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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

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Running Head

H_2 blockers increase incidence of docetaxel-induced skin toxicity

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.

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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

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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.

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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.

References

1.   Harvey V, Mouridsen H, Semiglazov V, Jakobsen E, Voznyi E, Robinson BA, Groult V,

Murawsky M, Cold S (2006) Phase III trial comparing three doses of docetaxel for second-line treatment

of advanced breast cancer. J Clin Oncol 24 (31):4963-4970. doi:JCO.2005.05.0294 [pii]

10.1200/JCO.2005.05.0294

2.   Vogel CL, Wojtukiewicz MZ, Carroll RR, Tjulandin SA, Barajas-Figueroa LJ,

Wiens BL, Neumann TA, Schwartzberg LS (2005) First and subsequent cycle use of pegfilgrastim

prevents febrile neutropenia in patients with breast cancer: a multicenter, double-blind, placebo-controlled

phase III study. J Clin Oncol 23 (6):1178-1184. doi:23/6/1178 [pii] 10.1200/JCO.2005.09.102

3.   Piccart MJ, Klijn J, Paridaens R, Nooij M, Mauriac L, Coleman R, Bontenbal M,

Awada A, Selleslags J, Van Vreckem A, Van Glabbeke M (1997) Corticosteroids significantly delay the

onset of docetaxel-induced fluid retention: final results of a randomized study of the European

Organization for Research and Treatment of Cancer Investigational Drug Branch for Breast Cancer. J

Clin Oncol 15 (9):3149-3155

4.   Y. Suh CC, S. Oh, B. Song, S. Jung (2008) Comparison of one-day premedication

for TAC chemotherapy with three-day regimen for node-positive breast cancer patients. J Clin Oncol 26:

2008 (May 20 suppl; abstr 621)

5.   McCune JS, Hawke RL, LeCluyse EL, Gillenwater HH, Hamilton G, Ritchie J,

Lindley C (2000) In vivo and in vitro induction of human cytochrome P4503A4 by dexamethasone. Clin

Pharmacol Ther 68 (4):356-366. doi:S0009-9236(00)50713-9 [pii] 10.1067/mcp.2000.110215

6.   Ishiguro H, Yano I, Toi M (2009) Important drug interactions for clinical oncologists.

In Caldwell GW, Atta-ur-Rahman, Yan Z, Choudhary MI, et al. (eds) Frontiers in Drug Design and

Discovery, Vol. 4. Dubai: Bentham Science Publishers   pp 97-121.

7.   Murray LS, Jodrell DI, Morrison JG, Cook A, Kerr DJ, Whiting B, Kaye SB,

Cassidy J (1998) The effect of cimetidine on the pharmacokinetics of epirubicin in patients with advanced

breast cancer: preliminary evidence of a potentially common drug interaction. Clin Oncol (R Coll Radiol)

10 (1):35-38

8.   Harvey VJ, Slevin ML, Dilloway MR, Clark PI, Johnston A, Lant AF (1984) The

influence of cimetidine on the pharmacokinetics of 5-fluorouracil. Br J Clin Pharmacol 18 (3):421-430

9.   Koch M, Dezi A, Ferrario F, Capurso I (1996) Prevention of nonsteroidal

anti-inflammatory drug-induced gastrointestinal mucosal injury. A meta-analysis of randomized

controlled clinical trials. Arch Intern Med 156 (20):2321-2332

10.   O'Shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub JP, Cervantes G,

Fumoleau P, Jones S, Lui WY, Mauriac L, Twelves C, Van Hazel G, Verma S, Leonard R (2002)

Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated

patients with advanced breast cancer: phase III trial results. J Clin Oncol 20 (12):2812-2823

11.   Chan S, Romieu G, Huober J, Delozier T, Tubiana-Hulin M, Schneeweiss A, Lluch

A, Llombart A, du Bois A, Kreienberg R, Mayordomo JI, Anton A, Harrison M, Jones A, Carrasco E,

Vaury AT, Frimodt-Moller B, Fumoleau P (2009) Phase III study of gemcitabine plus docetaxel

compared with capecitabine plus docetaxel for anthracycline-pretreated patients with metastatic breast

cancer. J Clin Oncol 27 (11):1753-1760. doi:JCO.2007.15.8485 [pii] 10.1200/JCO.2007.15.8485

12.   Marre F, Sanderink GJ, de Sousa G, Gaillard C, Martinet M, Rahmani R (1996)

Hepatic biotransformation of docetaxel (Taxotere) in vitro: involvement of the CYP3A subfamily in

humans. Cancer Res 56 (6):1296-1302

13.   Clarke SJ, Rivory LP (1999) Clinical pharmacokinetics of docetaxel. Clin

Pharmacokinet 36 (2):99-114

14.   Engels FK, Ten Tije AJ, Baker SD, Lee CK, Loos WJ, Vulto AG, Verweij J,

Sparreboom A (2004) Effect of cytochrome P450 3A4 inhibition on the pharmacokinetics of docetaxel.

Clin Pharmacol Ther 75 (5):448-454. doi:10.1016/j.clpt.2004.01.001 S0009923604000074 [pii]

15.   Lamba JK, Lin YS, Schuetz EG, Thummel KE (2002) Genetic contribution to

variable human CYP3A-mediated metabolism. Adv Drug Deliv Rev 54 (10):1271-1294.

doi:S0169409X02000662 [pii]

16.   Felici A, Verweij J, Sparreboom A (2002) Dosing strategies for anticancer drugs: the

good, the bad and body-surface area. Eur J Cancer 38 (13):1677-1684. doi:S095980490200151X [pii]

17.   Bruno R, Hille D, Riva A, Vivier N, ten Bokkel Huinnink WW, van Oosterom AT,

Kaye SB, Verweij J, Fossella FV, Valero V, Rigas JR, Seidman AD, Chevallier B, Fumoleau P, Burris

HA, Ravdin PM, Sheiner LB (1998) Population pharmacokinetics/pharmacodynamics of docetaxel in

phase II studies in patients with cancer. J Clin Oncol 16 (1):187-196

18.   Scotte F, Tourani JM, Banu E, Peyromaure M, Levy E, Marsan S, Magherini E,

Fabre-Guillevin E, Andrieu JM, Oudard S (2005) Multicenter study of a frozen glove to prevent

docetaxel-induced onycholysis and cutaneous toxicity of the hand. J Clin Oncol 23 (19):4424-4429.

doi:23/19/4424 [pii] 10.1200/JCO.2005.15.651

19.   Battegay EJ (1995) Angiogenesis: mechanistic insights, neovascular diseases, and

therapeutic prospects. J Mol Med 73 (7):333-346

20.   Wasner G, Hilpert F, Schattschneider J, Binder A, Pfisterer J, Baron R (2002)

Docetaxel-induced nail changes--a neurogenic mechanism: a case report. J Neurooncol 58 (2):167-174

21.   Mukohara T, Takeda K, Miyazaki M, Takifuji N, Terakawa K, Negoro S (2001)

Japanese experience with second-line chemotherapy with low-dose (60 mg/M2) docetaxel in patients with

advanced non-small-cell lung cancer. Cancer Chemother Pharmacol 48 (5):356-360

22.   Semb KA, Aamdal S, Oian P (1998) Capillary protein leak syndrome appears to

explain fluid retention in cancer patients who receive docetaxel treatment. J Clin Oncol 16

(10):3426-3432

23.   Weiss RB, Donehower RC, Wiernik PH, Ohnuma T, Gralla RJ, Trump DL, Baker

JR, Jr., Van Echo DA, Von Hoff DD, Leyland-Jones B (1990) Hypersensitivity reactions from taxol. J

Clin Oncol 8 (7):1263-1268

24.   Taha AS, Hudson N, Hawkey CJ, Swannell AJ, Trye PN, Cottrell J, Mann SG,

Simon TJ, Sturrock RD, Russell RI (1996) Famotidine for the prevention of gastric and duodenal ulcers

caused by nonsteroidal antiinflammatory drugs. N Engl J Med 334 (22):1435-1439

25.   Bjornsson TD, Callaghan JT, Einolf HJ, Fischer V, Gan L, Grimm S, Kao J, King SP,

Miwa G, Ni L, Kumar G, McLeod J, Obach RS, Roberts S, Roe A, Shah A, Snikeris F, Sullivan JT,

Tweedie D, Vega JM, Walsh J, Wrighton SA (2003) The conduct of in vitro and in vivo drug-drug

interaction studies: a Pharmaceutical Research and Manufacturers of America (PhRMA) perspective.

Drug Metab Dispos 31 (7):815-832. doi:10.1124/dmd.31.7.815 31/7/815 [pii]

26.   de Jonge ME, Huitema AD, van Dam SM, Rodenhuis S, Beijnen JH (2005)

Population pharmacokinetics of cyclophosphamide and its metabolites 4-hydroxycyclophosphamide,

2-dechloroethylcyclophosphamide, and phosphoramide mustard in a high-dose combination with

Thiotepa and Carboplatin. Ther Drug Monit 27 (6):756-765. doi:00007691-200512000-00018 [pii]

27.   Buzdar AU, Cuzick J (2006) Anastrozole as an adjuvant endocrine treatment for

postmenopausal patients with breast cancer: emerging data. Clin Cancer Res 12 (3 Pt 2):1037s-1048s.

doi:12/3/1037s [pii] 10.1158/1078-0432.CCR-05-2458

28.	Stearns V, Johnson MD, Rae JM, Morocho A, Novielli A, Bhargava P, Hayes DF,

Desta Z, Flockhart DA (2003) Active tamoxifen metabolite plasma concentrations after coadministration

of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. J Natl Cancer Inst 95

(23):1758-1764

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.

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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.

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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.
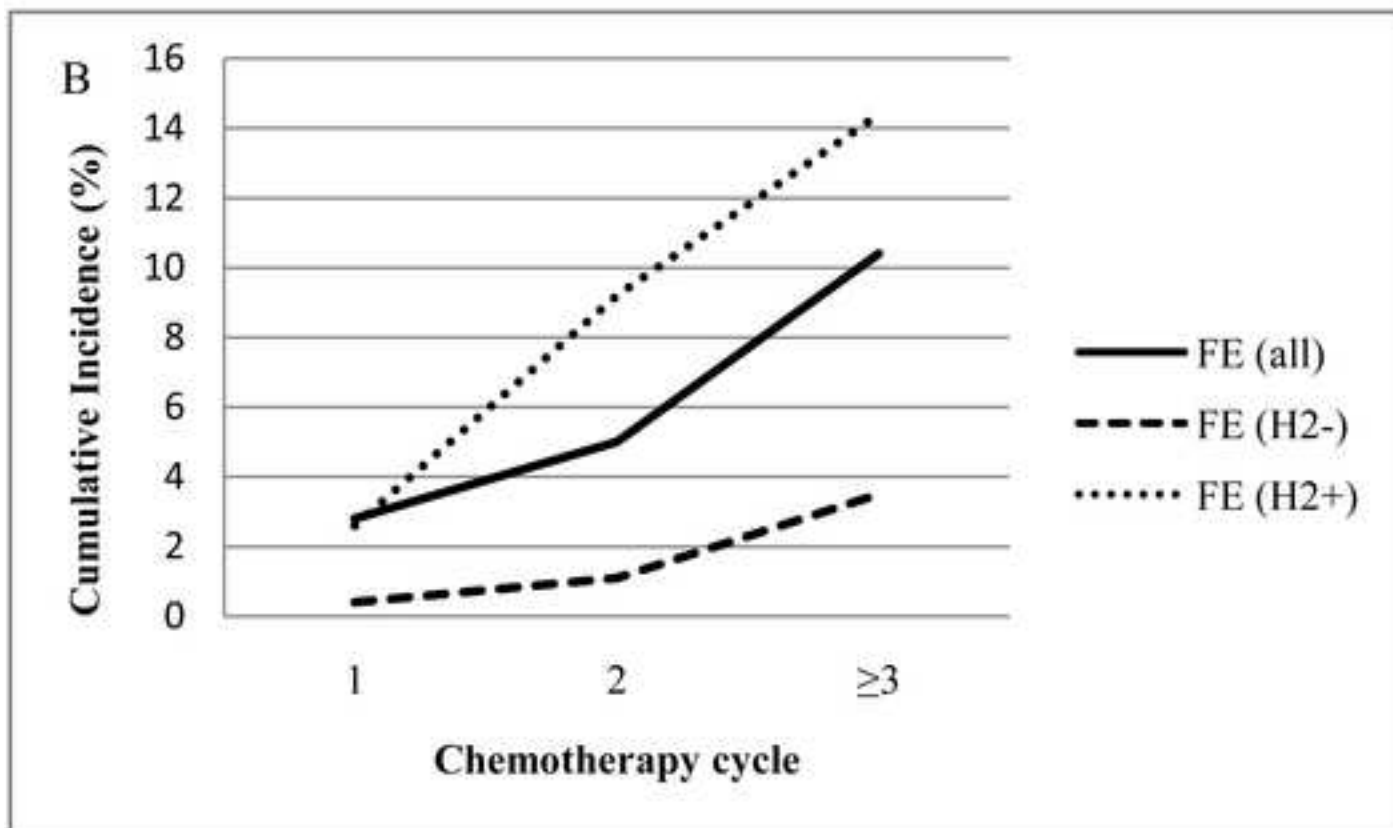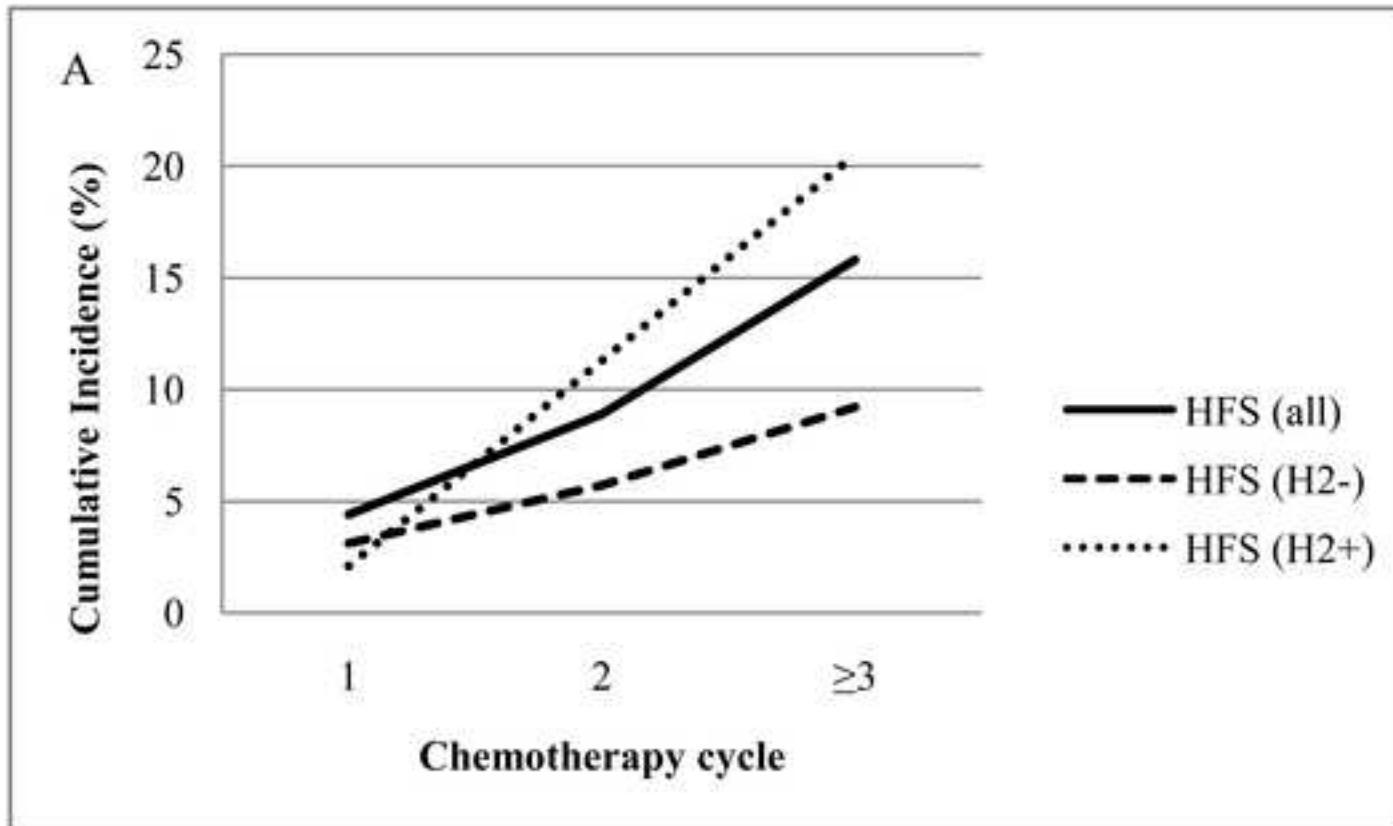
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