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ORIGINAL ARTICLE

Pharmacoethnicity of docetaxel-induced severe neutropenia: integrated analysis of published phase II and III trials

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Abstract
Background Ethnic differences in drug susceptibility and toxicity are a major concern, not only in drug development but also in the clinical setting. We review the toxicity profiles of docetaxel according to dose and ethnicity.
Methods We analyzed phase II and III clinical trials that included a once-every-3-weeks single-agent docetaxel arm. Logistic regression analysis was applied to identify the significant variables affecting the reported incidence of docetaxel-induced severe neutropenia.
Results Multivariate logistic regression analysis identified studies conducted in Asia [odds ratio (OR) 19.0; 95% confidence interval (95% CI) 3.64–99.0] and docetaxel dose (OR 1.08; 95% CI 1.03–1.13) as independent variables for the incidence of grade 3/4 neutropenia.
Conclusions There is a significant difference in the incidence of docetaxel-induced severe neutropenia between Asian and non-Asian clinical studies. Physicians and pharmacists should consider ethnic diversity in docetaxel toxicity when interpreting the results of clinical trials.

Keywords Ethnic differences · Docetaxel · Logistic regression · Neutropenia

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Introduction

One of the major concerns in the international harmonization of drug development is the issue of pharmacoethnicity. Pharmacoethnicity can be described as ethnic diversity in drug response or toxicity, which includes a large number of factors including genetic and environmental components and social divergence [1, 2].

In the area of oncology, some reports have discussed ethnic differences in treatment effects and toxicity. For example, gefitinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor that has been used for the treatment of EGFR-positive non-small-cell lung cancer, was reported to have a minimal effect on survival in a large multi-regional placebo-controlled phase III trial, despite a significant increase in survival in patients of Asian origin [3]. This diversity might be explained, in part, by differences in the frequency of EGFR mutations, a major predictive factor of gefitinib efficacy [4]. Other studies examined the combination of irinotecan and cisplatin for the treatment of advanced small cell lung cancer. The use of irinotecan plus cisplatin for the treatment of extensive-stage small cell lung cancer was first reported by Japanese researchers (JCOG 9511), and it was shown to have a superior survival effect over the conventional standard regimen of etoposide plus cisplatin [5]. However, trials in North America failed to confirm the survival benefit of irinotecan-containing regimens [6, 7]. One of these studies, the SWOG S0124 trial, included pharmacogenomic investigations. The authors stated the potential importance of pharmacogenomics in interpreting the results of clinical trials in cancer therapy [6].

In 2008, the combination of 75 mg/m^2 docetaxel with prednisolone was approved in Japan for the treatment of hormone-refractory prostate cancer on the basis of results

from a Japanese phase II trial [8] and a Western phase III trial (TAX327) [9]. In these two clinical studies, several differences were found, including the doses of docetaxel and their outcomes and safety profiles. In the Japanese phase II trial, 70 mg/m^2 docetaxel was used, whereas the TAX327 trial used 75 mg/m^2 docetaxel. Grade 3/4 neutropenia and febrile neutropenia occurred in 93.0 and 16.3% of patients in the Japanese study compared to 32 and 3% of patients in the TAX327 trial, respectively. These results suggested that docetaxel was more toxic to Japanese patients, despite the use of a lower dose. In Japan, docetaxel has been approved at doses of 60–70 mg/m^2 for the treatment of gastric cancer, non-small-cell lung cancer, esophageal cancer, ovarian cancer, and uterine corpus cancer. These approved doses of docetaxel in Japan are much lower than those in Western countries.

According to these observations, we analyzed the differences in the incidence of docetaxel-induced severe neutropenia between clinical trials conducted in Asian and non-Asian countries using published data as a model to study ethnic diversity in drug susceptibility.

Materials and methods

Search strategy

Phase II and III clinical trials that included a treatment arm of docetaxel monotherapy administered at 3-week intervals were considered in this review. Meeting abstracts were excluded. Studies that used glucocorticoids with docetaxel were also included. Only reports written in English or Japanese were included in the analysis.

An electronic database search was performed using PubMed, the Cochrane Controlled Trials Register by Ovid (EBM reviews, 4th quarter, 2009), and Ichushi-Web (a domestic medical literature database service provided by the NPO Japan Medical Abstracts Society) on November 30, 2009. The keyword used for the electronic database search of PubMed was "docetaxel" with limitations by the type of articles of "clinical trials, phase II", or "clinical trials, phase III". For the other databases, we used "docetaxel" as a keyword.

Selection criteria

Surveys and retrospective studies were not included in the analysis. Reports of interim analysis were also excluded. In addition, reports that contained the incidence of grade 3/4 neutropenia only as a percentage of treatment courses were excluded. Finally, studies adopting primary prevention with granulocyte-colony stimulating factor were also excluded.

Study selection

Two authors independently assessed the titles and abstracts of all identified articles. Disagreements between the reviewers were resolved by consensus. Two authors evaluated the full text of the selected papers and determined their inclusion or exclusion in the analysis according to the eligibility criteria.

Data extraction

Two authors extracted data for trial phase, treatment line, types of malignancy, number of patients treated with docetaxel, dose of docetaxel, median age, percentage of females, percentage of patients whose performance status (defined by the World Health Organization/Eastern Cooperative Oncology Group) was >1, the region where the study was conducted, and the incidence of grade 3/4 neutropenia as a percentage of patients.

Statistical analysis

Univariate and multivariate analyses were conducted to identify the factors influencing the higher incidence of grade 3/4 neutropenia in the docetaxel monotherapy arm in each report. A >70% incidence of grade 3/4 neutropenia was defined as a higher incidence. The dose of docetaxel, percentage of females, median age of participants, percentage of patients whose performance status was >1, treatment line, trial phase, and the region where the study was mainly conducted were considered as candidate variants. The treatment line was classified into 2 groups: the adjuvant, neoadjuvant, and first line were encoded as 0, while the second line or subsequent lines were encoded as 1. The region where the study was mainly conducted was grouped as Asia or non-Asia. The dose of docetaxel, median age of participants, and percentage of patients whose performance status was >1 were forcibly included into the multivariate analysis because they are known risk factors for the incidence of neutropenia with docetaxel. The variables that showed a moderate relationship ($p < 0.2$) with a higher incidence of grade 3/4 neutropenia in the univariate analysis were included in the multivariate analysis. The final model was built by stepwise logistic regression. The variables were selected using Wald's likelihood ratio, with p values of <0.1 for exclusion and <0.05 for inclusion. A Hosmer–Lemeshow goodness-of-fit test was performed to examine the calibration of the model. All statistical analyses were performed using SPSS statistics version 17.0 (SPSS Japan Inc., Tokyo, Japan).

Results

Literature search

We identified 1010 citations by database search, of which 153 articles were retrieved and reviewed. We excluded papers that did not contain adequate patient demographics or outcomes ($n = 21$), studies with a dosage regimen that did not meet our criteria ($n = 8$), and review papers or papers containing combined analyses ($n = 4$; Fig. 1). Ultimately, 128 arms from 120 studies were used for further analysis [8–127].

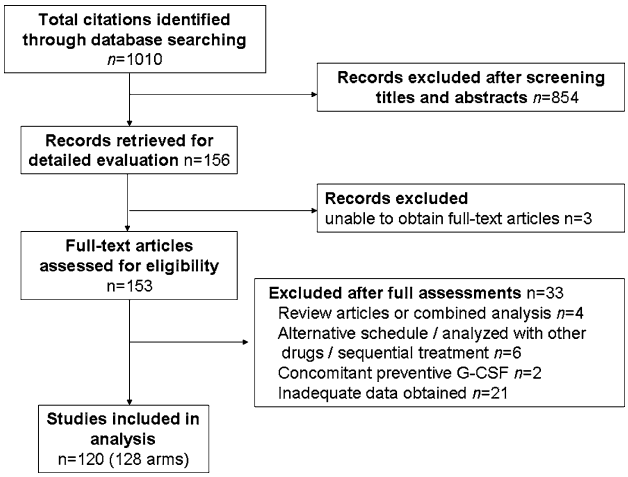

Fig. 1 Study selection

Characteristics of the reports

The characteristics of the reports reviewed are presented in Table 1. The size and number of the study arms classified by docetaxel dose were 1535 patients in 24 arms, 25 patients in 1 arm, 274 patients in 6 arms, 4034 patients in 30 arms, and 3880 patients in 67 arms for 60, 66, 70, 75, and 100 mg/m^2 docetaxel, respectively. Of these arms, the numbers of studies conducted in Asia and their participants were 1384 patients in 23 arms, 25 patients in 1 arm, 225 patients in 5 arms, 141 patients in 3 arms, and 35 patients in 1 arm for 60, 66, 70, 75, and 100 mg/m^2 docetaxel, respectively. The minimum number of participants in an arm was 12. The majority of the participants were non-small-cell lung cancer and breast cancer patients. The majority of studies conducted in Asia were Japanese studies (1609 Japanese participants in 28 arms out of 1810 Asian participants in 33 arms). The others Asian studies were conducted in South Korea, Taiwan, and Singapore. All of the studies conducted in Japan used docetaxel at doses of 70 mg/m^2 or lower. In particular, phase III trials conducted in Asia were performed using 60 mg/m^2 docetaxel. There were 10 reports written in Japanese that contained 745 Japanese participants.

Distribution of the reported incidence of grade 3/4 neutropenia

The relationship between the dose of docetaxel and the incidence of grade 3/4 neutropenia is presented in Fig. 2. The weighted means of the reported incidence of grade 3/4 neutropenia, which were calculated by dividing the total number of participants who experienced grade 3/4

Table 1 Characteristics of the study arms

Docetaxel dose (mg/m^2)	60		66		70		75		100	
Trial phase	II	III	II	III	II	III	II	III	II	III
Number of study arms (Asia)	19 (19)	5 (4)	1 (1)	0 (0)	6 (5)	0 (0)	18 (3)	12 (0)	53 (1)	12 (0)
Sample size (by arm)										
12–50	10	0	1	0	5	0	12	0	46	2
51–100	9	2	0	0	1	0	6	2	8	2
101–200	0	2	0	0	0	0	0	4	1	6
≥201	0	1	0	0	0	0	0	6	0	2
Total number of participants (in Asian studies)	839 (839)	696 (545)	25 (25)	0 (0)	274 (225)	0 (0)	824 (141)	3210 (0)	2290 (35)	1590 (0)
Types of tumor										
Non-small-cell lung	5	3	1	0	1	0	11	8	8	5
Breast	4	2	0	0	0	0	1	3	14	7
Others	10	0	0	0	5	0	6	1	33	0

neutropenia by the total number of participants for each docetaxel dose, were 70.1, 68.9, 50.0, and 75.3% for 60, 70, 75, and 100 mg/m^2, respectively.

Logistic regression

The results from the univariate and multivariate logistic regression analyses are shown in Table 2. From the univariate analysis, studies conducted in Asia ($p = 0.073$), treatment line ($p = 0.057$), and the percentage of females ($p = 0.082$) were included in the subsequent multivariate analysis. The dose of docetaxel ($p = 0.266$), the median age of participants ($p = 0.300$), and the percentage of patients whose performance status was >1 ($p = 0.287$) did not meet the criteria, but were forcibly included in the subsequent multivariate analysis. Trial phase ($p = 0.276$) was excluded. Multivariate analysis identified studies conducted in Asia [odds ratio (OR) 19.0; 95% confidence interval (95% CI) 3.64–99.0; $p < 0.001$] and the dose of docetaxel (OR 1.08; 95% CI 1.03–1.13; $p = 0.001$) as independent variables for the incidence of grade 3/4 neutropenia. The percentage of patients whose performance status was >1 (OR 0.99; 95% CI 0.96–1.02; $p = 0.444$) and the median age of participants (OR 1.02; 95% CI 0.94–1.10; $p = 0.598$) were not identified as significant variables. The percentage of females and treatment line were not included in the final model. The Hosmer–Lemeshow goodness-of-fit test suggested a good calibration ($p = 0.492$). The predictive accuracy of this model was 76.6%.

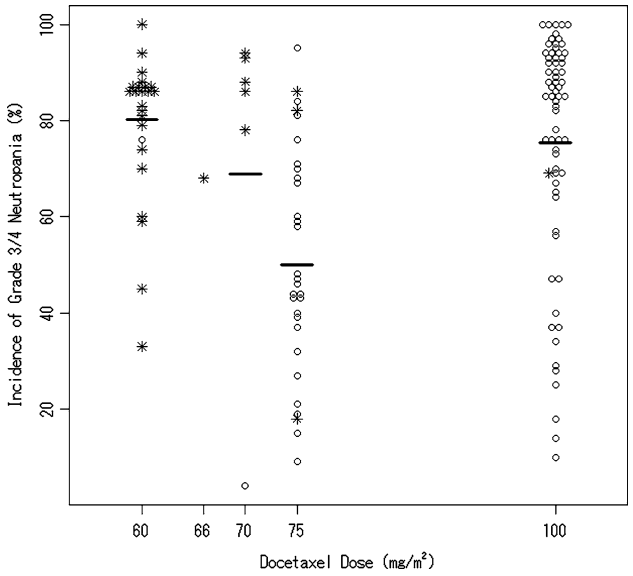

Fig. 2 Incidence of severe neutropenia. The incidence of grade 3/4 neutropenia reported in each paper was plotted. *Each symbol* represents a treatment arm that included a single-agent docetaxel arm. The *open circles* represent studies conducted in non-Asian countries. The *asterisks* represent studies conducted in Asian countries. The *horizontal bars* represent the weighted means of the reported incidence of grade 3/4 neutropenia for each docetaxel dose, for which sample size was used as a weight

Discussion

We confirmed that docetaxel had a higher toxicity in Asian studies than in non-Asian studies. The studies performed in Asia showed an almost 19 times higher risk for severe neutropenia compared with the non-Asian studies.

Docetaxel has been one of the most important cytotoxic drugs in the treatment of major tumors such as breast cancer, non-small-cell lung cancer, and prostate cancer. This indicates that docetaxel will be used as a reference regimen in future clinical trials. However, the heterogeneity of docetaxel-induced toxicity profiles between Asian and non-Asian countries is a major problem due to the resulting variations in the recommended dose of docetaxel. This also represents a serious concern in the clinical setting. Physicians and pharmacists should consider ethnic diversity in docetaxel toxicity when interpreting the results of clinical trials.

One of the possible mechanisms that influence the ethnic diversity in docetaxel toxicity is pharmacogenomic differences in drug-metabolizing enzymes and/or drug transporters. Recently, a US–Japan common-arm trial reported diversity in the clinical outcomes, including survival and neutropenia, between US and Japanese non-small-cell

Table 2 Logistic regression analysis

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*	OR	95% CI	*p*
Studies conducted in Asia	2.20	0.93–5.22	0.073	19.0	3.64–99.0	<0.001
Docetaxel dose	1.01	0.99–1.03	0.266	1.08	1.03–1.13	0.001
PS >1	0.99	0.96–1.01	0.287	0.99	0.96–1.02	0.444
Median age	0.97	0.91–1.03	0.300	1.02	0.94–1.10	0.598
Percentage of female	1.01	1.00–1.02	0.082	Excluded		
Treatment line (≥2nd line)	0.50	0.24–1.02	0.057	Excluded		

OR odds ratio, *CI* confidence interval, *PS >1* percentage of the participants whose performance status was >1

cancer patients who received the same cytotoxic chemotherapy regimen, paclitaxel plus carboplatin [128]. The researchers discussed the possible causes of these differences and suggested that the allelic distribution of the genes involved in paclitaxel disposition or DNA repair was a significant factor. Such an approach may be very useful in determining the mechanisms that cause ethnic differences in drug effects and toxicity. Docetaxel pharmacokinetics is dominated by the hepatic cytochrome P450 3A (CYP3A) subfamily and P-glycoprotein, which are partly involved in paclitaxel disposition [129]. These facts indicate that similar pharmacogenomic differences might have some role in the ethnic differences in docetaxel toxicity. Population pharmacokinetic studies of docetaxel were performed in Western countries and Japan to harmonize drug development in the two regions. In these studies, researchers concluded that the systemic clearance of docetaxel was almost similar between Western and Japanese participants with the same variables, including hepatic function, serum albumin level, serum α_1-acid glycoprotein (AAG) level, and age [130, 131].

Individualized dosing of docetaxel is one of the potential solutions for pharmacoethnicity. On the other hand, there are many barriers and unknown variables in achieving satisfactory individualization. Yamamoto et al. [132] reported that docetaxel dosing based on CYP3A function using the hydration ratio of externally administered cortisol as a probe improved pharmacokinetic variability, but not pharmacodynamic variability. These results indicate a possible divergence in systemic pharmacokinetics and local exposure of the drug. Systemic exposure of cytotoxic agents is not the only factor but is one of the major factors that influence myelotoxicity, because drug transport into hematopoietic progenitor cells may be a critical point in the differential expression of toxicity [133, 134].

Our study has some limitations in terms of design. The classification criterion used in our analysis might not accurately reflect the ethnicity of the participants because we classified studies by the region in which they were mainly conducted, not by the race of the participants. We decided to use this criterion because most of the published studies did not report the demographic background of the participants with respect to race. We believe that the results of our study might reflect not only racial differences but also other regional factors such as environment and social divergence. This study was based on the published data, which were aggregated as means or medians; however, this approach loses considerable information about each participant. For example, the effects of some variables including the patients' age and performance status, which are known to be variables that affect chemotherapy-induced neutropenia, were not significant in our study. In addition, we could not obtain some variables for the majority of the study subjects. For example, the interval of complete blood count (CBC interval) monitoring affects the incidence of severe neutropenia. Only 84 of the 128 arms (65%) contained information about the CBC interval. In the sub-analysis using these 84 arms, the CBC interval showed a significant negative relationship with outcome in the univariate analysis. Bruno et al. [135] reported that the AAG level, docetaxel clearance, baseline count of neutrophils, and number of previous regimens were significant predictors of grade 4 neutropenia. In our analysis, we could not obtain data on the AAG level from each paper because it was not routinely measured in the clinical setting or clinical trials. The baseline neutrophil count and hepatic enzyme level were not taken into consideration in our analysis because most of the studies have eligibility criteria according to blood cell counts and blood chemicals.

In conclusion, there is a significant difference in the incidence of docetaxel-induced severe neutropenia between Asian and non-Asian studies. Physicians and pharmacists should therefore consider ethnic diversity in docetaxel toxicity when interpreting the results of clinical trials.

Conflict of interest The authors declare no conflict of interest.

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