# Preventive effects of dexamethasone premedication on the development of infusion-related reactions in breast cancer patients receiving trastuzumab

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**Abstract**

Aim To clarify the incidence and risk factors of infusion-related reactions (IRRs) to trastuzumab in breast cancer patients and verify the preventive effects of glucocorticoids. Methods The electronic medical record data at the time of trastuzumab administration were retrospectively reviewed. The following exclusion criteria were applied to 229 breast cancer patients who received trastuzumab at Osaka Medical and Pharmaceutical University Hospital during the 4-year study period: missing information on human epidermal growth factor receptor type 2 (HER2) status (n=1); missing information on eosinophils (n=11); or use of treatments other than trastuzumab (n=41). Results The 176 patients included in the study received 2,320 infusions. Fifty-eight patients (33.0%) experienced IRRs, and IRRs occurred in 80 (3.4%) of the 2,320 infusions. Owing to the hierarchical structure of the data, the independence of the observed values was evaluated using the intraclass correlation coefficient. Multivariate multilevel logistic regression analysis showed that premedication with dexamethasone was effective in lowering IRR risk with trastuzumab (mg; per unit; odds ratio, OR=0.62; 95% confidence interval, 95% CI, 0.44-0.86; p=0.005). Preoperative status (OR=34.7; 95% CI, 5.0–242.0; p<0.001) and high doses of trastuzumab (mg/kg; per unit; OR=59.6; 95% CI, 19.7–180.0; p<0.001) were independent risk factors for IRRs. Conclusion The results of this study suggest that premedication with dexamethasone has a protective effect against IRRs caused by trastuzumab in breast cancer treatment. Future studies are needed to determine the optimal dosing of dexamethasone to prevent IRRs and the impact of dexamethasone on the efficacy of trastuzumab treatment.

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**Running title:** Trastuzumab infusion-related reactions

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**Keywords:** breast cancer, dexamethasone, human epidermal growth factor receptor type 2, infusion-related reaction, trastuzumab

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**What is already known about this subject:**

*Trastuzumab treatment leads to a high incidence of infusion-related reactions.

*Infusion-related reactions can be fatal without proper treatment.

*There is no established method of infusion-related reaction prophylaxis with trastuzumab.

**What this study adds:**

*Premedication with dexamethasone is effective in preventing infusion-related reactions due to trastuzumab.

*Preoperative patients and patients receiving high trastuzumab doses are at risk of developing infusion-related reactions with trastuzumab.

# Abstract

### Aim

To clarify the incidence and risk factors of infusion-related reactions (IRRs) to trastuzumab in breast cancer patients and verify the preventive effects of glucocorticoids.

### Methods

The electronic medical record data at the time of trastuzumab administration were retrospectively reviewed. The following exclusion criteria were applied to 229 breast cancer patients who received trastuzumab at Osaka Medical and Pharmaceutical University Hospital during the 4-year study period: missing information on human epidermal growth factor receptor type 2 (HER2) status ($n$ =1); missing information on eosinophils ($n$ =11); or use of treatments other than trastuzumab ($n$ =41).

### Results

The 176 patients included in the study received 2,320 infusions. Fifty-eight patients (33.0%) experienced IRRs, and IRRs occurred in 80 (3.4%) of the 2,320 infusions. Owing to the hierarchical structure of the data, the independence of the observed values was evaluated using the intraclass correlation coefficient. Multivariate multilevel logistic regression analysis showed that premedication with dexamethasone was effective in lowering IRR risk with trastuzumab (mg; per unit; odds ratio, OR=0.62; 95% confidence interval, 95% CI, 0.44-0.86;$p$ =0.005). Preoperative status (OR=34.7; 95% CI, 5.0–242.0;$p$ <0.001) and high doses of trastuzumab (mg/kg; per unit; OR=59.6; 95% CI, 19.7–180.0; $p$ <0.001) were independent risk factors for IRRs.

### Conclusion

The results of this study suggest that premedication with dexamethasone has a protective effect against IRRs caused by trastuzumab in breast cancer treatment. Future studies are needed to determine the optimal dosing of dexamethasone to prevent IRRs and the impact of dexamethasone on the efficacy of trastuzumab treatment.


# Introduction

Over the past decade, monoclonal antibodies have gained attention as a systemic anticancer therapy[1] and are now widely used in the treatment of various malignancies. In general, monoclonal antibodies are less toxic and better tolerated than conventional cytotoxic chemotherapeutic agents. However, as with other injected anticancer agents, monoclonal antibodies can cause infusion-related reactions (IRRs).[1–3] Most IRRs are mild and include chills, fever, nausea, skin rash, and pruritus. Severe side effects are less frequent but can include low blood pressure, tracheal spasm, and angioedema and can be fatal without proper care.[2,4]IRRs usually develop within the first few minutes of the first infusion.[5,6]

Trastuzumab, a humanized monoclonal antibody developed to block human epidermal growth factor receptor type 2 (HER2) from binding to tyrosine kinases,[7] is used for treating cancers that overexpress HER2.[1] Currently, it is the first-line treatment for almost all stages of breast cancer as well as advanced or recurrent gastric cancer.[8–13] The HER2 gene,*HER2/neu* (*c-erbB-2* ), was first discovered by Schechter et al. in 1984,[14] and this receptor is overexpressed in 25–30%[15] of early-stage breast cancers and 10–34%[14] of invasive breast cancers. Overexpression of HER2 adversely affects clinical outcomes.[8,16]However, the prognoses of these malignancies have remarkably improved with the introduction of trastuzumab, a monoclonal antibody against the extracellular domain of HER2. Trastuzumab has shown efficacy as a monotherapy[17] in metastatic breast cancer as well as in combination with chemotherapy in metastatic and early-stage breast cancer, reducing the recurrence rate by up to 50%, regardless of age or other prognostic factors.[9,18–20]

The probability that a patient will develop an IRR depends on the type of monoclonal antibody used and the disease.[21]Estimates of IRR rates for common agents range from 2% to 15%,[22] whereas those for taxanes and platinum are 40% and 16%, respectively. The IRR rates for monoclonal antibodies rituximab, trastuzumab, and cetuximab are 77%, 40%, and 20.5%, respectively, which are relatively high.[2,23] The incidence of IRR for the same drug varies from report to report. A report revealed the IRR incidence of trastuzumab to range from 3.4%[24] to 5.9%.[25] Trastuzumab is generally considered to be a safe drug, as there have been no reports of hematologic toxicity commonly associated with chemotherapy[10]; moreover, trastuzumab has demonstrated favorable safety profiles in patients older than 70 years.[25] However, IRRs and cardiac toxicity[10] have emerged as major safety concerns.[18,19,26–28] Cook et al. reported that 0.3% of breast cancer patients experienced a serious IRR in response to trastuzumab, based on postmarketing surveillance data.[28] Therefore, it is imperative that clinicians are aware of the potential for IRRs when administering trastuzumab and implement protocols to prevent and manage these reactions to minimize their impacts on further treatment.

The degree of antibody humanization influences the frequency of IRRs,[29] but the mechanisms underlying IRRs associated with monoclonal antibodies remain to be elucidated.[2]IRRs after rituximab administration occur at a significantly higher rate in patients with tumors than in patients with rheumatoid arthritis.[30,31] Byrd et al. reported increased levels of cytokines, such as tumor necrosis factor-α, interleukin (IL)-6, IL-8, and interferon-γ in patients with rituximab-induced IRRs compared to those in a group without IRRs.[32] Larger tumor loads are known to promote more severe cytokine release.[33,34] Although IRRs occur almost exclusively with the first infusion,[1–3,35–37] IgE-mediated hypersensitivity requires prior sensitization and is not expected to occur with the first infusion of monoclonal antibodies. Cytokine-dependent mechanisms in IRRs have been proposed,[2] since cytokines can cause a variety of symptoms characteristic of IRRs and cytokine-dependent mechanisms are independent of prior sensitization. Previous findings suggest that the etiology of IRRs to monoclonal antibody preparations may involve cytokine release due to tumor cell destruction, unlike IgE-mediated type 1 allergic reactions observed in patients with normal hypersensitivity.[1,2,5,35,36,38]

There is little information on the risk factors for IRRs associated with trastuzumab. Of all factors evaluated by Thompson et al., high body mass index (BMI), stage IV, and no prior medication use (diphenhydramine, meperidine, or hydrocortisone) were significantly associated with increased IRR risk by multivariate logistic regression analysis.[39] However, their study did not analyze effective premedications.

Premedications with histamine $H_1$ receptor antagonist, acetaminophen, or glucocorticoids are common methods to prevent IRRs associated with the use of monoclonal antibodies.[1,35]Tokuda et al. reported a decreased incidence of IRR when a non-steroidal anti-inflammatory drug (NSAID) was administered 30 minutes before trastuzumab administration.[40] In a study of cetuximab plus irinotecan in heavily metastatic colorectal cancer that had progressed on prior irinotecan therapy (MABEL trial), the effects of premedication on the incidence of IRR were examined using retrospective analysis. Histamine $H_1$ receptor antagonist alone and histamine $H_1$ receptor antagonist plus glucocorticoids were compared as prophylactic premedication; the incidence of IRRs in any grade of colorectal cancer was 25.6% and 9.6%, respectively, and the incidence of IRRs in Grade 3/4 cases was 4.7% and 1.0%, respectively, suggesting the usefulness of glucocorticoids as premedication for monoclonal antibody regimens to prevent IRRs.[41] Among all adult patients prescribed rituximab for B-cell malignancies, the incidence of IRRs in patients premedicated with glucocorticoids for the first infusion was significantly lower than in patients who were not (8.3% versus 41.2%,$p$ =0.017).[37]

To the best of our knowledge, the benefits of premedication with glucocorticoids for trastuzumab treatments are not clear, as clinical data have not demonstrated the efficacy of prophylactic administration of glucocorticoids for IRR after trastuzumab.[42] It is common practice to slow down or interrupt the infusion rate when IRRs occur. In addition, IRRs can cause logistic problems for infusion centers. Patients with IRRs require an average of 54 minutes (range 10–100 minutes) of dose interruption, which can result in longer chair time at the infusion center and delayed scheduled dosing for other patients. These interruptions also affect the ability to move patients within the center, often requiring additional medications, supplies, and clinical staff time, creating an economic burden on the health care system.[39] Establishment of efficacious

IRR prophylaxis methods not only help to improve patient safety but also reduce treatment time delays due to IRR occurrence and, ultimately, improve the scheduling of chemotherapy departments. Prevention and management of trastuzumab-induced IRRs has become increasingly important in recent years, as registry data in Japan and the United Kingdom indicate that breast cancer incidence is on the rise.[43,44] In this retrospective observational study, we aimed to determine the incidence of IRRs during trastuzumab therapy in breast cancer patients as well as the associated risk factors; we also aimed to validate the protective effect of glucocorticoid premedication.

# Methods

## Study subjects

All patients who had received trastuzumab at Osaka Medical and Pharmaceutical University Hospital from January 1, 2017 to December 31, 2020 were identified and the following exclusion criteria were applied: gastric cancer, missing information on HER2 status, missing eosinophil information, or use of other treatments. This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Osaka Medical and Pharmaceutical University (Approval ID: 2020-175). Since this is a retrospective observational study without intervention or invasion, the requirement for informed consent was waived. This study was conducted according to the STROBE statement.[45]

## Outcome variable

The severity of IRRs was assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, and the outcome measure was the occurrence of an IRR of grade 1 or higher after starting trastuzumab administration. For each patient, all electronic medical record data at the time of trastuzumab administration were retrospectively reviewed for potential IRR cases by a clinical pharmacist with specific training in screening and treatment of adverse effects in cancer chemotherapy.

## Explanatory variables

Patients received repeated doses of trastuzumab. The data analyzed in this study were obtained from multiple doses administered to the same individual; that is, it had a two-level hierarchical structure consisting of a macro-level (patient level, level 2) and micro-level (infusion level, level 1). With reference to previous studies,[39,42] the following factors were examined in this study. The macro-level variables were height, HER2 status, estrogen receptor (ER) status, progesterone receptor (PR) status, allergy history, and baseline eosinophil levels; the micro-level variables were age, stage, metastasis, concomitant medications, number of courses, weight, BMI, status (preoperative, postoperative, and/or recurrent progression), trastuzumab dose, and dexamethasone dose. Eosinophils were not measured for each dose of trastuzumab; therefore, baseline values were used as macro-level variables.

## Data processing

Centering at the pooled mean was performed for the following macro-level variables: height, HER2 status, ER status, PR status, allergy history, and baseline eosinophil levels. Although age, stage, metastasis, and concomitant medications were micro-level variables, centering at the pooled mean was applied because there was little variation within individual patients. On the other hand, centering within the cluster was applied to the following micro-level variables: the number of courses, weight, BMI, status (preoperative, postoperative, and/or recurrent progression), trastuzumab dose, and dexamethasone dose.[46]

### Statistical analysis

Descriptive statistics at the macro- and micro-levels were calculated. Fisher's exact test was used for nominal variables, Wilcoxon rank-sum test was used for continuous variables, and Cochran-Armitage trend test was used for ordered variables (stage, trastuzumab dose, and dexamethasone dose) to examine the trends of IRR occurrence rate. Owing to the hierarchical structure of the data, the independence of the observed values was evaluated using the intraclass correlation coefficient (ICC).[47] Subsequently, four models, including a null model, were tested using multilevel logistic regression analysis to identify the preventive effects of dexamethasone premedication on IRR occurrence as well as the relationships between the macro- and micro-level independent risk factors and IRR development. Model 0, the null model, is a model with no objective or explanatory variables and was used to determine ICC. ICC is a measure to assess similarity within a group,[47] and in this study, the patients represented the group and one infusion of trastuzumab represented the individual. Model 1 incorporated micro-level variables, Model 2 incorporated macro-level variables, and Model 3 incorporated both micro- and macro-level variables. For the selection of candidate explanatory variables, $p$ -values from univariate analysis were considered. Akaike's information criterion (AIC), Bayesian information criterion (BIC), and likelihood ratio tests were used to compare model goodness-of-fit. Variance inflation factors (VIFs) of [?]10 were considered evidence of multicollinearity. All $p$ -values were reported using two-tailed tests, and the significance level was set at 5%. Analyses were performed using R version 4.0.2 (R Development Core Team, Vienna, Austria).

## Results

### Study subjects

Of 229 patients identified during the 4-year study period (January 1, 2017, to December 31, 2020), 176 patients met the inclusion criteria and received 2,320 infusions that could be evaluated. Patients were excluded for the following reasons: missing information on HER2 status ($n$ =1); missing information on eosinophils ($n$ =11); or first infusion of trastuzumab before January 1, 2017 ($n$ =41) (Figure 1).

### Demographic and clinical characteristics of the patients

The baseline patient and tumor characteristics of this cohort are summarized in Table 1, and the treatment characteristics are described in Table 2. The final sample ($n$ =176) had a median age of 56 years (interquartile range, IQR: 48–69 years), and most patients had nonmetastatic disease (stages I–III, 85.8%). Of the 176 patients evaluated, 58 patients (33.0%) experienced IRRs, and IRRs occurred in 80 infusions (3.4%) of the total 2,320 infusions. Dexamethasone was administered as a premedication in 281 of the 2,320 trastuzumab infusions (12.1%). However, these dexamethasone doses were intended to prevent adverse events from concurrent chemotherapy (e.g., taxane prior to trastuzumab infusion). Most patients received trastuzumab with a loading dose of 8 mg/kg for 90 min, followed by 6 mg/kg for 30 min every three weeks. Sixty-nine IRRs occurred during the 8 mg/kg loading dose for 90 min (69 of 271, 25.5%), and no IRRs occurred during a 4 mg/kg loading dose for 90 min (0 of 2, 0%). Eleven IRRs occurred during maintenance infusions of 6 mg/kg for 30 min (11 of 2,025, 0.5%), and no IRRs were documented with the 2 mg/kg maintenance dose ($n$ =22) in this cohort of patients.

### Details of infusion-related reaction

Information related to the IRRs in this cohort is shown in Table 3. Most reactions occurred during the first dose (53 of 58, 91.4%). Symptoms included chills ($n$ =57), decreased $SpO_2$($n$ =8), dyspnea ($n$ =7), hypotension ($n$ =1), pyrexia ($n$ =35), nausea ($n$ =19), shivering ($n$ =25), and vomiting ($n$ =6). Most of the reactions were grade 1 or 2 (79 of 80, 98.8%). One patient experienced grade 3 reactions. IRRs to trastuzumab were effectively managed by temporarily discontinuing infusion and/or administering supportive

medications such as NSAIDs. IRRs to trastuzumab occurred 60 minutes on median (IQR, 45–70 minutes) after the infusion. Patients who had IRRs to trastuzumab spent additional time in the chemotherapy center until their symptoms had resolved. Symptoms related to IRRs were resolved in all patients.

### Preventive effects of dexamethasone against IRRs

Since the null model yielded an ICC of 0.36, it was determined that analysis using the hierarchical structure was necessary.[47] Figure 2 shows the unadjusted risk of developing IRR obtained by univariate multilevel logistic regression analysis. Univariate analysis revealed that metastasis (odds ratio, OR=2.72; 95% confidence interval, 95% CI, 1.13–6.55; $p$ =0.026), preoperative status (OR=4.74; 95% CI, 2.18–10.31;$p$ <0.001), trastuzumab dose (mg/kg; per unit; OR=58.8; 95% CI, 22.0–157.0; $p$ <0.001), and eosinophil (/μL; per 100 units; OR=1.30; 95% CI, 1.04–1.63; $p$ =0.020) were significantly associated with increased risk of IRRs. On the other hand, course (per unit; OR=0.79; 95% CI, 0.73–0.86;$p$ <0.001) and postoperative status (OR=0.22; 95% CI, 0.10–0.47; $p$ <0.001) were significantly associated with a lower risk of IRRs.

The results of the multivariate multilevel logistic regression analysis are shown in Figure 3. In model 1, which included micro-level variables, dexamethasone and the four covariates that were statistically significant by univariate analysis were included in the multivariate analysis, and higher doses of dexamethasone premedication were associated with significantly lower risks of IRR after starting trastuzumab. In model 2, which included macro-level variables, higher baseline eosinophil levels resulted in higher IRR risk. In model 3, which included micro- and macro-level variables, dexamethasone and five covariates that were statistically significant by univariate analysis were incorporated to obtain an adjusted OR, which showed that dexamethasone premedication suppressed IRRs after starting trastuzumab (mg; per unit; OR=0.62; 95% CI, 0.44-0.86; $p$ =0.005). In addition, preoperative status (OR=34.7; 95% CI, 5.0–242.0;$p$ <0.001) and high dose of trastuzumab (mg/kg; per unit; OR=59.6; 95% CI, 19.7–180.0; $p$ <0.001) were independent risk factors for IRR. VIFs were less than 2 in all models and there was no multicollinearity among the explanatory variables (max=1.85; min=1.01).

#### *Goodness-of-fit measures*

Table 4 shows the results of a comparison of the data's suitability for the model. Based on the results of the AIC, BIC, or likelihood ratio tests, the goodness-of-fit was high for model 1 and model 3, which included micro-level variables.

## Discussion

In this retrospective observational study, we tested whether premedication with dexamethasone is effective in preventing trastuzumab-associated IRR in patients with HER2-positive breast cancer based on electronic medical record data. To the best of our knowledge, this study is the first to show that dexamethasone premedication is effective in preventing IRRs caused by trastuzumab.

In our study, premedication with dexamethasone reduced the incidence of IRR (final model OR=0.616; 95%CI, 0.440-0.861; $p$ =0.005) (Figure 3). Hemophagocytic lymphohistiocytosis occurring in rheumatic disease (macrophage activation syndrome) is treated with glucocorticoids, IL-1 blockade, or cyclosporine A.[48,49] Glucocorticoids remain the first-line drugs for adult-onset Still's disease characterized by excessive cytokine production.[50]Thus, the results of this study showing that dexamethasone was effective in preventing IRRs caused by trastuzumab support the hypothesis that IRRs are cytokine-dependent. In a previous observational study, IRRs were prevented when all patients received an intravenous histamine $H_1$ receptor antagonist (5 mg of dichlorpheniramine) as a premedication and 6.6 mg premedication with dexamethasone as an antiemetic agent for cetuximab therapy.[51] The dexamethasone premedication used in the patients in our study was also intended as an antiemetic for other chemotherapy regimens administered in combination

with trastuzumab, at doses of 6.6 mg or 8.25 mg. These suggest that doses such as those used as antiemetics are effective in reducing IRR risk with cetuximab and trastuzumab. There is little information on the addition of premedication to regimens that do not traditionally require premedication, such as trastuzumab monotherapy.[39] Because unnecessary premedication may result in dexamethasone-induced adverse events, it is necessary to identify patients at high IRR risk and determine the need for dexamethasone premedication. For example, preoperative status and high-dose trastuzumab (i.e., first course patients) were identified as risk factors for trastuzumab-induced IRR, and these patients may require premedication with dexamethasone. A previous observational study revealed no differences in IRR prophylaxis for cetuximab between dexamethasone doses of 6.6 mg and 13.2 mg.[51] Our results show that the OR was 0.616 per 1 mg increase in dexamethasone, which indicates that if 8 mg were premedicated, the OR would be 0.02, or a 1 in 50 risk of IRR occurrence. Further studies are needed to determine the optimal dose of dexamethasone to avoid unnecessary exposure.

In the current study, the risk of IRR in patients with breast cancer was higher in preoperative patients and in patients receiving high trastuzumab doses (Figure 3). The frequency of IRRs after rituximab administration is clearly higher in patients with tumors than in patients with rheumatoid arthritis.[30,31]Administration of rituximab to patients with a large number of tumor cells in the blood may increase the likelihood of a severe initial IRR.[33,34] In a study investigating IRRs in response to rituximab in patients with B-cell lymphoma, multivariate logistic regression analysis confirmed that low-grade lymphomas (OR=2.81;$p$ =0.017) and bulky disease (OR=2.52; $p$ =0.037) were independent risk factors.[52] The IRR risk factor identified in the present study, preoperative status, reflects a high tumor count, and a higher dose of trastuzumab indicates more tumors to be destroyed. In other words, these reports are consistent with the results of the present study, as they indicate patients with high cytokine release. Conversely, patients who received postoperative adjuvant chemotherapy have fewer tumor cells than preoperative patients and therefore do not release as many cytokines; postoperative immune dysfunction may be the reason for their low IRR risk.

Of all factors evaluated in a study by Thompson et al., high BMI, stage IV, and no prior medication use (diphenhydramine, meperidine, or hydrocortisone) were significantly associated with higher risks of trastuzumab-induced IRRs in breast cancer patients.[39]In contrast, in our results, BMI was not associated with IRR risk. We attribute the differences between these studies to differences in BMI distribution in our cohort. The numbers of patients with BMI ($kg/m^2$) <18.5, 18.5–24.9, 25.0–29.9, and 30[?] were 0, 60, 55, and 82, respectively. In the previous study, they were 17, 113, 36, and 10, respectively, at baseline. The lower distribution of BMI in the present study may account for the disparities in results. Cochran-Armitage trend testing in our study also showed a statistically significant trend towards increased IRR incidence with advancing stage (Table 2). Furthermore, stage IV (i.e. metastasis) was associated with higher risk of IRR in univariate analysis (Figure 2) but not statistically significant in multivariate analysis. There are several possible reasons for this. First, metastasis was not detected because of the higher IRR risk of preoperative or trastuzumab dosage used as variables in this study. Second, the variables used in the multivariate analysis were different. Third, the patient background, such as BMI, was different. However, the details underlying this finding are not known, and the IRR risk in patients with stage IV breast cancer needs further investigation.

In the present study, high eosinophil levels were a risk factor for IRR occurrence in univariate analysis (Figure 2), but no statistically significant association was found when adjusted for other factors by multivariate analysis (Figure 3). In a previous study, low eosinophil levels were associated with trastuzumab-induced IRR in breast cancer patients.[53] High eosinophil counts were a risk factor for cetuximab-induced IRR in patients with squamous cell carcinoma of the head and neck.[42] Therefore, the influence of blood eosinophils on the development of IRRs caused by monoclonal antibody preparations shows conflicting results. In addition, eosinophil levels being used as a baseline characteristic in our study may have been a factor in the lack of associations with increased IRR risk. Because eosinophil data was not available for each infusion in our study, we were unable to obtain eosinophil levels at a consistent time point prior to each trastuzumab infusion, rather than at baseline, to assess the role of eosinophils in IRR development as a micro-level variable.

Although the risk of IRR is clearly higher with monoclonal antibody preparations at the first dose,[37,39] course was not associated with the development of IRRs in during multivariate analysis (Figure 3). Since the dose of trastuzumab treatment was higher at the first dose (8 mg/kg) than at the maintenance dose (6 mg/kg), the same patient is at higher risk for IRRs with the first dose.

In this retrospective study of breast cancer patients treated with trastuzumab, the overall incidence of IRR was 3.4% of all infusions. Most IRRs occurred during the first dose (53 of 58 patients, 91.4%). The incidence of IRRs was higher with the first course and the first dose of 8 mg/kg, which is consistent with previous reports.[3] Previous studies have reported a relatively high incidence of IRRs with trastuzumab (40%,[2]3.4%,[24] or 5.9%).[25] Although the incidence of IRR in our study was on the low side, the wide range in IRR incidence between different reports seems to result from differences in comorbidities or premedication use.[37] The use of trastuzumab has expanded to salivary gland and colorectal cancers, and the differences in IRR occurrence by disease state should be examined in the future.

There are several limitations to our study. First, we cannot distinguish whether the IRRs that occurred were due to trastuzumab or other chemotherapy. To minimize this effect, we qualified IRRs only as those symptoms that developed within 120 minutes of the start of trastuzumab infusion, based on reports that most trastuzumab IRRs occur during trastuzumab administration or within 2 hours after initiation.[2] Second, it is not known from our study whether dexamethasone premedication affects the efficacy with trastuzumab. While previous studies have shown that pretreatment with glucocorticoids does not affect the efficacy of rituximab at 24 weeks in the treatment of rheumatoid arthritis,[54] there is no similar evidence for trastuzumab for breast cancer. However, studies using BT-474 breast cancer cells suggest that dexamethasone at least partially inhibits the growth-suppressing effects of trastuzumab;[55] therefore, clinical evaluations are needed.

In conclusion, to investigate how to prevent trastuzumab-induced IRR in breast cancer, we analyzed a model adjusted for patient background and found that premedication with dexamethasone is effective in preventing trastuzumab-induced IRR. However, the current lack of information on the risks of dexamethasone-induced adverse events and its effect on trastuzumab efficacy makes it impractical to unreservedly recommend premedication with dexamethasone based solely on this study. It is essential to select patients at high risk for IRR for dexamethasone premedication, such as those of preoperative status and who are receiving high trastuzumab doses based on the results of this study. In addition, dexamethasone should be limited to a minimal dose to lower IRR risk and avoid prolonged infusion time, and dexamethasone premedication should not be used in patients at high risk for dexamethasone-associated adverse events. Future studies are needed to determine the optimal dose of dexamethasone to prevent IRRs and the impacts of dexamethasone on the efficacy of trastuzumab in breast cancer.

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## Conflicts of interest statement

The authors declare no competing interests.

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## Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## Author contributions

**Emi Goto:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data Curation, Writing - Original Draft, Supervision.

**Takeo Hata:** Methodology, Software, Validation, Formal analysis, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing.

**Masami Nishihara:** Writing - Review & Editing.

**Masashi Neo:** Writing - Review & Editing.

**Mitsuhiko Iwamoto:** Resources, Writing - Review & Editing.

**Kosei Kimura:** Resources, Writing - Review & Editing.

**Masahiro Goto:** Writing - Review & Editing.

**Yoshiyuki Rikitake:** Conceptualization, Writing - Review & Editing, Project administration.

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# Tables

Table 1. Demographic and clinical characteristics of patients at baseline.

| Characteristics | Overall |
|---|---|

| | |
|---|---|
| Patients, n (%) | 176 (100) |
| Age, year, median (IQR) | 56 (48–69) |
| Sex, n (%) | |
| Female | 176 (100) |
| Male | 0 (0) |
| Height, m, median (IQR) | 1.57 (1.52–1.60) |
| BW, kg, median (IQR) | 55 (50–60) |
| BMI, kg/m$^2$, median (IQR) | 22.1 (20.0–25.1) |
| Eosinophil, /μL, median (IQR) | 86 (36–155) |
| HER2, n (%)[a] | |
| 1+ | 1 (0.6) |
| 2+ | 62 (35.2) |
| 3+ | 113 (64.2) |
| ER positive, n (%) | 123 (69.9) |
| PR positive, n (%) | 85 (48.3) |
| Stage, n (%) | |
| I | 34 (19.3) |
| II | 97 (55.1) |
| III | 20 (11.4) |
| IV | 25 (14.2) |
| Metastasis, n (%) | 25 (14.2) |
| Status, n (%) | |
| Preoperative | 63 (35.8) |
| Postoperative | 88 (50.0) |
| Recurrent progression | 25 (14.2) |
| History of allergies, n (%)[b] | |
| Any | 83 (47.2) |
| Drug | 30 (17.0) |
| Food | 27 (15.3) |
| Contrast media | 14 (8.0) |
| Pollinosis | 32 (18.2) |

BMI, body mass index; BW, body weight; ER, estrogen receptor; HER2, human epidermal growth factor receptor type 2; IQR, interquartile range; PR, progesterone receptor.

a: Determined using immunohistochemical (IHC) method

b: Total does not add up to 100% because there were patients who were not applicable or had multiple applicable cases.

Table 2. Summary of IRR onset data from trastuzumab infusion (micro-level).

| Characteristics | Overall | Incidence | Non-incidence | *p*-value |
|---|---|---|---|---|
| Patients, n (%) | 176 (100) | 58 (33.0) | 118 (77.0) | |
| Frequency of dose, n (%) | 2320 (100) | 80 (3.4) | 2240 (96.6) | |
| Course, median (IQR) | 8 (4–14) | 1 (1–4) | 9 (4–14) | <0.001* |
| Age, year, median (IQR) | 56 (47–67) | 55 (47–66) | 56 (47–68) | 0.762 |
| BW, kg, median (IQR) | 54 (50–60) | 56 (50–61) | 54 (49–60) | 0.126 |
| BMI, kg/m$^2$, median (IQR) | 21.8 (19.6–24.8) | 22.2 (19.9–24.9) | 21.8 (19.6–24.8) | 0.407 |
| Stage, n (%) | | | | 0.021* |
| I | 481 (20.7) | 9 (1.9) | 472 (98.1) | |
| II | 1235 (53.2) | 45 (3.6) | 1190 (96.4) | |

| | | | | |
|---|---|---|---|---|
| III | 283 (12.2) | 9 (3.2) | 274 (96.8) | |
| IV | 321 (13.8) | 17 (5.3) | 304 (94.7) | |
| Stage, n (%) | | | | 0.195 |
| I or II | 1716 (74.0) | 54 (3.1) | 1662 (96.9) | |
| III or IV | 604 (26.0) | 26 (4.3) | 578 (95.7) | |
| Metastasis, n (%) | 321 (13.8) | 17 (5.3) | 304 (94.7) | 0.067 |
| Status, n (%) | | | | <0.001* |
| Preoperative | 269 (11.6) | 25 (9.3) | 244 (90.7) | |
| Postoperative | 1729 (74.5) | 38 (2.2) | 1691 (97.8) | |
| Recurrent progression | 322 (13.9) | 17 (5.3) | 305 (94.7) | |
| Dose, mg/body, median (IQR) | 328 (300–378) | 425 (382–482) | 327 (300–368) | <0.001* |
| Dose, n (%) | | | | <0.001* |
| 2 mg/kg | 22 (0.9) | 0 (0) | 22 (100) | |
| 4 mg/kg | 2 (0.1) | 0 (0) | 2 (100) | |
| 6 mg/kg | 2025 (87.3) | 11 (0.5) | 2014 (99.5) | |
| 8 mg/kg | 271 (11.7) | 69 (25.5) | 202 (74.5) | |
| Dexamethasone iv, n (%) | | | | 0.258 |
| 0 mg | 2039 (87.9) | 73 (3.6) | 1966 (96.4) | |
| 6.6 mg | 250 (10.8) | 7 (2.8) | 243 (97.2) | |
| 8.25 mg | 31 (1.3) | 0 (0) | 31 (100) | |
| Dexamethasone iv, n (%) | 281 (12.1) | 7 (2.5) | 274 (97.5) | 0.484 |
| Glucocorticoids po, n (%) | 22 (0.9) | 0 (0) | 22 (100) | 1.000 |
| NSAIDs, n (%) | 84 (3.6) | 6 (7.1) | 78 (92.9) | 0.067 |
| Acetaminophen, n (%) | 11 (0.5) | 2 (18.2) | 9 (81.8) | 0.053 |
| $H_1$AT, n (%) | 148 (6.4) | 2 (1.4) | 146 (98.6) | 0.238 |

BMI, body mass index; BW, body weight; $H_1$AT, histamine $H_1$ receptor antagonist; IQR, interquartile range; IRR, infusion-related reaction; NSAIDs, non-steroidal anti-inflammatory drugs. *, $p$ <0.05.

Table 3. Details of observed IRRs (micro-level).

| Characteristics | Overall |
|---|---|
| Frequency of dose, n (%) | 2320 (100) |
| IRR, n (%) | |
| Grade 1 | 37 (1.6) |
| Grade 2 | 42 (1.8) |
| Grade 3 | 1 (0.0) |
| All grade | 80 (3.4) |
| Onset time, minutes, median (IQR) | 60 (45–70) |
| Symptom, n (%) | |
| Chill | 57 (2.5) |
| Decrease in $SpO_2$ | 8 (0.3) |
| Dyspnea | 7 (0.3) |
| Hypotension | 1 (0) |
| Pyrexia | 35 (1.5) |
| Nausea | 19 (0.8) |
| Shivering | 25 (1.1) |
| Vomiting | 6 (0.3) |

IQR, interquartile range; IRR, infusion-related reaction; $SpO_2$, percutaneous oxygen saturation.

Table 4. Goodness-of-fit measures.

| | NP | AIC | BIC | Log-L | D | $\chi^2$ | Df | $p$-value |
|---|---|---|---|---|---|---|---|---|
| Null model | 2 | 671 | 683 | -334 | 667 | | | |
| Model 2 | 3 | 668 | 685 | -331 | 662 | 5.39 | 1 | 0.020* |
| Model 1 | 7 | 407 | 448 | -197 | 393 | 268.21 | 4 | <0.001* |
| Model 3 | 8 | 405 | 452 | -195 | 390 | 3.78 | 1 | 0.052 |

AIC, Akaike's information criterion; BIC, Bayesian information criterion; D, deviance; Df, degree of freedom; Log-L, log-likelihood; NP, number of parameters. *, $p$ <0.05.

# Figure Legends

**Figure 1. Screening of the study population**

HER2, human epidermal growth factor receptor type 2.

**Figure 2. Univariate analysis of the relationships between IRRs and patient characteristics**

BMI, body mass index; BW, body weight; CI, confidence interval; ER, estrogen receptor; $H_1$AT, histamine $H_1$receptor antagonist; HER2, human epidermal growth factor receptor type 2; IRR, infusion-related reaction; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; PR, progesterone receptor. *,$p$ <0.05.

**Figure 3. Multivariate analysis of the relationship between IRRs and patient characteristics**

CI, confidence interval; IRR, infusion-related reaction; OR, odds ratio. *, $p$ <0.05.

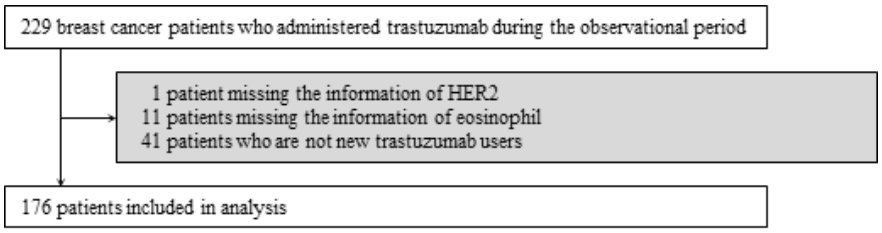
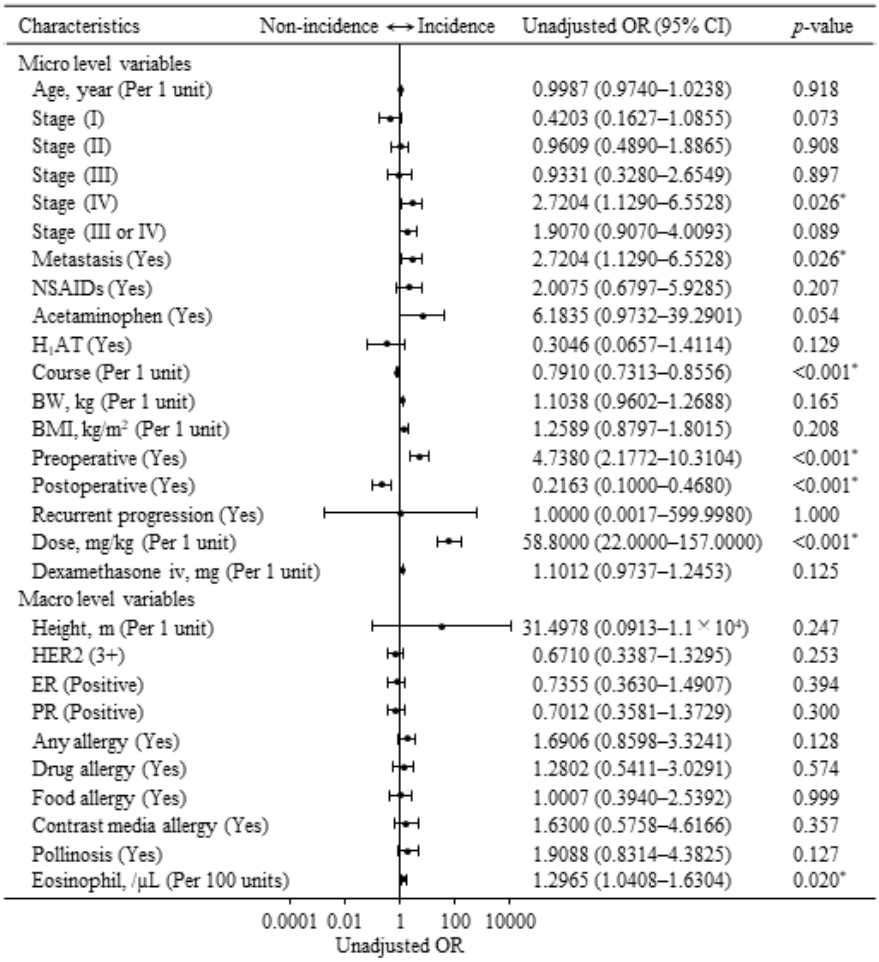


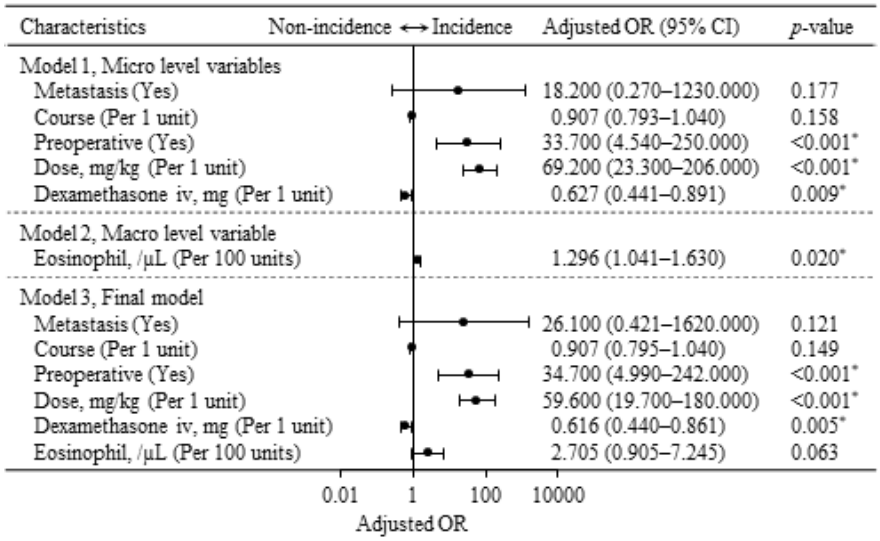

Figure 1. Screening of the study population
HER2, human epidermal growth factor receptor type 2.

Figure 2. Univariate analysis of the relationship between the IRRs and patient characteristics




BMI, body mass index; BW, body weight; CI, confidence interval; ER, estrogen receptor; $H_1$AT, histamine $H_1$ receptor antagonist; HER2, human epidermal growth factor receptor type 2; IRR, infusion-related reaction; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; PR, progesterone receptor. *, $p<0.05$.

Figure 3. Multivariate analysis of the relationship between the IRRs and patient characteristics




CI, confidence interval; IRR, infusion-related reaction; OR, odds ratio. *, $p<0.05$.