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SHORT COMMUNICATION

Logistic regression analysis for febrile neutropenia (FN) induced by docetaxel in Japanese cancer patients

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Abstract
Purpose Fever occurring in a neutropenic patient remains a common life-threatening complication of cancer chemotherapy, and febrile neutropenia (FN) is recognized as a dose-limiting factor (DLF) in cancer chemotherapy. The aim of this study is to evaluate the significant covariate associated with the risk of FN occurrence in Japanese patients.
Methods A stepwise logistic regression was conducted using data from Japanese cancer patients treated with docetaxel. Based on those results, an equation was established which predicts the probability of FN occurrence.
Results From the result of a stepwise multivariate logistic regression analysis, performance status factor (PS*), which is set to 1 if performance status factor is 2 or 3, and to 0 otherwise and area under the plasma concentration versus time curve (AUC) were selected as covariates significantly associated ($p < 0.05$) with FN occurrence. The obtained equation to predict the probability (P) of docetaxel-induced FN occurrence is $P = 1/[1 + \exp\{-(1.29 \times \mathrm{AUC} + 1.41 \times \mathrm{PS}^* - 3.52)\}]$. A receiver operating characteristic (ROC) curve analysis revealed that the best cut-off value of FN probability to differentiate between the presence and absence of FN was 0.61.
Conclusions An equation was developed to predict the probability of FN occurrence for Japanese patients treated with docetaxel. It was found that FN may not occur when the probability of FN occurrence calculated by the predictive equation is less than 0.61. Therefore, the predictive equation for FN occurrence may be used for selecting the appropriate dose to avoid the occurrence of FN.

Keywords Docetaxel · Febrile neutropenia · Logistic regression analysis · Neutrophils · Japanese cancer patients

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Introduction

Fever occurring in neutropenic patients remains a common life-threatening complication of cancer chemotherapy [1]. Febrile neutropenia (FN) requires treatment with broad-spectrum antibiotics [2–7], and the standard setting of care has been patient hospitalization with close monitoring until fever resolution and recovery from neutropenia. Therefore, FN is recognized as a dose-limiting factor (DLF) of cancer chemotherapy.

Docetaxel is a widely used anticancer agent that is active against breast, non-small cell lung, ovarian, head and neck, gastric, and prostate cancers [8–13]. FN is a common complication of docetaxel therapy [14]. Bruno et al. [14] reported that α_1-acid glycoprotein (AGP) and clearance of docetaxel (CL) are significant covariates associated with the risk of FN occurrence, using a stepwise

logistic regression analysis for subjects enrolled in Phase 2 studies in Europe and United State. However, in clinical studies for the development of anticancer drugs, particular patients with moderate to severe liver dysfunction or poor performance status are commonly excluded, and there have been several studies for chemotherapy-induced FN occurrence [15, 16]. However, there have been no studies except for the study of Bruno et al. [14] which evaluated the significant covariate associated with the risk of docetaxel-induced FN occurrence. Therefore, in this study, a stepwise logistic regression analysis was conducted using data from Japanese cancer patients treated with docetaxel including patients with liver failure or poor performance status, who should fall within the exclusion criteria in conventional clinical studies for new drug development. The population pharmacokinetic (PK) part of this study has already been reported [17], where a three-compartment open model fitted well with the observed data.

Materials and methods

Patient selection

Two hundred patients were enrolled into the present clinical research of docetaxel (as single agent or combination chemotherapy), which was conducted at the hospitals of National Cancer Center Hospital East in Japan. The eligibility criteria included histologically or cytologically confirmed solid cancers against which docetaxel is active, age $\geq$20 years, Eastern Cooperative Oncology Group performance status 0–3, at least 3 weeks since the last chemotherapy (6 weeks for mitomycin and nitrosoureas), and adequate hematological values (white blood cells $\geq$3,000/μL, platelet count $\geq$75,000/μL). The exclusion criteria were active infection, severe heart disease, uncontrolled hypertension or diabetes mellitus, pregnant/nursing women, or seropositive for human immunodeficiency virus, hepatitis C virus, hepatitis B surface antigen or syphilis. Patients who received granulocyte colony stimulating factors after docetaxel administration were excluded from this analysis. This study was approved by the Institutional Review Board of the National Cancer Center Hospital East, Japan, and all patients gave their written informed consent.

Treatment and follow-up

Docetaxel was infused intravenously over 1 h every 3 weeks. Most patients received the approved dose in Japan of 60 mg/m^2, but attending physicians were allowed to reduce the dose depending on liver function, performance status (PS), or the extent of prior chemotherapy. The physical examination and toxicity assessment included blood chemistry and complete blood cell counts with differential counts as well as platelet counts, and were performed before treatment and repeated at least weekly during the first course. Dexamethasone (8 or 16 mg) was administered before the docetaxel regimen to prevent emesis. The data obtained during the first course were used for an analysis in the present study.

Drug quantification

Blood sampling for drug quantification was carried out before and 30 min during the docetaxel infusion, at the end of the infusion, and 0.17, 1, 5, 10 and 24 h after the end of infusion. Heparinized blood was centrifuged immediately, and plasma samples were frozen at −80°C until analysis. The concentration of docetaxel in plasma was determined using a high-performance liquid chromatography (HPLC) as previously reported [18].

Population pharmacokinetic analysis

Pharmacokinetic parameters for individual patients were calculated using the Bayesian estimation after the population pharmacokinetic parameters were estimated in the entire population. These calculations were carried out using nonlinear mixed-effect modeling software, NONMEM (version V, level 1.1; GloboMax, Ellicot City, MD, USA). A method of first-order conditional estimation (FOCE) with an INTERACTION option was employed. NONMEM was running with a Compaq Visual FORTRAN 6.6 compiler (Hewlett–Packard Company, Palo Alto, CA, USA), on a Pentium 4 central processing unit, under the Windows XP operating system (Microsoft Corporation, Redmond, WA, USA). A three-compartment open model with zero-order administration (i.e. constant intravenous infusion) and first-order elimination (ADVAN 11 and TRANS 4) was used to describe the plasma concentration-time course of docetaxel in the entire population. The PK model was parameterized in terms of clearance (CL), the volume of the central compartment (V_1), inter-compartment clearance between the central and peripheral-1 compartments (Q_2), the volume of the peripheral-1 compartment (V_2), inter-compartment clearance between the central and peripheral-2 compartments (Q_3), and the volume of the peripheral-2 compartment (V_3). The interindividual variability was modeled assuming a log-normal distribution for interindividual variability of these pharmacokinetic parameters. For example, for clearance,

$$CL_j = \widehat{CL} \cdot \exp(\eta_{jCL}) \quad (1)$$

where CL_j and $\widehat{CL}$ are the estimated values in an individual j and the population mean for clearance, respectively, and η_{jCL} is the individual random perturbation from the population mean. Intrapatient residual variability was also described by a proportional model. The AUC was calculated as dose/CL in each patient.

Statistical analysis

FN was defined as a fever of greater than 38°C, which required antibiotics. The variables included for statistical analysis are as follows: age, sex, performance status (PS), regiment of prior chemotherapy, radiotherapy, albumin, α_1-acid glycoprotein, alanine aminotransferase, hemoglobin, pretreatment absolute neutrophil counts, the area under the plasma concentration vs. time curve (AUC), and peak concentration at the end of infusion (Cmax). To identify the factors associated with FN, continuous variables were compared between patients with and without FN using the Mann–Whitney's U test, and differences in the distribution of dichotomized variables were evaluated with the Fisher's exact test. Subsequently, factors that were significant ($p \leq 0.05$) were evaluated as potential covariates of categorical end-point (i.e., absence and presence of FN) in a stepwise multivariate logistic regression with backward selection. The backward selection model started with all candidate variables in the model. At each step, a variable that is not significant ($p > 0.05$ by a likelihood ratio test) was removed. This process continued until no non-significant variables remained. Statistic analyses were performed using statistics software, the Statistical Package for Social Systems (version 15J, SPSS Japan Corporation, Tokyo, Japan) and S-plus Professional Edition (version 6.2, Insightful Corporation, WA, USA).

Validation of the model

Since 200 patients is a small sample to develop a predictive model, the multivariate logistic regression model was validated using the technique of bootstrap resampling [19]. This technique is efficient and provides nearly unbiased estimates of the predictive accuracy of the model [20]. 200 samples were drawn at random with replacement, which have same numbers of successes and failures as original sample, then, a backward selection model which was applied to original dataset was fitted repeatedly to the 200 samples. The criterial statistics of model validation are mean and coefficient of variance (CV%) of area under a receiver operating characteristic (ROC) curve obtained from samples, which were calculated normally.

Results

The characteristics of the 200 patients treated in the present study are summarized in Table 1. FN occurred in 9 patients. Almost 90% of the patients had good PS (0 or 1), and 14% had previously received more than 3 regimens of chemotherapy. The Japanese standard dose of docetaxel is 60 mg/m^2, but some patients received reduced doses because of poor PS, liver dysfunction, or extensive prior treatments.

When the characteristics of the patients who did or did not develop FN were compared, the distribution of performance status factor (PS*), which is set to 1 if PS is 2 or 3, and to 0 otherwise, was significantly different, and pretreatment serum levels of albumin (ALB) in patients with FN was significantly lower than in those without (Table 2). Among the pharmacokinetic parameters, AUC was significantly lower in patients with FN. To investigate whether these variables are significantly associated with FN occurrence, a stepwise logistic regression with backward selection was

Table 1 Patient characteristics and the dose of docetaxel

Characteristic	Median and range or No.
Age (years)	57 (21–86)
Sex: female/male (*n*)	114/86
Disease: BC/NSCLC/H-N/Others (*n*)	79/68/31/22
Performance status: 0/1/2/3 (*n*)	46/131/17/6
Combination chemotherapy: Cisplatin/doxorubicin/irinotecan (*n*)	66/6/31
Regimens of prior chemotherapy (*n*)	
<3	172
≥3	28
Radiotherapy (*n*)	
Yes	65
No	135
Albumin (g/dL)	3.7 (1.3–4.6)
α_1-Acid glycoprotein (mg/dL)	97 (19–259)
Alanine aminotransferase (IU/L)	19 (5.0–255)
Hemoglobin (g/dL)	12 (7.5–16)
Pretreatment absolute neutrophil counts (per μL)	3910 (1023–15650)
Dose per body surface area (*n*)	
≥60 mg/m^2	37
≥40 to <60 mg/m^2	69
≥20 to <40 mg/m^2	77
<20 mg/m^2	17

carried out. AUC ($p < 0.001$) and PS* ($p < 0.001$) were selected among the variables listed in Table 2, with CV (%) of 13.5 and 22.1, respectively.

Table 3 shows the coefficients of covariates. Therefore, an equation was implemented which predicts the probability (P) of FN occurrence using these coefficients of significant covariates as follows:

$$P = \frac{1}{1 + \exp[-(1.29 \cdot \mathrm{AUC} + 1.41 \cdot \mathrm{PS}^* - 3.52)]} \quad (2)$$

A solid curve in Fig. 1 represents the probability of FN predicted from Eq. 2 at various AUC when PS* was set at 0. A dotted curve in Fig. 1 represents the probability of FN predicted from Eq. 2 at various AUC when PS* was set at 1.

Figure 2 shows an ROC curve for the probability of FN occurrence, which was predicted from the Eq. 2. The ROC curve indicates that the cut-off value at approximately 0.61 gives the best score of sensitivity and 1-specificity, and the area under an ROC curve is 0.85.

Table 4 shows a contingency, which compares the predicted and observed FN occurrences at the cut-off value of 0.61.

As a result of the model validation using a bootstrap method which created 200 samples of the original dataset,

Table 2 Characteristics and pharmacokinetic parameters of docetaxel in patients with or without febrile neutropenia

	Fever (+)	Fever (−)	p
Patients (n)	9	191	
Age (years)			
Median	59	57	0.470
Range	48–67	21–86	
Sex (n)			
Female	7	107	0.305
Male	2	84	
Performance status (n)			
0–1	5	172	0.0120
2–3	4	19	
Regimens of prior chemotherapy (n)			
0–2	6	165	0.116
≥3	3	25	
Radiotherapy (n)			
Yes	3	62	1.00
No	6	129	
Albumin (g/dL)			
Median	3.5	3.8	0.0280
Range	1.3–3.8	2.6–4.6	
α_1-Acid glycoprotein (mg/dL)			
Median	98	97	0.568
Range	57–241	19–259	
Alanine aminotransferase (IU/L)			
Median	26	19	0.667
Range	8–188	5–255	
Hemoglobin (g/dL)			
Median	11.6	12.2	0.188
Range	8.2–13.7	7.5–16.1	
Pretreatment absolute neutrophil counts (per μL)			
Median	3720	3920	0.795
Range	2270–7310	1023–15650	
Area under the plasma concentration vs. time curve (AUC) (mg*h/L)			
Median	3.03	1.78	0.00100
Range	1.99–4.29	0.451–7.58	
Peak concentration at the end of infusion (Cmax) (mg/L)			
Median	13.7	8.96	0.0830
Range	5.56–17.1	3.73–24.2	

Table 3 Logistic regression model for febrile neutropenia (N = 200)

Variable	Regression coefficient (SE)	p
Area under the plasma concentration versus time curve (AUC) (mg*h/L)	1.29 (0.174)	<0.001
Performance status* (PS*) (0 for PS 0/1 or 1 for PS 2/3)	1.41 (0.311)	<0.001
Intercept	−3.52 (0.434)	<0.001

AUC, area under the plasma concentration versus time curve

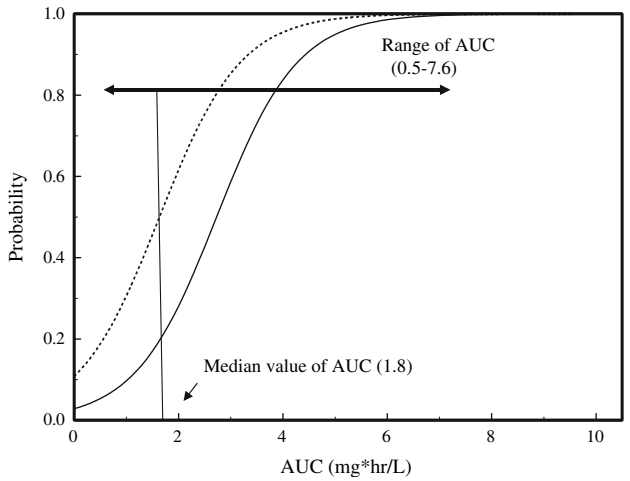

Fig. 1 A solid curve represents the probability of FN predicted from Eq. 2 at various AUC when performance status factor (PS*) was set at 0. A dotted curve represents the probability of FN predicted from Eq. 2 at various AUC when PS* was set at 1

all samples were converged normally, and AUC and PS* remained significant in the model for 195 samples. On the other hand, only AUC remained significant in the model for 5 samples. The area under an ROC curve of 200 samples (using bootstrapping) was calculated to be 0.85 as a mean value, with a CV (%) of 2.5. From these lines of evidence, this model was implied to have robustness and a good ability to discriminate between patients with and without fever.

Discussion

The population PK parameters and their interindividual variability of docetaxel in Japanese cancer patients have been reported [17]. In this study, the probability of FN occurrence was further investigated using the same patient population. Bruno et al. [14] reported that the AGP and CL of docetaxel are related with the risk of FN occurrence, using a logistic regression analysis for subjects in Europe and Western and USA. In this study, a stepwise logistic regression analysis was performed to evaluate the risk of FN occurrence using clinical data taken from Japanese

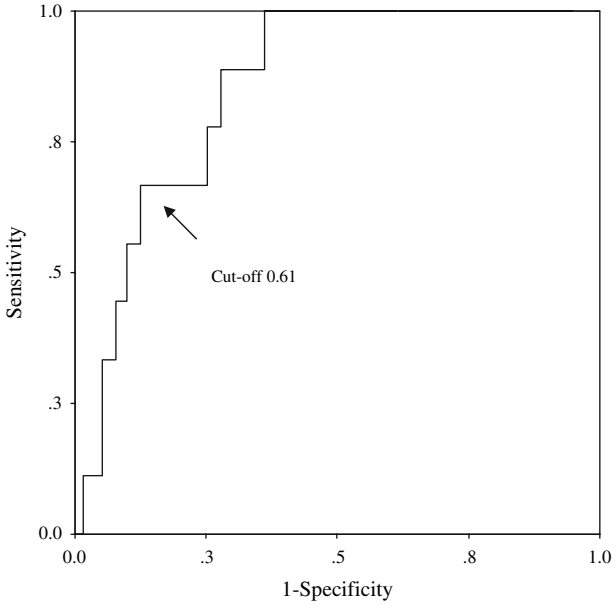

Fig. 2 Receiver-operating-characteristic (ROC) curve for the probability of febrile neutropenia predicted from this model in differentiating between those patients with and without febrile neutropenia

Table 4 Predictive performance of logistic regression model[a]

Group		Observed	
		Fever (+)	Fever (−)
Predicted	Fever (+)	6	25
	Fever (−)	3	166

[a] Cut-off value = 0.61

cancer patients treated with docetaxel, for the first time. Bruno et al [14], who studied the docetaxel-induced FN occurrence, reported the rate of FN as 4.7%, which is close to the result of our study. On the other hand, the rate of FN was reportedly higher (20–40%) in other cancer chemotherapy such as CHOP and ACVBP regimens for patients with non-Hodgkin's lymphoma [15, 16].

Figure 1 shows that when the patients with PS* classed at 1 received doses which provide the median value of AUC (1.8 mg*h/L) in this study, the probability of FN occurrence at PS* = 1 is expected to increase 2.5-fold as compared with that at PS* = 0.

From Table 4, the predictive value of fever (+), calculated as true positive/(true positive + false positive = 6/(6 + 25) = 0.19. This implies that the predict performance of the Eq. 2 is not high enough. In contrast, the predictive value of fever (−) was calculated as true negative/(true negative + false negative) = 166/(166 + 3) = 0.98. This implies that FN may not occur when the probability of FN occurrence calculated by Eq. 2 is less than 0.61. To

Table 5 Comparison the two groups where the dose ≤ cut-off dose and dose > cut-off dose[a]

Group	Dose ≤ cut-off dose[b]	Dose > cut-off dose[b]
Fever (−)	166	25
Fever (+)	3	6

[a] $p = 0.001$ (Fisher's exact test)

[b] Cut-off dose was a value which provided that the probability of febrile neutropenia was 0.61

support this hypothesis, Fisher's exact test for FN frequency was employed to compare the group administered with doses (normalized by body surface area (BSA)) more than the cut-off dose ($D_{\text{cut-off}}$, i.e. the dose which provides the FN probability of 0.61) with the group administered with doses less than $D_{\text{cut-off}}$. $D_{\text{cut-off}}$ was finally calculated as

$$D_{cut-off} = \frac{(3.02 - 1.09 \cdot \text{PS}^*) \cdot \text{CL}}{\text{BSA}} \quad (3)$$

where CL was given by a Bayesian post hoc analysis of the population PK model. As a result, the group administered with doses more than $D_{\text{cut-off}}$ showed a significantly higher frequency of FN ($p = 0.001$; Table 5). This indicates that patients administered with doses more than $D_{\text{cut-off}}$ tend to exhibit FN. In other words, the $D_{\text{cut-off}}$ calculated from Eq. 3 may be considered as a criterion when physicians do dose-adjustment to avoid FN occurrence. However, the condition used to decide dose of docetaxel using Eq. 3 is merely a reflection of toxicity associated with FN, but clinical efficacy (tumor regression) should also be taken into account in the clinical settings.

In the previous phase II study [14], the dose used was constant and was not changed, whereas in this study the dose was adjusted due to liver failure and/or prior chemotherapy because the patients have been treated under routine oncology practice. This conditional difference may be the reason why significant covariates were different between that trial and the present results of a logistic regression analysis for FN occurrence.

In conclusion, an equation was developed to predict the probability of FN occurrence in Japanese patients treated with docetaxel. This equation, which incorporates AUC and PS* as significant covariates, may therefore be useful for selecting the appropriate dose in order to avoid the occurrence of FN.

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