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Corresponding Author: Hiroshi Ishiguro

Corresponding Author's Institution:

First Author: Kosuke Kawaguchi

Order of Authors: Kosuke Kawaguchi;Hiroshi Ishiguro;Satoshi Morita;Seigo Nakamura;Shinji Ohno;Norikazu Masuda;Hiroji Iwata;Kenjiro Aogi;Katsumasa Kuroi;Masakazu Toi

Original article for Breast Cancer Research and Treatment

Correlation between docetaxel-induced skin toxicity and the use of steroids and H_2 blockers: A multi-institution survey

K. Kawaguchi[1)2)], H. Ishiguro[3)], S. Morita[4)], S. Nakamura[5)], S. Ohno[6)], N. Masuda[7)], H. Iwata[8)], K. Aogi[9)], K. Kuroi[10)], M. Toi[1)]; Japan Breast Cancer Research Group (JBCRG)

1) Department of Breast Surgery, Kyoto University Hospital, Kyoto, Japan

2) Department of Surgery, Osaka Red Cross Hospital, Osaka, Japan

3) Outpatient Oncology Unit, Kyoto University Hospital, Kyoto, Japan

4) Department of Biostatistics and Epidemiology, Yokohama City University Medical Center, Yokohama, Japan

5) Breast Center, Showa University Hospital, Tokyo, Japan

6) Division of Breast Oncology, National Kyushu Cancer Center, Fukuoka, Japan

7) Department of Surgery, Breast Oncology, Osaka National Hospital, Osaka, Japan

8) Department of Breast Oncology, Aichi Cancer Center Hospital, Nagoya, Japan

9) Department of Surgery, National Hospital Organization, National Shikoku Cancer Center, Matsuyama, Japan

10) Department of Surgery, Division of Clinical Trials and Research, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan

Corresponding author

Hiroshi Ishiguro, MD, PhD, FACP

Outpatient Oncology Unit

Kyoto University Hospital

54 Shogoin-kawaharacho, Sakyo-ku

Kyoto, 606-8507, Japan

Phone +81-75-751-4770

Fax: +81-75-751-4772

Email: hishimd@kuhp.kyoto-u.ac.jp

Running Head

H_2 blockers increase incidence of docetaxel-induced skin toxicity

Part of this study was presented as a poster discussion in the "Patient Care: Cancer-Related Complications" session (abstract number 9536) at the 2009 Annual Meeting of the American Society of Clinical Oncology.

The authors have no conflict of interest to declare.

Abstract

Background

Steroids and H_2 blockers are commonly used as supportive care for taxane-containing chemotherapy, but they also affect docetaxel's primary metabolizer, cytochrome P_{450} 3A4. This retrospective observational study was performed to better understand the effects of these compounds on docetaxel-induced skin toxicities, specifically hand-foot syndrome (HFS) and facial erythema (FE), a relationship that is currently poorly understood.

Patients and methods

Member institutions of the Japan Breast Cancer Research Group were invited to complete a questionnaire on the occurrence of grade 2 or higher HFS and FE among patients treated between April 2007 and March 2008 with docetaxel as an adjuvant or neoadjuvant chemotherapeutic treatment for breast cancer.

Results

We obtained data for 993 patients from 20 institutions. Twenty percent received H_2 blockers, and all patients received dexamethasone. Univariate and multivariate analyses revealed that H_2 blockers are associated with a significantly higher incidence of both HFS and FE. The incidence of FE was significantly higher for the docetaxel + cyclophosphamide (TC) regimen than for non-TC regimens combined. Dexamethasone usage did not affect the incidence of either HFS or FE.

Conclusion

Use of H_2 blockers as premedication in breast cancer patients receiving docetaxel significantly increases the risk of both HFS and FE.

Key words

CYP3A4, docetaxel, drug exposure, facial erythema, hand-foot syndrome, H_2 blocker

INTRODUCTION

Docetaxel is one of the most active chemotherapeutic agents against breast cancer [1]. Data from a randomized trial show an increased tumor response with increasing docetaxel dose within a dose range of 60–100 mg/m^2 administered every 3 weeks [1]. In general, the incidence and severity of adverse events increases with docetaxel dose. Previously, docetaxel dose was limited by hematologic toxicities such as febrile neutropenia [2]; however, their impact has been drastically reduced by the use of granulocyte colony-stimulating factor (GCSF) as prophylaxis. Thus, in recent years, non-hematologic toxicities have become more clinically important. The incidence and severity of a number of non-hematologic toxicities, such as fluid retention (FR), are associated with increasing docetaxel dose [1]. In our own clinical practice, we have recently experienced many cases of docetaxel-induced hand-foot syndrome (HFS) and facial (cheek) erythema (FE), especially among patients receiving relatively high doses of docetaxel for adjuvant and neoadjuvant chemotherapy.

Corticosteroids administered over 3 days, starting 2 days prior to chemotherapy, have been shown to delay the onset of docetaxel-induced FR. In one study, patients who received methylprednisolone premedication had significantly delayed onset of FR. and received a significantly higher median cumulative dose of docetaxel before the onset of FR [3]. Among patients treated with TAC (docetaxel, doxorubicin, cyclophosphamide) and given corticosteroid premedication (starting 1 day prior to chemotherapy), Suh et al. [4] found that corticosteroid postmedication (three 8 mg doses, b.i.d., until 1 day after chemotherapy) yielded no improvement in the incidence of severe FR on day 2.

Both docetaxel-induced cumulative FR and the means by which corticosteroids delay its onset remain poorly understood. One possible explanation involves induction of the cytochrome P_{450} (CYP) system. Clinically relevant doses of dexamethasone (e.g. 8 mg orally two times a day for 5 days), reportedly increase hepatic cytochrome P_{450} 3A4 (CYP3A4) activity by an average of 25.7% [5]. Thus, dexamethasone treatment could potentially bring about a clinically significant increase in the clearance of CYP3A4 substrates such as docetaxel.

H_2 blockers, such as cimetidine and ranitidine, are weak inhibitors of CYP3A4 [6]. A single dose of cimetidine (800 mg orally) was found to have a small but significant effect (30% increase) on the area under the concentration–time curve (AUC) of midazolam. Five days of cimetidine treatment (400 mg orally b.i.d.) increased the AUC of epirubicin by 50% (not statistically significant due to a small sample size) [7]. Cimetidine also reportedly affects the pharmacokinetics of 5-fluorouracil (5-FU): pretreatment with cimetidine for 4 weeks led to an increased 5-FU plasma concentration and AUC [8]. For oral 5-FU, the AUC was increased by 72% and for intravenous 5-FU, the AUC was increased by 27% and total body clearance was decreased by 28% [8].

Although H_2 blocker premedication is not mandatory for docetaxel, it is commonly prescribed in Japan, probably as a result of the common practice of administering H_2 blocker premedication for paclitaxel treatment. Another possible explanation is that clinicians are aiming to minimize the gastrointestinal side effects of dexamethasone, although there is no convincing evidence to support this usage [9].We hypothesized that H_2 blockers would increase the incidence of docetaxel-induced skin toxicity, given their inhibitory effect on the enzymes that metabolize docetaxel. We also hypothesized that use of steroids prior to chemotherapy would decrease the incidence of these toxicities via the reverse action. In the present retrospective observational study, we aimed to gather data to investigate these hypotheses.

PATIENTS AND METHODS

Nearly 100 institutions belonging to the Japan Breast Cancer Research Group were invited to complete a questionnaire, asking them to use existing medical records to retrospectively investigate the occurrence of grade 2 or higher HFS and FE among patients treated between April 2007 and March 2008 with docetaxel as an adjuvant or neoadjuvant chemotherapeutic treatment for breast cancer. Twenty of these institutions returned data on patients. We asked that cases of HFS and FE be classified in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

The following data were collected on a per-institution basis: (1) docetaxel dose; (2) chemotherapeutic agents concurrently administered; (3) whether steroids or H_2 blockers were used; (4) occurrence of grade 2 or higher HFS or FE. Furthermore, we also ascertained the standard doses and regimens for steroids and H_2 blockers used by each institution (i.e. data on doses and regimens for docetaxel, steroids and H_2 blockers was based on institutional policy rather than individual patients' records).

Statistical analyses were performed using the chi-squared test and multivariate logistic regression.

This observational study using only the existing medical records was approved by the Ethics Committee of Kyoto University Graduate School of Medicine, and performed according to the Declaration of Helsinki and the Ethical Guidelines for Epidemiological Research of the Ministry of Education, Culture, Sports, Science, and Technology and the Ministry of Health, Labour, and Welfare of Japan. Although informed consent from patients is not a formal requirement for a study of this type (as per the above-mentioned guidelines), each subject was publicly provided with the opportunity to opt out of this study.

RESULTS

Patient characteristics

Of the nearly 100 institutions that were invited to participate, questionnaires were returned by 22, of which two institutions had no eligible patients, leaving 20 institutions that returned data. Data on 993 patients was available. Details of the drugs received by the 993 patients are provided in Table 1.

The chemotherapeutic regimens used were as follows: docetaxel monotherapy (T), docetaxel + cyclophosphamide (TC), docetaxel + capecitabine (TX), and docetaxel + trastuzumab (TH). A total of 760 (76.5%) patients received docetaxel at a dose of 75 mg/m^2, and 852 patients were treated with docetaxel monotherapy. H_2 blockers were administered to about 20% of patients. Three H_2 blockers, ranitidine, famotidine and lafutidine, were used. Dexamethasone was the only steroid administered, and all patients in the present study received dexamethasone. The dose of dexamethasone used on days 1 and 2 varied, depending on the chemotherapeutic regimen used and institutional preference, but 8 mg was the most commonly used dose on both days.

Univariate analysis of factors affecting skin toxicity incidence

Table 2 shows the relationship between the incidence of HFS and FE and the institutional policy with respect to H_2 blockers, steroids and chemotherapeutic regimen. HFS and FE occurred in 15.8% and 10.4% of patients, respectively. The incidence of FE but not HFS differed significantly between the TC regimen and other regimens combined (FE: odds ratio [OR] 2.73, $P = 0.010$; HFS: OR 0.58, $P = 0.245$). Given that the TX regimen was used in a very small number of patients (less than 5%), we did not compare the incidence of HFS and FE in this group with that of other regimens, particularly given that the TX regimen is already known to be associated with a higher incidence of HFS [10,11]. Use of H_2 blockers significantly increased the incidence of both HFS (OR 2.55, $P < 0.001$) and FE (OR 3.00, $P < 0.001$). Lafutidine was associated with a significantly higher OR than the other two H_2 blockers for both HFS (OR 11.73, $P < 0.001$) and FE (OR 18.48, $P < 0.001$). There was no general relationship between the dose of steroid on day 1 and/or day 2 and the incidence of either HFS or FE, although there was a small but significantly higher incidence of FE among patients receiving >8 mg of dexamethasone on day 1 compared with those who received ≤8 mg (OR 1.80, $P = 0.006$).

Cumulative incidence of HFS and FE

The cumulative incidences of HFS and FE are depicted in Figure 1. Given that most adjuvant and neo-adjuvant docetaxel-based chemotherapy regimens involve four cycles, we investigated cumulative toxicity for cycles 1 and 2, and cycles 3 and after. Grade 2 or higher HFS occurred in 5% of patients in cycle 1, and increased as chemotherapy continued. When an H_2 blocker was used, 20% of patients developed grade 2 or higher HFS by cycles 3 and after. The cumulative incidence of HFS in the absence of an H_2 blocker was about half that seen when an H_2 blocker was used.

The incidence of FE was also affected by the use of an H_2 blocker. In the absence of an H_2 blocker, the cumulative incidence of FE by cycles 3 and after was less than a quarter of that seen when an H_2 blocker was used.

Multivariate analysis of factors affecting skin toxicity incidence

Tables 3 and 4 show the relationships between steroid (day 1: Table 3; day 2: Table 4) and H_2 blocker institutional policies, chemotherapy regimen and HFS and FE incidence as determined by multivariate logistic regression analysis. Use of a steroid on days 1 and 2 was a confounding factor, so we performed separate analysis for patients who used steroids on these days.

The two multivariate logistic regression analyses show that use of H_2 blockers significantly increased the incidence of HFS and FE. Lafutidine had the strongest influence on the incidence of both HFS and FE. Ranitidine seemed to have the least influence, although there was still a significant increase in the incidence of FE (OR 2.58; $P = 0.029$) with day 2 steroid use, and a non-significant increase in FE incidence with day 1 steroid use (OR 2.17; $P = 0.101$)

Both multivariate analyses showed that the TC regimen was associated with a significantly increased risk of FE but not HFS relative to the other regimens combined. There was no relationship between the dose of dexamethasone given as premedication on day 1 or after chemotherapy on day 2 and the incidence of either HFS or FE.

DISCUSSION

This was a retrospective multi-institutional observational study designed to investigate the correlation between docetaxel-induced skin toxicity and the use of steroids and/or H_2 blockers. We found that H_2 blockers, especially lafutidine, significantly increased the incidence of HFS and FE. The dose of dexamethasone, given either as premedication on day 1 or after chemotherapy on day 2, did not affect the incidence of either HFS or FE. We also found that the TC regimen is associated with a significantly higher risk of FE but not HFS relative to other regimens.

The major limitations of our study are, first, that this is a retrospective analysis, with all the associated drawbacks. Second, the doses and regimens of steroids and H_2 blockers used in our analysis are based on institutional policies rather than individual patients' data. Although we found that lafutidine was associated with a significantly higher incidence of HFS and FE, only one institution used lafutidine, so observer bias may have contributed to this outcome. A further drawback is that pharmacokinetic data from the patients were not available. The best study design to answer the question of whether H_2 blockers increase the incidence of skin toxicity due to increased docetaxel AUC would be a randomized controlled trial, comparing docetaxel with or without H_2 blockers, with HFS and FE incidences as endpoints, and including an analysis of docetaxel pharmacokinetics. However, it would not only be prohibitively expensive to conduct such a trial, but also unethical to assign patients to the H_2 blocker arm, because it would place them at risk of an adverse outcome in the absence of apparent clinical benefit.

In vitro studies indicate that CYP3A4 is the major enzyme involved in docetaxel metabolism [12]. Less than 10% of unmetabolized docetaxel is excreted into the feces, and total urinary excretion is also less than 10% [13]. Total activity of enzymes in the CYP3A family has been identified as a strong predictor of docetaxel clearance and most likely accounts to a large extent for the observed inter-individual variability in drug clearance and plasma concentration AUC. Although the fact that docetaxel is predominantly metabolized by CYP3A makes the agent subject to a host of enzyme-mediated drug interactions, little data is available on potential interactions in humans [14]. CYP3A expression varies as much as 40-fold between individuals, which may be due to factors including genetic mutations and up- or down-regulation by environmental stimuli [15]. In fact, there is a wide overlap in the AUC values of patients receiving different doses of docetaxel (e.g. 75 and 100 mg/m^2), in spite of drug dose being calculated on the basis of body surface area [16], which could be explained by a drug–environment interaction.

A decrease in total body clearance and an increase in the AUC of docetaxel is associated with increased frequency and severity of side effects [17]. The AUC of docetaxel is reportedly a significant predictor of severe neutropenia, with a 50% decrease in docetaxel clearance corresponding to a 4.3-fold increase in the risk of grade 4 neutropenia and a 3.0-fold increase in the risk of febrile neutropenia [17]. Skin toxicities, such as HFS and FE, and nail toxicity, especially those higher than grade 2, affect patient compliance and the dose intensity of chemotherapy, both of which might lower the efficacy of treatment. A recent study has indicated that skin toxicity occurs in 53% of patients and nail toxicity occurs in 51% of patients receiving docetaxel [18]. Battegay [19] suggested that the antiangiogenic properties of taxanes may be involved in the pathogenesis of nail toxicity. Wasner et al. [20] suggested the existence of a neurogenically mediated inflammatory process. However, little is known about the mechanism underlying drug-induced HFS and FE, except that the two conditions seem to be dose related. In a Japanese study involving a low dose of docetaxel (60 mg/m^2), there was a generally low incidence HFS and FE [21].

In order to decrease the incidence of docetaxel toxicity, especially FR, dexamethasone (8 mg orally b.i.d. for 3 consecutive days starting 24 hours before docetaxel infusion) is often used. This seems to be effective for reducing the incidence and severity of FR [22], but the effect on skin toxicity is not well understood. In our analysis, the dose of steroid on either day 1 or day 2 had little impact on the incidence of grade 2 or higher HFS and FE. Since most institutions included in this study start dexamethasone therapy just prior to chemotherapy infusion, we were unable to determine whether dexamethasone given the day before chemotherapy has any effect on the incidence of skin toxicity. Since dexamethasone at doses used clinically increases CYP3A4 activity (with extensive inter-subject variability) [5], an increase in docetaxel clearance might be a factor explaining the lower incidence of FR, although this hypothesis requires confirmation by a well-designed clinical pharmacology study.

For paclitaxel, the incidence of infusion reactions can be reduced by the intravenous administration of H_1 receptor antagonists plus H_2 receptor antagonists 30 minutes prior to paclitaxel infusion [23], an approach that has become the standard premedication for paclitaxel administration. Although H_1 and H_2 receptor antagonists are not mandatory premedications for docetaxel, some physicians opt to use similar premedications for docetaxel as for paclitaxel, hoping that this might reduce the risk of infusion reactions and other toxicities associated with docetaxel treatment. Another rationale for using H_2 receptor antagonists is to protect the gastric mucosa against dexamethasone premedication. Standard doses of H_2 receptor antagonists are not effective for preventing non-steroidal anti-inflammatory drug (NSAID)-induced gastric mucosal damage [9,24]. Whether H_2 receptor antagonists are effective in reducing the incidence of gastric mucosal damage due to dexamethasone has not been established, and they are not routinely recommended unless a concurrent dose of a NSAID is prescribed. H_2 receptor antagonists are classified as weak inhibitors of CYP3A4 activity [25]. Clinically significant drug interactions with H_2 receptor antagonists, especially with cimetidine and chemotherapeutic agents such as epirubicin and 5-FU have been reported [7,8], although the contribution of CYP3A4 to the metabolism of epirubicin and 5-FU has not been studied extensively. It is possible that concurrent administration of H_2 receptor antagonists inhibits the CYP3A4-mediated metabolism of docetaxel, causing higher incidences of HFS and FE, although we do not have pharmacokinetic data to confirm this. Since H_2 receptor antagonists such as cimetidine are likely to be co-prescribed or self-administered with anti-neoplastic drugs, oncologists should be aware of this potential drug interaction.

Cyclophosphamide, used in the TC regimen, is inactivated by side-chain oxidation mediated by CYP3A4, the same enzyme involved in docetaxel metabolism [26]. This competition might be the one of the mechanisms involved in the increased toxicity of the TC regimen, as observed in the present study. However, it is difficult to explain why the TC regimen was associated with an increased frequency of FE but not HFS. One possible explanation is that in our analysis the high incidence of HFS in the TX regimen, a non-TC regimen, diminished the difference between TC and combined non-TC regimens, despite the very small number of patients treated using the TX regimen. An alternative explanation is that different mechanisms underlie the occurrence of HFS and FE.

Our retrospective observational study suggests that concurrent use of H_2 receptor antagonists with docetaxel-based regimens may increase the incidence of grade 2 or higher skin toxicities such as FE and HFS, possibly via an inhibitory effect of H_2 receptor antagonists on the CYP3A4-mediated clearance of docetaxel. Also, the TC regimen may increase FE but not HFS. The dose of dexamethasone on days 1 and 2 seems to play no role in skin toxicity.

The occurrence of a specific side-effect can be used to predict the likelihood of treatment success, with dose-related toxicity possibly indicating an adequate concentration for efficacy. For aromatase inhibitors and tamoxifen, there is some evidence that women with vasomotor symptoms have a lower risk of recurrence than those without [27]. Co-administration of tamoxifen with the selective serotonin reuptake inhibitor paroxetine to reduce vasomotor symptoms inhibits the activation of tamoxifen to its main active metabolite, endoxifen, possibly resulting in reduced treatment efficacy [28]. It remains unclear whether dexamethasone given 24 hours prior to chemotherapy reduces the severity of peripheral edema via the stimulation of CYP3A4 enzyme, leading to lower docetaxel exposure. Only clinical pharmacological studies will answer this question. However, it is certainly clear that we must always consider the possibility that any treatment to reduce drug toxicity might also result in a decrease in drug exposure.

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FIGURE

Figure 1. Cumulative incidence of (A) hand-foot syndrome (HFS) and (B) facial erythema (FE) among patients treated with docetaxel as an adjuvant or neoadjuvant chemotherapeutic treatment for breast cancer (*N* = 993). All, all patients; H2+, patients who received an H_2 blocker; H2-, patients who did not receive an H_2 blocker.

TABLES

Table 1. Details of medications received by patients treated with docetaxel as an adjuvant or neoadjuvant chemotherapeutic treatment for breast cancer

Factor	Category	No. of patients	No. of institutions
Total no. patients		993 (100.0%)	20
Docetaxel dose (mg/m^2)	25	6 (0.6%)	1
	60	10 (1.0%)	3
	70	35 (3.5%)	1
	75	760 (76.5%)	15
	80	80 (8.1%)	1
	Other	102 (10.3%)	3
Regimen	T	852 (85.8%)	20
	TC	74 (7.5%)	11
	TX	43 (4.3%)	8
	TH	24 (2.4%)	6
Medication			
H2 Blocker	-	718 (72.3%)	12
	+	195 (19.6%)	6
	Ranitidine	87 (8.8%)	3
	Famotidine	73 (7.4%)	2
	Lafutidine	35 (3.5%)	1
	Dependent on patient	80 (8.1%)	2
D1 Dex (mg)	6	45 (4.5%)	1
	8	460 (46.3%)	9
	10	112 (11.3%)	2
	12	197 (19.8%)	4
	16	110 (11.1%)	3
	20	6 (0.6%)	1
	21	62 (6.2%)	1
	24	1 (0.1%)	1
D2 Dex (mg)	0	80 (8.1%)	5

	2	146 (14.7%)	3
	4	158 (15.9%)	6
	8	532 (53.6%)	8
	16	75 (7.6%)	2
	18	2 (0.2%)	1

T, docetaxel monotherapy; TC, docetaxel + cyclophosphamide; TX, docetaxel + capecitabine; TH, docetaxel + trastuzumab; D1 Dex, dose of dexamethasone used on day 1; D2 Dex, dose of dexamethasone used on day 2.

Table 2. Relationship between the incidence of hand-food syndrome (HFS) and facial erythema (FE) and institutional policies for use of H_2 blockers, steroids, and chemotherapy regimens (univariate analysis)

		Incidence	Odds ratio	95% CI	*P* value
HFS					
H2 blocker	-	66/718 (9.2%)	Reference	—	—
	+	40/195 (20.5%)	2.55	(1.66, 3.92)	<0.001
	Ranitidine	7/87 (8.1%)	0.86	(0.38, 1.95)	0.725
	Famotidine	14/73 (19.2%)	2.34	(1.24, 4.43)	0.009
	Lafutidine	19/35 (54.3%)	11.73	(5.76, 23.89)	<0.001
D1 steroid (mg/day)	≤8	76/505 (15.0%)	Reference	—	—
	>8	81/488 (16.6%)	1.12	(0.80, 1.58)	0.504
D2 steroid (mg/day)	≤8	143/916 (15.6%)	Reference	—	—
	>8	14/77 (18.2%)	1.20	(0.66, 2.20)	0.553
Regimen	Non-TC	149/919 (16.2%)	Reference		-
	TC	8/74 (10.8%)	0.58	(0.23, 1.46)	0.245
FE					
H2 blocker	-	25/718 (3.5%)	Reference	—	—
	+	28/195 (14.4%)	3.00	(2.64, 8.18)	<0.001
	Ranitidine	8/87 (9.2%)	2	(1.23, 6.43)	0.015
	Famotidine	6/73 (8.2%)	1	(0.98, 6.26)	0.054
	Lafutidine	14/35 (40.0%)	18.48	(8.43, 40.52)	<0.001
D1 steroid (mg/day)	≤8	39/505 (7.7%)	Reference	—	—
	>8	64/488 (13.1%)	1.80	(1.19, 2.74)	0.006
D2 steroid (mg/day)	≤8	100/916 (10.9%)	Reference	—	—
	>8	3/77 (10.3%)	0.33	(0.10, 1.07)	0.065
Regimen	Non-TC	91/919 (9.9%)	Reference	—	—
	TC	12/74 (16.2%)	2.73	(1.27, 5.85)	0.010

TC, docetaxel + cyclophosphamide; Non-TC, includes docetaxel monotherapy, docetaxel + capecitabine, and docetaxel + trastuzumab. D1 steroid, dose of dexamethasone used on day 1; D2 steroid, dose of dexamethasone used on day 2.

Table 3. Relationship between incidence of hand-foot syndrome (HFS) and facial erythema (FE) and institutional policies on day 1 steroid dose, H_2 blocker usage and chemotherapy regimen (multivariate analysis)

Event	Factor	Usage	Odds ratio	95% CI	*P* value
HFS	H_2 blocker	-	Reference	—	—
		+	2.88	(1.78, 4.67)	<0.001
		Ranitidine	1.10	(0.46, 2.64)	0.833
		Famotidine	2.45	(1.28, 4.67)	0.007
		Lafutidine	14.52	(6.61, 31.89)	<0.001
	D1 steroid (mg/day)	≤8	Reference	—	—
		>8	0.70	(0.43, 1.13)	0.145
	Regimen	Non-TC	Reference	—	—
		TC	0.77	(0.30, 1.99)	0.595
FE	H_2 blocker	-	Reference	—	—
		+	4.09	(2.17, 7.70)	<0.001
		Ranitidine	2.17	(0.86, 5.47)	0.101
		Famotidine	2.92	(1.12, 7.60)	0.028
		Lafutidine	18.75	(7.66, 45.92)	<0.001
	D1 steroid (mg/day)	≤8	3	—	—
		>8	2	(0.70, 3.01)	0.319
	Regimen	Non-TC	1	—	—
		TC	4.29	(1.89, 9.73)	<0.001

TC, docetaxel + cyclophosphamide; Non-TC, includes docetaxel monotherapy, docetaxel + capecitabine, and docetaxel + trastuzumab; D1 steroid, dose of dexamethasone used on day 1.

Table 4. Relationship between incidence of hand-foot syndrome (HFS) and facial erythema (FE) and institutional policies on day 2 steroid dose, H_2 blocker usage and chemotherapy regimen (multivariate analysis)

Event	Factor	Usage	Odds ratio	95% CI	*P* value
HFS	H_2 blocker	-	Reference	—	—
		+	2.42	(1.56, 3.74)	<0.001
		Ranitidine	0.91	(0.40, 2.06)	0.822
		Famotidine	1.85	(0.91, 3.74)	0.089
		Lafutidine	11.97	(5.84, 24.5)	<0.001
	D2 steroid (mg/day)	≤8	Reference	—	—
		>8	1.74	(0.86, 3.51)	0.121
	Regimen	Non-TC	Reference	—	—
		TC	0.74	(0.29, 1.90)	0.528
FE	H_2 blocker	-	Reference	—	—
		+	5.31	(2.97, 9.47)	<0.001
		Ranitidine	2.58	(1.11, 6.01)	0.029
		Famotidine	3.72	(1.35, 10.28)	0.011
		Lafutidine	22.46	(9.96, 50.63)	<0.001
	D2 steroid (mg/day)	≤8	3	—	—
		>8	2	(0.15, 2.09)	0.392
	Regimen	Non-TC	1	—	—
		TC	4.42	(1.95, 10.05)	<0.001

TC, docetaxel + cyclophosphamide; Non-TC, includes docetaxel monotherapy, docetaxel + capecitabine, and docetaxel + trastuzumab; D2 steroid, dose of dexamethasone used on day 2.

Figure
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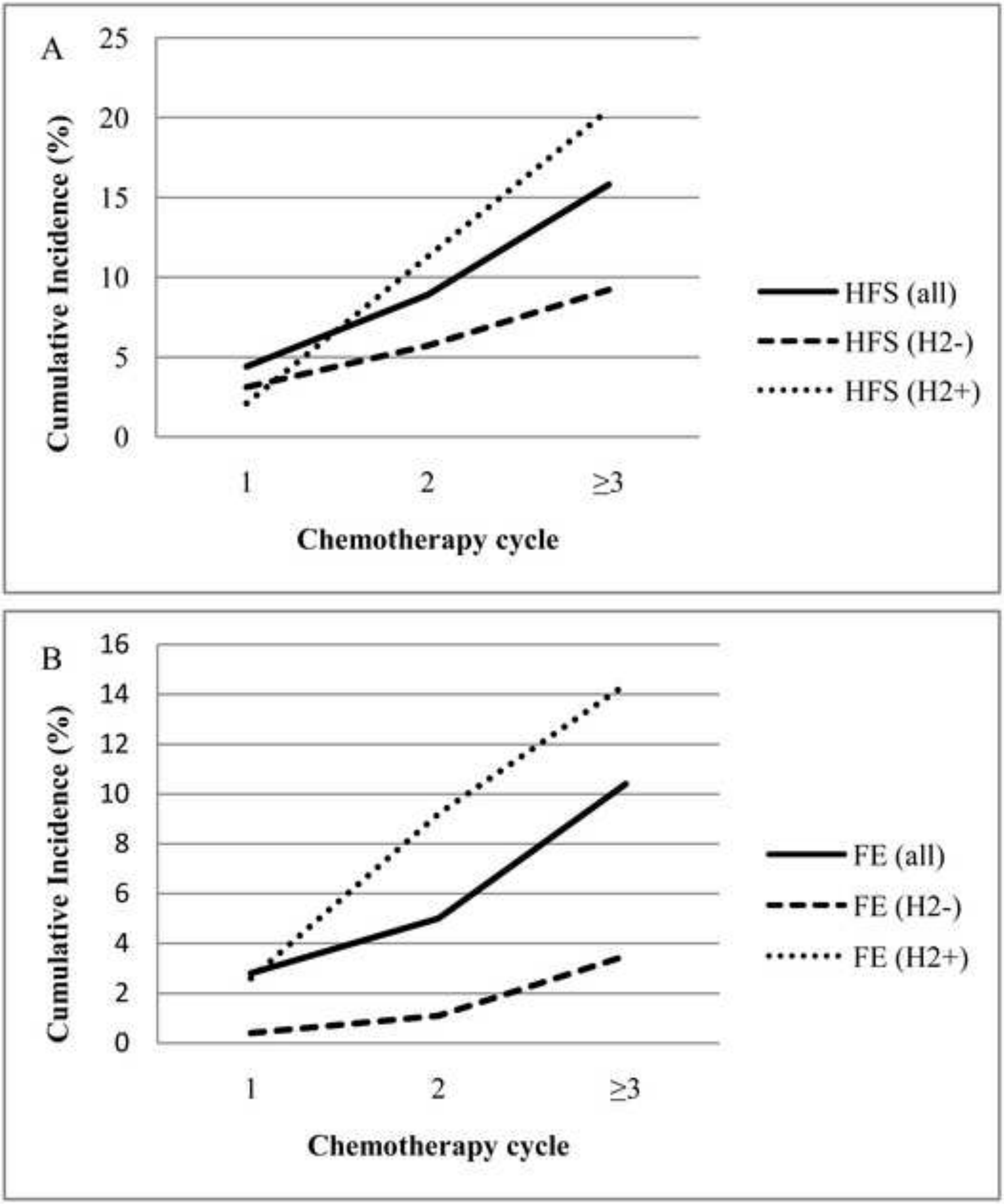

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Author(s): K Kawaguchi, H Ishiguro, S Morita, S Nakamura, S Ohno, N Masuda, H Iwata, K Aogi, K Kuroi, M Toi

Author's signature: H. Ishiguro, on behalf of all authors

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