

Regular Article

Effects of Diluent Volume and Administration Time on the Incidence of Anaphylaxis Following Docetaxel Therapy in Breast Cancer

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Hypersensitivity reactions, including anaphylaxis, are common side effects associated with docetaxel treatment in breast cancer patients. However, preventive measures have not yet been established. In this study, we retrospectively analyzed the risk factors for developing anaphylaxis in 182 female breast cancer patients treated with docetaxel. We found that 6.6% of all patients ($n = 12$) experienced anaphylaxis. Multivariate analyses indicated that concentration of docetaxel higher than 0.275 mg/m²/mL, docetaxel dose rate higher than 1.15 mg/m²/min, and white blood cell count less than 4290 cells/mL are risk factors for developing docetaxel-related anaphylaxis. In particular, concentrations of docetaxel or doses per administration time were associated with a high odds ratio (11.88 or 11.60) for docetaxel-related anaphylaxis. Moreover, patients receiving doses in 250 mL volume experienced anaphylaxis more frequently than those receiving doses in 500 mL (7.0 vs. 0.9%, $p = 0.0236$). Additionally, patients receiving treatments over 60 min tended to experience anaphylaxis more frequently than those who were treated over 90 min (6.7 vs. 1.1%, $p = 0.0637$). The present results indicate that high docetaxel concentrations, high dose rates, and low white blood cell counts are risk factors for developing docetaxel-related anaphylaxis, and administering docetaxel diluted in 500 mL over 90 min may limit docetaxel-induced hypersensitivity reactions.

Key words docetaxel; anaphylaxis; hypersensitivity reaction; diluent volume; administration time

INTRODUCTION

Docetaxel, an antineoplastic agent of the taxoid family, is prepared by hemisynthesis from 10-deacetyl-baccatin III, which is an inactive precursor derived from the European yew, *Taxus baccata*.¹⁾ Docetaxel promotes tubulin polymerization, forming stable microtubules and suppressing depolymerization. In addition, docetaxel promotes the formation of morphologically abnormal microtubule bundles.²⁾ Docetaxel is widely used in the treatment of various cancers, including breast, head and neck, lung, and stomach cancers. In particular, docetaxel is an essential postoperative adjuvant chemotherapy in breast cancer patients, as indicated abundantly in several clinical studies.³⁾ However, docetaxel is known to cause adverse effects in some patients. Some of these adverse effects, such as bone marrow and gastrointestinal toxicities, have now become manageable due to the development of granulocyte colony-stimulating factor (G-CSF)⁴⁾ and serotonin type 3 receptor antagonists⁵⁾; consequently, adverse events related to cutaneous toxicities have gained significance.

Treatment with docetaxel sometimes causes hypersensitivity reactions, such as anaphylaxis, dyspnea, bronchospasm, urticaria, flushing, rashes, hypotension, and angioedema.^{6,7)} Although these symptoms indicate type I allergic reactions, they appear without any history of past exposure or sensitization; thus, these symptoms are presumed to be immunoglobulin E-independent reactions associated with mast cell degranulation.^{8,9)} Studies performed using information found in the U.S.

Food and Drug Administration (FDA) adverse event reporting system have reported that patients treated with docetaxel developed lethal hypersensitivity reactions at a higher rate than those treated with other chemotherapeutic agents, including the closely-related taxane drug, paclitaxel.^{10,11)}

Dexamethasone, diphenhydramine, and histamine type 2 receptor antagonists have been reported to be effective in the prophylaxis of hypersensitivity induced by paclitaxel.¹²⁾ However, despite premedication with such drugs, hypersensitivity reactions to paclitaxel have been found to occur in 41% of patients.¹³⁾ Although many reports indicated that patients with docetaxel-induced hypersensitivity reactions can be desensitized,^{14–18)} no strategies have been developed for the prevention of hypersensitivity. Moreover, discontinuation of docetaxel treatment due to the development of hypersensitivity adversely affects the patients as it results in narrowed treatment options and inability to receive a standard and effective treatment.

In this study, we analyzed the risk factors for docetaxel-induced anaphylaxis in breast cancer patients. In particular, we compared the incidence of anaphylaxis induced by docetaxel treatments, depending on the difference of diluent volumes and administration times.

PATIENTS AND METHODS

Patients This study included breast cancer patients who started monotherapy/combination chemotherapy with

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docetaxel between April 1, 2014 and February 28, 2017 in Kyushu University Hospital. No patients were excluded due to other severe toxicities or other complications. This study was approved by the ethics committee of Kyushu University Graduate School and Faculty of Medicine (Approval number 28-206), and was performed in accordance with the Declaration of Helsinki and its amendments.

Treatments Chemotherapeutic treatment consisted of docetaxel (75–100 mg/m²) administered intravenously on day 1 every 3 weeks. Doctors could choose an administration time of 60 or 90 min and a diluent volume of 250 or 500 mL for docetaxel used for breast cancer patients in our hospital. Dexamethasone (8.8 mg) and granisetron (3 mg) were administered intravenously as premedication prior to docetaxel. Dose reduction was performed in some patients based on the judgment of the patients' physicians. Other medications for underlying diseases, complications, and pain control were allowed.

Data Collection and Assessment The anaphylaxis was judged by doctors from the vital signs, skin symptoms, or other related symptoms. We retrospectively collected the anaphylaxis data from the electronic charts. Patient characteristics (e.g., age and body sizes), docetaxel doses, diluent volumes, administration times, treatment regimens, and laboratory data were collected from patients immediately before each treatment.

Statistical Analyses Differences between patients with and without anaphylaxis were identified using either Mann–Whitney *U* tests or Chi-square tests. Cut-off values were then determined using receiver operating characteristic (ROC) analyses of potential risk factors with *p*-values of <0.1. Odds ratios for risk factors were calculated using logistic regression analyses. We performed two independent multivariate analyses, because “dose/diluent volumes” and “dose/administration times” are relevant confounding factors for each other. We used Fisher's exact test to compare ratios of anaphylaxis in the first cycle between patients receiving treatments diluted in either 250 or 500 mL normal saline and between patients receiving treatments for either 60 or 90 min. Data were analyzed using StatView (Abacus Concepts, CA, U.S.A.). Differences and associations were considered significant when *p* < 0.05.

RESULTS

Patient Characteristics and Incidence of Anaphylaxis

Docetaxel was administered to 182 female breast cancer patients. Patient characteristics are shown in Table 1. Twelve of 182 patients (6.6%) experienced docetaxel-related anaphylaxis, but no hypersensitivity reactions were lethal. Only one patient presented anaphylaxis symptoms during the infusion of trastuzumab. We did not consider this case as docetaxel-related hypersensitivity, because the anaphylaxis was not caused by docetaxel. Almost all anaphylaxis incidents occurred during the first or second treatment with docetaxel.

Risk Factors for Docetaxel-Related Anaphylaxis A total of 767 docetaxel treatment cycles were performed in 182 patients, and anaphylaxis was recorded in only 12 of all treatment cycles. Table 2 shows comparisons of several factors between patient groups with and without anaphylactic reactions. Patient groups did not differ in body surface areas (BSA), body weights, heights, body mass index (BMI), or in chosen regimens. On the other hand, treatment dose, dose per

Table 1. Patient Characteristics and Incidence of Anaphylaxis

Characteristic	
Number of patients	182
Sex	
Male	0
Female	182 (100%)
Age, median (range)	56 (26–78)
Regimen	
Docetaxel alone	84 (46.2%)
Docetaxel and trastuzumab	69 (37.9%)
Docetaxel and cyclophosphamide	19 (10.4%)
Docetaxel, pertuzumab, and trastuzumab	7 (3.8%)
Docetaxel, doxorubicin, and cyclophosphamide	1 (0.5%)
Incidence of anaphylaxis	12 (6.6%)
First cycle	6 (3.3%)
Second cycle	5 (2.7%)
After third cycle	1 (0.5%)

diluent volumes, and dose/administration times in the anaphylaxis group were significantly higher than those in the no-anaphylaxis group (median: 73.0 vs. 67.9 mg/m², *p* = 0.0027; 0.29 vs. 0.24 mg/m²/mL, *p* = 0.0014; 1.20 vs. 1.00 mg/m²/min, *p* = 0.0017). Moreover, patients with anaphylaxis had lower levels of white blood cells (4120 vs. 5410 cells/mL, *p* = 0.0500) and higher serum albumin levels (4.4 vs. 4.0 g/dL, *p* = 0.0045) than those who did not experience anaphylaxis. We did not detect differences in any other laboratory variables between the patients with or without anaphylaxis. Patients with anaphylaxis tended to be younger than patients without anaphylaxis (48 vs. 58 years old, *p* = 0.0707).

In multivariate analyses, cut-off values were determined for age, dose per diluent volumes, dose/administration times, white blood cell counts, and serum albumin; all values had associated *p*-values of less than 0.1, as shown in Table 2. Respective cut-off values were <48 years of age, >0.275 mg/m²/mL docetaxel dose per diluent volumes, >1.15 mg/m²/min docetaxel administration times, <4290 white blood cells/mL, and >4.3 g/dL serum albumin (Fig. 1).

Dose volumes and administration times confounded each other; hence, we performed independent multivariate analyses for both (Table 3). In analyses of dose volumes with age, white blood cell counts, and serum albumin as independent variables, dose volumes (>0.275 mg/m²/mL) was identified as a risk factor for docetaxel-related anaphylaxis (odds ratio, 11.88; 95% confidence interval 2.43–58.16; *p* = 0.0023). Moreover, analyses of administration times with age, white blood cell counts, and serum albumin as independent variables showed that administration times of >1.15 mg/m²/min was a risk factor for anaphylaxis (odds ratio, 11.60; 95% confidence interval 2.37–56.79; *p* = 0.0025). White blood cell counts (<4290 cells/mL) was also a risk factor in both analyses.

Effects of Diluent Volumes and Administration Times on Anaphylaxis Patients treated with docetaxel in a diluent volume of 250 mL experienced anaphylaxis more frequently than those treated with docetaxel in a diluent volume of 500 mL (7.0 vs. 0.9%, *p* = 0.0236, Table 4). Moreover, patients who were treated over 60 min tended to experience anaphylaxis more frequently than those who were treated over 90 min (6.7 vs. 1.1%, *p* = 0.0637, Table 4).

Table 2. Risk Factors for Docetaxel-Related Anaphylaxis (Univariate Analyses)

Factor	Without anaphylaxis 755 cycles	With anaphylaxis 12 cycles	<i>p</i> -Values
Age	58 (26–78)	48 (36–70)	0.0707 ^{a)}
Body size			
BSA (m ²)	1.53 (1.23–2.00)	1.47 (1.41–1.64)	0.1476 ^{a)}
Body weight (kg)	54.3 (37.7–100.0)	50.5 (45.0–60.0)	0.1210 ^{a)}
Height (m)	1.56 (1.41–1.71)	1.55 (1.48–1.65)	0.8566 ^{a)}
BMI (kg/m ²)	21.8 (15.2–40.1)	21.8 (16.5–22.7)	0.3501 ^{a)}
Administration			
Dose of docetaxel (mg/m ²)	67.9 (37.1–78.9)	73.0 (66.0–75.1)	0.0027^{a)}
Dose/diluent volumes (mg/m ² /mL)	0.24 (0.10–0.32)	0.29 (0.15–0.30)	0.0014^{a)}
Dose/administration times (mg/m ² /min)	1.00 (0.48–1.32)	1.20 (0.83–1.25)	0.0017^{a)}
Regimens			0.7737 ^{b)}
Docetaxel alone	371 (49.1%)	6 (50.0%)	
Docetaxel and trastuzumab	251 (33.2%)	4 (33.3%)	
Docetaxel and cyclophosphamide	66 (8.7%)	2 (16.7%)	
Docetaxel, pertuzumab, and trastuzumab	56 (7.4%)	0	
Docetaxel, doxorubicin, and cyclophosphamide	5 (0.7%)	0	
Laboratory data			
WBC (counts/mL)	5410 (1540–14540)	4120 (3400–10190)	0.0500^{a)}
NEUT (counts/mL)	3586 (639–10938)	2491 (1918–7755)	0.0652 ^{a)}
Alb (g/dL)	4.0 (2.6–4.9)	4.4 (3.8–4.7)	0.0045^{a)}
CCr (mL/min)	94.2 (11.8–216.3)	104.4 (54.0–158.5)	0.2907 ^{a)}
BUN (mg/dL)	12 (4–28)	12 (8–19)	0.9417 ^{a)}
AST (U/L)	24 (10–162)	21 (16–43)	0.2058 ^{a)}
ALT (U/L)	18 (6–114)	15 (16–43)	0.2033 ^{a)}
CRP (mg/dL)	0.10 (0.01–10.22)	0.08 (0.02–0.68)	0.7605 ^{a)}

BSA, body surface area; BMI, body mass index; WBC, white blood cells; NEUT, neutrophils; Alb, serum albumin; CCr, creatinine clearance calculated by Cockcroft–Gault equation; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein. *a)* Mann–Whitney *U* test; *b)* Chi-square test.

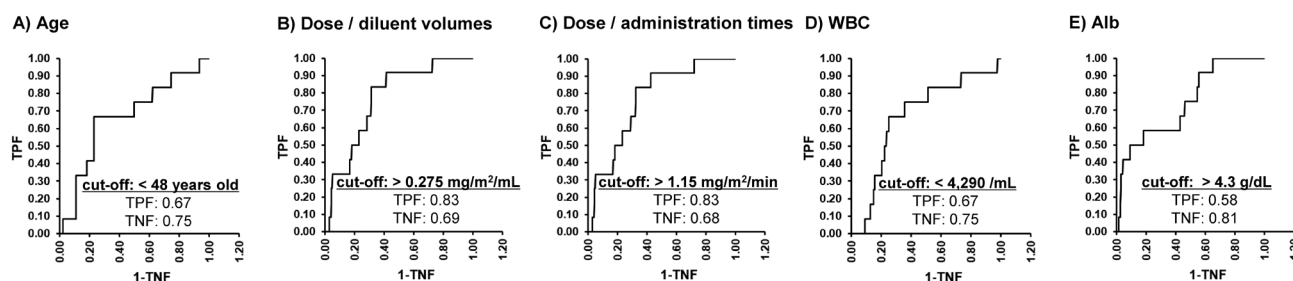


Fig. 1. ROC Analyses of Anaphylaxis and Cut-Off Values for Age (A), Dose/Diluent Volumes (B), Dose/Administration Times (C), White Blood Cell (WBC) Counts (D), and Serum Albumin (Alb) Levels (E)

Cut-off values, true positive fractions (TPF), and true negative fractions (TNF) are shown in each figure.

DISCUSSION

Anaphylactic reactions occurred in 6.6% of patients treated with docetaxel, and in almost all cases, symptoms appeared during the first or second treatment cycles. These results are in agreement with previous studies, which reported docetaxel-related hypersensitivity in 3–28% of patients and severe reactions in 1–5% of the patients.^{19–23)} Although lethal hypersensitivity reactions were identified as serious side effects of docetaxel in studies using the FDA adverse event reporting systems,^{10,11)} no fatal anaphylactic reactions occurred in the present study.

Our analyses indicated that concentration of docetaxel >0.275 mg/m²/mL, dosing rate >1.15 mg/m²/min, and white blood cell counts <4290 cells/mL are risk factors for the development of docetaxel-related anaphylaxis. Moreover, in our logistic regression analyses, dose volumes and administra-

tion times of docetaxel were associated with high odds ratios (11.88 and 11.60, respectively). Thus, it may be preferable to avoid docetaxel concentrations higher than 0.275 mg/m²/mL and administration rates more than 1.15 mg/m²/min.

In our hospital, two docetaxel regimens were used, with dilution volumes of 250 or 500 mL and administration times of 60 or 90 min. In breast cancer patients, docetaxel is generally used at a dose of 75^{24–27)} or 100 mg/m².^{28–30)} Hence, when docetaxel is administered at a dose of 75 or 100 mg/m² in a volume of 250 mL, the concentration of docetaxel is 0.3 or 0.4 mg/m²/mL, both of which are higher than 0.275 mg/m²/mL. In contrast, when docetaxel is administered at the same dose, in a volume of 500 mL, the docetaxel concentration achieved is either 0.15 or 0.2 mg/m²/mL. In these conditions, the corresponding administration rate of docetaxel infused over 60 min is 1.25 or 1.667 mg/m²/min, which is above the cut-off value of 1.15 mg/m²/min. However, the administration rate of docetaxel

Table 3. Risk Factors for Docetaxel-Related Anaphylaxis (Multivariate Analyses)

Factor	Odds ratio (95% CI)	<i>p</i> -Values
First cycle	2.66 (0.71–9.94)	0.1469
Age (<48 years old)	3.53 (0.93–13.33)	0.0634
Dose/diluent volumes (>0.275 mg/m ² /mL)	11.88 (2.43–58.16)	0.0023
WBC (<4290 counts/mL)	3.76 (1.04–13.62)	0.0437
Alb (>4.3 g/dL)	2.81 (0.75–10.52)	0.1243
Factor	Odds ratio (95% CI)	<i>p</i> -Values
First cycle	2.62 (0.70–9.76)	0.1516
Age (<48 years old)	3.47 (0.94–13.40)	0.0626
Dose/administration times (>1.15 mg/m ² /min)	11.60 (2.37–56.79)	0.0025
WBC (<4290 counts/mL)	3.82 (1.06–13.82)	0.0410
Alb (>4.3 g/dL)	2.87 (0.77–10.74)	0.1164

WBC, white blood cells; Alb, serum albumin; 95% CI, 95% confidence interval. We performed two independent multivariate analyses, because “dose/diluent volumes” and “dose/administration times” are relevant confounding factors for each other. The upper table shows the result from multivariate analysis using “dose/diluent volumes,” and lower one shows the results using “dose/administration times.”

Table 4. Effects of Diluent Volumes and Administration Times on the Incidence of Docetaxel-Related Anaphylaxis

Administration	Without anaphylaxis	With anaphylaxis	Ratio	<i>p</i> -Values
Diluent volume				
250 mL	66	5	7.0%	0.0236
500 mL	110	1	0.9%	
Administration time				
60 min	70	5	6.7%	0.0637
90 min	86	1	1.1%	

over 90 min is determined as 0.833 or 1.111 mg/m²/min, with the incidence of anaphylaxis in patients administered the drug in a 500 mL volume being significantly lower than that in patients receiving docetaxel in a 250 mL volume. Moreover, 90-min treatments tended to induce anaphylaxis less frequently than 60-min treatments. These observations suggest that increasing the dilution volume administered and extending the duration of administration could be effective strategies to avoid docetaxel-related anaphylaxis. However, we did not define optimal concentrations or dilution volumes for the evasion of anaphylaxis, since almost all patients using the diluent volume of 500 mL were administered docetaxel over 90 min. Few patients were administered docetaxel in a volume of 500 mL over 60 min, or in a volume of 250 mL over 90 min.

Younger age and high levels of albumin were identified as potential risk factors in the univariate analysis, as shown in Table 2. A previous report also indicated that younger age is a predictor for hypersensitivity in patients receiving paclitaxel-based therapy.³¹⁾ Hence, there is a relationship between hypersensitivity to taxanes and age. Meanwhile, docetaxel is a drug with a high protein-binding rate, and its effects are expected to change with alternations in the blood levels of proteins such as alpha 1-acid glycoprotein.³²⁾ Consistent with this idea is the hypothesis that albumin levels might cause changes in docetaxel-related anaphylaxis. Therefore, scrupulous clinical

attention is required for patients presenting these risk factors.

The multivariate analyses in our study indicated low levels of white blood cells to be a risk factor for docetaxel-related anaphylaxis. There are no reports showing that leukopenia is related to the hypersensitivity caused by drugs such as the taxanes. On the other hand, activated basophils, one of the types of leukocytes, produce large amounts of T helper type 2 (Th2) cytokines,³³⁾ and basophil CD203c is expected as a promising biomarker for the prediction of severe carboplatin-related anaphylaxis.³⁴⁾ Further investigation is necessary to elucidate the mechanism of docetaxel-related anaphylaxis.

In general, docetaxel is used with human epidermal growth factor receptor type 2 (HER2)-targeting drugs, such as trastuzumab and pertuzumab, in many cases. These molecularly targeted drugs are known as high-risk drugs for hypersensitivity. In our study, there were no differences in the rates of hypersensitivity for each regimen, as shown in Table 2. Thus, the molecularly targeted drugs, such as trastuzumab and pertuzumab, might not increase the risk of hypersensitivity of docetaxel.

Limitations of the present study include the fact that our study does not fully address differences in incidence rates between original and generic docetaxel,³⁵⁾ effects of CYP1B1 gene polymorphisms,³⁶⁾ and the influence of dexamethasone premedication.^{37,38)} The retrospective nature of the study limits the conclusions that can be drawn. In addition, all patients were treated at a single institution. Further studies such as prospective, multi-center research are expected to clearly define the conditions to prevent docetaxel hypersensitivity reactions.

In conclusion, we report that high concentration of docetaxel, high administration rates, and low white blood cell counts are risk factors for docetaxel-related anaphylaxis. In addition, anaphylaxis rates were significantly lower in patients treated with a diluted docetaxel volume of 500 mL than in those treated with a volume of 250 mL, and tended to be lower in patients treated over a duration of 90 min rather than in those treated over 60 min. Our study findings indicate that the incidence of docetaxel-induced hypersensitivity reactions could be reduced by altering the treatment method to administer a volume of 500 mL over 90 min.

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Conflict of Interest The authors declare no conflict of interest.

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