients (25%) in the initial induction group and none in the switching group (P=0.0073). It was suggested that IRs with PHESGO were more likely to occur at the time of first administration, similar to existing intravenous formulations. The study also examined patients who switched to an intravenous formulation after receiving PHESGO; skin and subcutaneous tissue disorders occurred in five patients, three of whom continued on a slower dose rate, and two of whom discontinued PHESGO and switched to pertuzumab and trastuzumab for intravenous infusion. With PHESGO, IRs are also more likely to occur the first time, and when skin and subcutaneous tissue disorders occur, there is a tendency to switch formulations in groups with a history of intravenous formulation use.

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Abbreviations: IRs, infusion reactions; HER2, human epidermal growth factor receptor type 2; CTCAE, Common Terminology Criteria for Adverse Events

Key words: fixed-dose combination, infusion reaction, switching, subcutaneous injection, injection site reaction

Introduction

PHESGO®, a fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection (1-5), is used in Japan for treating human epidermal growth factor receptor type 2 (HER2)-positive breast cancer and advanced or recurrent unresectable colorectal cancer that has progressed after chemotherapy (6). As of March 31, 2023, it has been approved for the treatment of early-stage and metastatic breast cancer in more than 100 countries and regions worldwide, including six countries in Europe and the United States (the United States, the United Kingdom, Germany, France, Canada, and Australia). Previously, these drugs were only available via intravenous infusion. However, the introduction of PHESGO has made subcutaneous injection an option. PHESGO differs from conventional intravenous formulations in several ways. First, it changes the route of administration. Second, it offers a fixed-dose formulation, irrespective of body weight: 15 ml (1,200 mg pertuzumab, 600 mg trastuzumab) for the initial dose and 10 ml (600 mg pertuzumab, 600 mg trastuzumab) for maintenance and subsequent doses. This contrasts with conventional intravenous trastuzumab formulations, which have a fixed-dose per unit of body weight. Third, PHESGO significantly reduces administration time. While intravenous pertuzumab and trastuzumab typically take 60 and 90 min respectively, PHESGO is administered in 8 min for the initial dose and 5 min for subsequent doses. Shorter dosing times at the same dose can increase the risk of infusion reactions (IRs) (7). However, subcutaneous injection is absorbed more slowly than intravenous injection, potentially reducing IR incidence. Despite reports of IRs with trastuzumab (8-11), and overseas use of PHESGO (12), there are no reports from actual clinical settings in Japan, making safety information scarce. PHESGO appears to have many advantages over existing intravenous formulations, such as reduced administration

time and no need for weight-based dose adjustment. However, patients may switch back to the intravenous formulation after switching to PHESGO. Therefore, investigating IR information on PHESGO and the safety situation associated with switching could help select a formulation that meets patient requirements. In this study, we investigated safety information, particularly IR information, and patient preference regarding the drug when side effects occurred in patients with HER2-positive breast and colorectal cancer. In addition, the clinical trials aimed to accumulate safety data for patients with breast cancer, as information for patients with colorectal cancer is extremely limited.

Patients and methods

Patients and study design. The medical records of colorectal or breast cancer patients who received PHESGO at the Saitama Cancer Center (Saitama, Japan) between January and March 2024. All patients with colorectal or breast cancer who received PHESGO were included in the study, with no exclusion criteria. This study was approved by the institutional review board of Saitama Cancer Center (approval no. 1816; approved May 8, 2024). It was confirmed at the time of sample collection that comprehensive consent had been obtained. We examined the IRs in the group that switched from pertuzumab + trastuzumab intravenous formulations to PHESGO and the group that used PHESGO from the start (Fig. 1).

Treatment. Patients treated with PHESGO alone or in combination with docetaxel (DTX) or paclitaxel (PTX).

Survey items. Baseline patient characteristics, such as the number of males and females, median age, and age range, sex, weight, BMI, HER2 score, combination regimen, cancer stages, dosing time, injection site reactions, and IR expression status, were recorded. IRs were defined as the occurrence of symptoms such as fever, chills, hypersensitivity, psychogenic reactions, pruritus, urticaria, diarrhea, systemic disorders, or immune system disorders on the day of administration or the day after. IR presence and symptom details were extracted from electronic medical records. IRs of Grade 1 or higher were evaluated based on the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE. Ver. 5.0).

The study also investigated whether PHESGO was used as initial induction or as a switch from the intravenous formulation, to determine the difference in the frequency of IRs between these two groups. Additionally, the study examined the reasons for patients switching from PHESGO to the intravenous formulation.

Statistical analysis. Statistical analysis was performed using JMP17 Pro (SAS Institute, Cary, NC, USA). The Fisher's exact test was used to compare patient characteristics and the expression of IR in the initial induction group and the switching group. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Baseline clinical characteristics. The study encompassed 51 patients (2 males and 49 females; median age 56 years, range 33-84 years), with 16 in the initial induction group and 35 in the switching group (Table I).

IR expression. IRs of Grade 1 or higher were observed in four patients (25%) in the initial induction group, while no patients (0%) in the switching group experienced IRs (Table II). This significant difference in IR occurrence between the two groups was statistically significant (P=0.0073). IRs were characterized by symptoms such as fever, chill, and diarrhea, which manifested on the day of treatment or the following day. All patients who developed IRs were in the initial induction group, including patients with colorectal cancer (Table III). Five of the 51 patients experienced skin and subcutaneous tissue disorders, all of whom were in the switching group and had breast cancer. Three of these patients continued on a slower dose rate, while two switched from PHESGO to the intravenous formulation of pertuzumab and trastuzumab (Table IV). All patients experienced pain at the administration site.

Discussion

Pertuzumab and trastuzumab, when administered as intravenous formulations, are known to cause IR, especially with the first dose (2,11). This study reveals that IRs occurred exclusively in the initial induction group (Table II), suggesting that the risk of IRs is also elevated with subcutaneous formulations upon first administration. Interestingly, all four cases with IRs involved patients with colorectal cancer. This suggests that the frequency of IRs might vary based on the type of cancer. However, given that all cases were first inductions, it is plausible that the occurrence of IRs is influenced more by whether the patient was a first induction rather than the type of cancer. Regardless, due to the small sample size, further accumulation of cases is necessary for a more comprehensive understanding. Considering that none of the cases in the switching group developed IR, we believe the most significant factor is whether it is the first induction or not. Due to small sample size limitations, this study did not examine cancer types, and this is an issue for future research direction.

One factor contributing to IRs with intravenous trastuzumab is the high dose per unit time. Specifically, the biweekly dose of 4 mg/kg and the triweekly dose of 6 mg/kg are more likely to cause IRs than the weekly dose of 2 mg/kg (7). IRs are also more likely to occur when the dose per unit time is higher for 30-min doses than for 90-min doses, suggesting that the first dose should be administered over a longer duration. This study found that IRs occurred in 4 (25%) patients treated with PHESGO (Table II), a rate comparable to that reported for intravenous formulations of pertuzumab and trastuzumab (9,11,13). The dose of trastuzumab in PHESGO is 600 mg, equivalent to a body weight of 75 kg, compared to the loading dose of 8 mg/kg for the intravenous formulation. Similarly, the dose of pertuzumab in PHESGO is higher than in the intravenous formulation PERJETA® (loading dose: 840 mg, maintenance dose: 420 mg). Despite these higher doses and the simultaneous administration of two drugs in PHESGO, the frequency of IRs is similar to that of the intravenous formulation. This suggests that IRs may be less likely to occur with PHESGO than with two drugs in the intravenous formulation. This phenomenon is thought to be due to the nature of the subcutaneous route

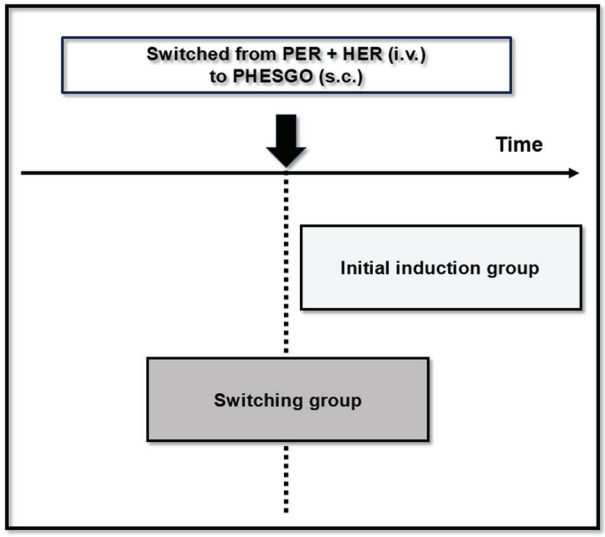

Figure 1. Study design. The switching group switched from pertuzumab + trastuzumab to PHESGO® and the initial induction group received PHESGO as initial therapy.

of administration. Absorption from the subcutis into the body occurs in a rate-limiting step, suppressing a rapid rise in blood concentration, even if the drug is administered at a faster rate or in a larger volume. However, 2 out of 51 patients switched to the intravenous formulation after receiving PHESGO. The main reason for this switch was site reactions (Table IV), suggesting that the potential disadvantages of skin and subcutaneous tissue damage from injections might outweigh the benefits of shorter administration times and reduced risk of IRs. Pain perception varies among individuals and can be influenced by the administration technique, leading to several formulation switches due to injection site reactions. Some patients, who have been on maintenance therapy for several years, might have switched to PHESGO once and then returned to the intravenous formulation due to familiarity with the previous method of administration. In this study, all patients who switched from PHESGO to the intravenous formulation had previously been treated with the intravenous formulation. Initially, the study focused solely on patients who were treated with PHESGO. However, it is likely that a small subset of these patients were given the option to switch to PHESGO but chose to continue with their conventional treatment. This is not necessarily a drawback; instead, it underscores the importance of having a variety of treatment options. The factors that patients' consider when choosing a treatment can vary widely, including the time and location of administration, the method of administration, the cost, and their expectations or concerns about new medications. Patients' satisfaction plays a crucial role in the continuation of treatment. For instance, shorter administration times can lead to reduced hospital stays, potentially enhancing patient satisfaction (14,15). In a previous study of a crossover trial comparing subcutaneous and intravenous formulations of pertuzumab + trastuzumab, the subcutaneous formulation was overwhelmingly preferred by a larger percentage of patients (4). The main reason for this preference was the shorter time required at the clinic. However, a higher percentage of patients reported preferring the intravenous formulation because of a lower level of injection site pain and a more comfortable experience during administration. In this study, two patients switched from subcutaneous to intravenous formulations (Table IV), suggesting that, as in previous reports, pain during administration is a factor in the choice of formulation. The method of administration is also a key factor in treatment adherence, as it empowers patients to participate in their own treatment decisions. The introduction of PHESGO is significant in this context. It is crucial that

Table I. Patients' baseline characteristics.

Characteristic	Initial induction group (n=16)	Switching group (n=35)
Age, years		
Mean (SD)	59.8 (12.3)	57.1 (12.1)
Median (range)	56.0 (43-84)	58.0 (33-77)
Weight, kg		
Mean (SD)	59.6 (11.3)	54.6 (10.1)
Median (range)	56.3 (46.0-87.0)	51.1 (35.3-78.6)
BMI		
Mean (SD)	23.9 (3.6)	22.6 (3.5)
Median (range)	23.7 (19.1-30.6)	22.5 (15.4-30.9)
Cancer type		
Breast cancer	12	35
Stage		
IA	0	4
IB	1	0
IIA	4	6
IIB	5	3
IIIA	1	4
IV	1	18
Colorectal cancer	4	0
Stage		
IV	4	0
HER2 score		
2+	6	3
3+	10	32
Combination regimen		
DTX	11	6
PTX	0	1
None	5	28

SD, standard deviation; BMI, body mass index; HER2, human epidermal growth factor receptor 2; DTX, docetaxel; PTX, paclitaxel.

Table II. Incidence of infusion reactions.

Infusion reaction	Initial induction group (n=16)	Switching group (n=35)	P-value
Yes	4 (25%)	0 (0%)	0.0073
No	12 (75%)	35 (100%)	

Table III. Detailed information.

Patient no.	Group	Cancer type	Combination regimen	Adverse events	Grade
21	Initial induction group	Colorectal cancer	None	Fever, Chill	II
22	Initial induction group	Colorectal cancer	None	Fever	I
24	Initial induction group	Colorectal cancer	None	Fever	I
50	Initial induction group	Colorectal cancer	None	Fever, Diarrhea	II

Table IV. Side effects excluding infusion reactions.

Patient no.	Group	Cancer type	Side effect	Coping strategy
3	Switching group	Breast cancer	Injection site reaction	Decreased dosing rate
8	Switching group	Breast cancer	Injection site reaction	Decreased dosing rate
17	Switching group	Breast cancer	Injection site reaction	Switch from subcutaneous to intravenous administration
34	Switching group	Breast cancer	Injection site reaction	Decreased dosing rate
48	Switching group	Breast cancer	Injection site reaction	Switch from subcutaneous to intravenous administration

patients are confident in the treatment's effectiveness and are comfortable with its administration.

The study's limitations encompass a brief research period and a limited number of cases. There were a few instances in this study where patients with a history of intravenous treatment transitioned to PHESGO, and then reverted back to intravenous treatment (Table IV). However, no patients who initiated treatment with PHESGO switched to intravenous treatment, though such a transition is anticipated in the future. Conversely, the study's strength lies in its novelty. To date, the only report on PHESGO involving a switch from an intravenous formulation in Japanese patients is the FeDeriCa study, which involved 20 Japanese participants. There is undeniably a lack of clinical information regarding the switch between formulations. Actual clinical data are essential for making informed decisions about formulation selection and switching (5). It is the first to present IR data on PHESGO and its practical application, with a particular focus on the safety of transitioning to PHESGO, within a Japanese context. Although, we believe it is important to accumulate more information in the future because of its novelty and preliminary results. We intend to extend the study and longer prospective studies with a larger cohort as a future direction.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

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

Ethics approval and consent to participate

The present study was approved by the institutional review board of Saitama Cancer Center (approval no. 1816; approved May 8, 2024). 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 patients, guaranteeing the opportunity for patients to refuse participation.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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