—Regular Articles—

Clinical Trial Simulations for Dosage Optimization of Docetaxel in Patients with Liver Dysfunction, Based on a Log-binominal Regression for Febrile Neutropenia

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(Received December 26, 2008; Accepted March 4, 2009; Published online April 17, 2009)

This study was aimed to perform clinical trial simulations to evaluate the dose reduction strategy of docetaxel for Japanese patients with liver dysfunction, which we previously proposed. For this purpose, a log-binominal regression (LBR) was performed for febrile neutropenia (FN) induced by docetaxel in these patients. A LBR analysis was conducted using clinical data from cancer patients treated with docetaxel and incorporated in the subsequent trial simulation. Virtual patients with liver dysfunction were randomly assigned to receive the Japanese standard dose (60 mg/m^2) or reduced dose (40 or 50 mg/m^2) of docetaxel. The primary endpoint was overall survival of the reduced dose to the standard dose. The secondary endpoint was the number of patients who experienced FN in response to the two treatment regimens. From the LBR analysis, the performance status and the area under the plasma concentration-time curve (AUC) were selected as covariates associated significantly ($p<0.05$) with FN occurrence. From the results of the present trial simulation, the median proportion of patients who experienced FN was decreased by about 20% in the reduced dose arm. Non-inferiority criteria, the reduced dose group to the standard dose group were met in 85.5% of the simulated clinical trials with a decrease in the FN frequency. In conclusion, clinical trial simulation models for the efficacy (survival) and toxicity (FN) was first performed in Japanese patients, and the feasibility of docetaxel therapy for liver-dysfunction patients under the dose reduction strategy was supported.

Key words——clinical trial simulation; liver dysfunction; dose optimization; docetaxel

INTRODUCTION

Docetaxel has been widely used to treat breast, non-small-cell lung, ovarian, head and neck, gastric, esophageal and prostate cancers.[1–10] Docetaxel is mainly eliminated from the body by the hepatic metabolism. Population pharmacokinetic (PPK) models of docetaxel have been developed using data obtained from patients treated in clinical trials[11] where body surface area (BSA), Albumin (ALB), age, α_1-acid glycoprotein (AGP) and liver function were found to be the significant covariates for docetaxel clearance. Docetaxel clearance was decreased in patients with liver dysfunction. It may therefore be necessary to reduce the dose of docetaxel for these patients because the frequency of toxic events may increase.

More recently, a PPK model has been developed which incorporated liver function as a multi-categorical covariate of docetaxel clearance for Japanese patients, and dose reduction strategies by 20–40% of the standard dose (*i.e.*, 60 mg/m^2) have been proposed, depending upon the severity of liver dysfunction.[12] In order to evaluate the efficacy and safety of these recommended dose reduction strategies, a clinical trial study needs to be conducted where a sufficient number of patients are allocated and the decision for dose adjustment could be made. However, in real situations, it is difficult to recruit a sufficient number of patients with liver dysfunction for clinical trials because patients with moderate to severe liver dysfunction are usually excluded. Recently, clinical trial simulations, which is a Monte Carlo prediction technique based on population pharmacokinetic/pharmacodynamic (PPK/PD) models, have been utilized to estimate the outcome of clinical trials before embarking on an expensive clinical trial.[13,14] Therefore, this study carried out, for the first time, clinical trial simulations in which the Japanese standard dose of docetaxel was compared with the reduced dose of the

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drug in cancer patients with liver dysfunction, from the standpoints of survival and the number of safety events (*e.g.*, febrile neutropenia (FN)) as the primary and secondary endpoints, respectively. Several dose-response models (*i.e.*, time to death, time to progression, time to drop-out, FN occurrence and neutropenia occurrence), when combined with models for the distribution of covariates in a target population and a particular study design, allow for the clinical trial simulations for that design.

The simulation process (as a validation step) was evaluated with the use of the phase II data[15] by comparing the predicted trial results obtained by the medians of simulation with the actual phase II trial outcomes. After successful validation, 200 clinical trial simulations in which a reduced dose (40 or 50 mg/m^2) of docetaxel was compared with the standard dose (60 mg/m^2) of docetaxel in non-small-cell lung cancer (NSCLC) patients with liver dysfunction were performed.

PATIENTS AND METHODS

Log-binominal Regression for Febrile Neutropenia Occurrence 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, an age $\geq$20 years, an 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$3000/μl, platelet count $\geq$75000/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. 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. Docetaxel was infused intravenously over 1 h every 3 weeks. Most patients received the approved dose in Japan of 60 mg/m^2, and attending physicians were allowed to reduce the dose depending on liver function, performance status (PS), or the extent of prior chemotherapy, and to administer granulocyte-colony stimulating factors (G-CSF) when patients had fever. The administration of G-CSF should not affect the occurrence of FN, because G-CSF was given after the FN event. FN was defined as a fever of greater than 38 °C which required antibiotics. The variables included for a log-binominal regression (LBR) were: PS, AGP and the area under the plasma concentration-time curve (AUC). The AUC was calculated as dose/the systemic docetaxel clearance in each patient. Docetaxel clearance of each patient was obtained from the PPK study of docetaxel developed for Japanese cancer patients.[12] An LBR was performed by a generalized linear modeling method with the log link function and the error term which has a binomial distribution.

Clinical Trial Simulation in Patients with Liver Dysfunction Liver dysfunction was defined as follows: alkaline phosphatase (ALP) is grade $\geq$1 and aspartate aminotransferase (AST)/alanine aminotransferase (ALT) is grade $\geq$2. These grades were categorized according to the National Cancer Center Institute-Common Toxicity Criteria version 2.

The randomized trial in patients with liver dysfunction was simulated using a clinical trial simulation platform based on the Monte Carlo technique. Simulated patients with liver dysfunction were randomly assigned centrally in a 1 : 1 ratio to receive the Japanese standard dose (60 mg/m^2) or a reduced dose (40 or 50 mg/m^2) of docetaxel as a 1 hour-infusion every 3 weeks. 40 mg/m^2 applied for patients with sever liver dysfunction (liver function index (HEP) grade 3) which described by ALP is grade $\geq$1 and AST/ALT is grade $\geq$3 and 50 mg/m^2 applied for patients with mild liver dysfunction (HEP2) which described by ALP is grade $\geq$1 and AST/ALT is grade=2. All of the patients were followed up for 24 months. FN events were simulated at the end of every cycle and once an event occurred; a 20% dose reduction was applied to the next cycle and thereafter. After two dosage reductions, the treatment was stopped. In addition, the treatment was stopped when progression occurred.

The primary endpoint was the overall survival and the secondary endpoint was to compare the number of patients who experienced FN between the two treatment regimens. These endpoints were evaluated every 3 weeks.

The number of patients needed for the study was based on the results of a previous phase II study.[15]

The study design provided 90% power to demonstrate the non-inferiority of the hazard ratio of the Japanese standard dose of docetaxel to a reduced dose of docetaxel for the overall survival, assuming a non-inferiority criterion of 15 percentage points with a one-sided 5% level of significance. In the result of the sample size estimate, at least 1000 patients per arm needed to be enrolled in this study. The hazard ratio and confidential interval were calculated using the Cox proportional hazard regression. Comparisons of secondary end points were assessed among treatments by Pearson's chi-square test with a two-sided 5% level of significance.

The randomized trial in patients with liver dysfunction was simulated and each simulated trial provided a value of the test statistic for the analysis and the number of successful trials (*i.e.*, those in which the upper limit of hazard ratio confidential interval above 1.15 and p-value of Person's chi-square test above 0.05 was rejected) was counted for the power of the analysis.

Settings of Clinical Trial Simulation Platform The models to predict the efficacy and safety of docetaxel were constructed by using the graphic modeler of Pharsight Trial Simulator (version 2.2, Pharsight Corp, Mountain View, CA, USA). Patient characteristics used for simulation were generated according to the distributions of various covariates extracted from Phase II study[15] or PPK study[12] (Table 1). ALB was found to be negatively correlated with AGP ($r=0.477$, $p=0.01$) and positively correlated with (BSA; $r=0.241$, $p=0.01$). These correlations were considered in the covariate generation process of the simulation. The PPK model of docetaxel developed for Japanese cancer patients is a 3-compartment model with a first-order elimination.[12] The pharmacokinetic model was parameterized in terms of CL (clearance), the volume of distribution of the central compartment (V_1) as well as those of two peripheral compartments (V_2 and V_3) and intercompartment clearances (Q_2 and Q_3). A log-normal distribution was assumed for the inter-individual variabilities of CL, V_1, V_3 and Q_3. For example, the inter-individual variability of CL was modeled as $CL_j=\hat{CL}\cdot\exp(\eta_{jCL})$, where CL_j and $\hat{CL}$ are the estimated values in an individual j and the population mean for docetaxel clearance, respectively and η_{jCL} is the individual random perturbation with a mean of zero and a variance ω^2_{CL}. Intra-individual residual variability (σ^2) was also described by a log-normal distribution model. The covariates (*i.e.*, AGP, ALB, BSA and HEP) were integrated in the PPK model as follows:

$$\hat{CL}=\theta_1\cdot(BSA/1.53)^{\theta_2}\cdot(ALB/3.7)^{\theta_3}\cdot(97/AGP)^{\theta_4}\cdot LIV\cdot EXP(\eta_1) \quad (1)$$

$$LIV=1+\theta_5\cdot HEP2+\theta_6\cdot HEP3 \quad (2)$$

where HEP2 is set to 1 if ALP is grade $\geq$1 and AST/ALT is grade=2 and to 0 otherwise and HEP3 is set to 1 if ALP is grade $\geq$1 and AST/ALT is grade $\geq$3 and to 0 otherwise.

The above PPK model then was used to simulate drug exposure (AUC and the maximum unbound drug concentration in plasma, Cmax,u), using model parameters summarized in Table 1. The logistic model of grade 4 neutropenia previously discussed was used to demonstrate the exposure to severe toxicity.[16] Accordingly, the logistic model was specified as follows:

$$\log\left[\frac{P}{1-P}\right]=\sum_{i=1}^{n}\theta_i\cdot X_i(t) \quad (3)$$

in which $\theta=(\theta_1, \theta_2, \ldots, \theta_n)$ is a vector of parameters and X is a vector of covariates and the parameters of this logistic model are summarized in Table 1. Both of these models were based on data obtained after the first course of treatment, but the assumption was made for the simulations that both models were applicable to the entire time course of treatment. A Weibull model was employed to express the time to death, time to progression and time to drop-out, as previously reported,[17] and thus the log hazard for these 3 events was specified as:

$$\log(\lambda(t,\theta))=\theta_1+\theta_2\cdot\log(t)+\sum_{i=3}^{n}\theta_i\cdot X_i(t) \quad (4)$$

in which $\theta=(\theta_1, \theta_2, \ldots, \theta_n)$ is a vector of the parameters and X is a vector of covariates. The parameters of these models are summarized in Table 1. In details, cumulative AUC, AGP and disease sites (1 in the presence of metastasis, otherwise 0) were employed for the prediction of time to progression and time to death, but were not considered for the prediction of time to drop-out, as previously reported,[17] Cmax,u and the cumulative AUC calculated from the PPK model were the inputs to the models for safety and survival, respectively.

Evaluation of the Clinical Trial Simulation Platform Using Phase II Study Data In order to evaluate the settings of the clinical trial simulation platform, time courses of death and summary statis-

Table 1. Distribution of Covariates PK/PD Parameters Used in the Simulation

Parameter and Characteristic	Mean and range	SD	%	Value
Covariates				
Albumin (g/dl)	3.68 (1.3–4.6)	0.464		
α_1-Acid glycoprotein (mg/dl)				
HEP1	106 (19–259)	43.4		
HEP2 or HEP3	127 (82–228)	47.4		
Body surface area (m^2)	1.54 (1.17–1.99)	0.16		
HEP1			91	
HEP2			5	
HEP3			4	
Disease sites				
Yes (1)			27	
No (0)			73	
Population PK model[a)]				
CL (l/h)				
θ_1				29.3
θ_2				1.11
θ_3				2
θ_4				0.251
θ_5				0.776
θ_6				0.623
θ_{V1} (l)				7.75
θ_{Q2} (l/h)				5.46
θ_{V2} (l)				8.69
θ_{Q3} (l/h)				19
θ_{V3} (l)				660
ω_{CL} (CV, %)				31
ω_{V1} (CV, %)				19
ω_{Q3} (CV, %)				31
ω_{V3} (CV, %)				38
σ (CV, %)				29
Logistic regression model for grade 4 neutropenia				
θ_1 (Cmax of unbound docetaxel (ng/ml))				9.1×10^{-3}
θ_2 (α_1-Acid glycoprotein (mg/dl))				-14.8×10^{-3}
Log-binominal regression for febrile neutropenia occurrence				
θ_1 (AUC (mg*h/l))				0.495[a)]
θ_2 (Performance status*)				1.62[a)]
θ_3 (α_1-Acid glycoprotein (mg/dl))				−0.004[a)]
θ_4 (Intercept)				−4.27[a)]
Time to progression model				
θ_1				−3.44
θ_2				0.762
θ_3 (Cumulative AUC (ug*h/l))				−0.0395
θ_4 (α_1-Acid glycoprotein (g/l))				1.21
θ_5 ($\geq$2 disease sites)				0.739
Time to death model				
θ_1				−4.94
θ_2				0.368
θ_3 (Cumulative AUC (ug*h/l))				−0.0745
θ_4 (α_1-Acid glycoprotein (g/l))				0.891
θ_5 ($\geq$2 disease sites)				0.938
Time to death model				
θ_1				−5.76
θ_2				1.05

a) Table 2 log transformation. SD; Standard deviation. HEP1 is set to 1 if ALP is grade$<$1 and AST/ALT is grade$\leq$1, and to 0 otherwise. HEP2 is set to 1 if ALP is grade$\geq$1 and AST/ALT is grade$=$2, and to 0 otherwise. HEP3 is set to 1 if ALP is grade$\geq$1 and AST/ALT is grade$\geq$3, and to 0 otherwise.

tics (*i.e.*, the median overall survival time and the median percentage of patients who experienced grade 4 neutropenia and FN) were compared between the results of the observed phase II study and simulation outcomes. These endpoints were evaluated every 3 weeks. Two hundred complete trials were stochastically simulated using the Monte Carlo technique. A total of 75 patients without liver dysfunction were enrolled and 60 mg/m^2 docetaxel was continuously administered as a 1 hour-infusion once every three weeks during the time the patient was participating in this phase II clinical trial simulation. All of the patients were followed up for 18 months. Grade 4 neutropenia events were simulated at the end of every cycle and once an event occurred; a 20% dose reduction was applied to the next cycle and thereafter. After two dosage reductions, the treatment was stopped. In addition, the treatment was stopped when progression occurred. Kaplan-Meier analyses were performed on each simulated trial. The value of several different statistics (*i.e.*, median survival time, 1-year survival, number of cycles per patient and the number of patients who experienced grade 4 neutropenia and FN) computed on the observed data sets described below, was referenced to the distribution of the similar statistics computed on the simulated trials.

The observed data sets for 75 Japanese patients were obtained from open, multi-center, nonrandomized, phase II trials conducted in Japan to evaluate the efficacy and safety of docetaxel, without liver dysfunction and prior therapy, in patients with NSCLC. The detailed protocols and eligibility criteria of these studies are presented elsewhere.[15] The starting dose of docetaxel was either 60 mg/m^2 given as a 1 to 2 hour-infusion every 3 to 4 weeks. The overall median survival time was 297 days (10.6 months), with a 1-year survival rate of 41%. A progression of disease according to the World Health Organization (WHO) criteria was seen in 31% of the patients. Grade 3 or 4 neutropenia was seen in 88% of the patients.

Statistical Analyses Statistical analyses were performed using statistical software programs, SPSS (version 15J, SPSS Japan Corporation, Tokyo, Japan), S-plus Professional Edition (version 6.2, Insightful Corporation, WA, USA) and a sample size calculator, PASS (version 2008, NCSS, UT, USA).

RESULTS

Log-binominal Regression for Febrile Neutropenia Occurrence FN occurred in 9 patients. Almost 90% of the patients had good PS (0 or 1) and 14% previously received chemotherapy of more than 3 regimens. 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.

Table 2 shows the result of LBR. The AUC (p=0.011) and performance status factor (PS*; p=0.011), which is set to 1 if PS is 2 or 3 and to 0 otherwise, were detected at a two sided 5% significance level as significant risk factors associated with FN occurrence, with a relative risk of 1.64 (95% confidence interval, 1.12–2.40) and 5.06 (95% confidence interval, 1.44–17.8), respectively.

In the evaluation of the clinical trial simulation platform, the median number of patients who experienced FN was 5 higher in the simulation than in the phase II study (20 *vs.* 15, respectively). However, the observed value was included in the range of simulated values. Therefore, this model was considered to be an effective one with a good ability to discriminate between patients with and without fever.

Evaluation of the Clinical Trial Simulation Platform Using Phase II Study Data As shown in Table 3, the observed values in the phase II study of the median number of treatment cycles administered, median cumulative dose and the number of patients that experienced FN were always included in the range of simulated values. The median number of patients who experienced grade 4 neutropenia was slightly higher in the simulation than in the phase II study. Nevertheless, the median overall survival time and 1-year survival rate were similar in the simulation and in

Table 2. Log-binominal Regression for the Occurrence of Febrile Neutropenia (n=200)

Variable	Relative risk (95% Confidence interval)	p
Area under the plasma concentration *vs.* time curve (AUC; mg*h/l)	1.64 (1.12–2.40)	0.011
Performance status* (0 for PS 0/1 or 1 for PS 2/3)	5.06 (1.44–17.8)	0.011
α_1-Acid glycoprotein (mg/dl)	0.996 (0.982–1.010)	0.553
Intercept	0.014 (0.003–0.082)	$<$0.001

the phase II study. Figure 1 demonstrates that a similar time course of death was observed in the Kaplan-Meier plots of the simulations and the phase II data.

Clinical Trial Simulation in Patients with Liver Dysfunction Table 4 shows the result of the simulation of phase III trial in 2000 patients with ''liver function index (HEP) 2 or 3'' liver dysfunction (*i.e.*, HEP2 is set to 1 if alkaline phosphatase (ALP) is grade ≥ 1 and aspartate aminotransferase (AST)/alanine aminotransferase (ALT) is grade $=2$ and to 0 otherwise and HEP3 is set to 1 if ALP is grade ≥ 1 and AST/ALT is grade ≥ 3 and to 0 otherwise). Both treatment arms were well balanced in the 200 simulated trials with respect to the baseline characteristics. The median number of treatment cycles was similar in both arms (3 cycles; range, 1 to 19). The median

Table 3. Evaluation of the Simulation (200 trials); Summary Statistics for Exposure, Toxicity Events, and Overall Survival for 75 Patients

	Phase Ⅱ	Simulation*
Treatment received		
Total cycles administered	210	227 (176–269)
Median	2 (1–7)	3 (1–8)
Median cumulative dose	130 (60–420)	161 (59–480)
Overall survival		
Median survival time (month)	10.6	11.25 (8.25–16.5)
1-year survival K-M estimate (%)	41	46.7 (28.8–65.6)
Toxicity		
Number of patients that experienced grade 4 neutropenia	42	52 (43–64)
Number of patients that experienced FN	15	20 (9–30)

K-M, Kaplan-Meier. * Data are presented as median (range).

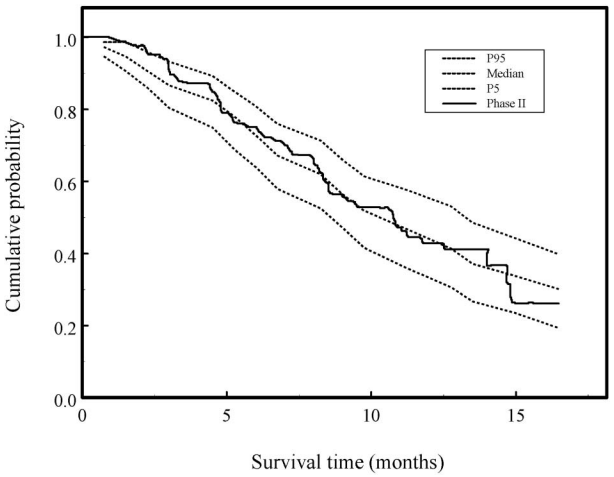

Fig. 1. Evaluation of the Simulation and Ability of the Simulation to Predict Survival in the Phase II Patients

Solid line, the Kaplan-Meier estimate of the cumulative probability of survival in the phase II patients ($n=75$). Dotted lines, the median, 5th (P5), and 95th (P95) percentiles of 200 Kaplan-Meier survival curves obtained from simulations of the phase II patients.

Table 4. Simulation of the Phase III Trial; Summary Statistics for Exposure, Toxicity Events, and Overall Survival in 2000 Patients with HEP2 or HEP3 Hepatic Dysfunction

	Simulation (200 trials)*	
	reduced dose arm	standard dose arm
	(40 mg/m^2 or 50 mg/m^2)	(60 mg/m^2)
Treatment received		
Total cycles administered	3677 (3462–3888)	3518 (3320–3751)
Median	3 (1–19)	3 (1–19)
Median cumulative dose	120 (35–760)	168 (53–1128)
Overall survival		
Median survival time (month)	11.25 (9.75–12.75)	11.25 (9.75–12.75)
1-year survival K-M estimate (%)	46.1 (42.6–51.3)	46.3 (42.1–50.8)
Toxicity		
Number of patients that experienced grade 4 neutropenia	649 (610–692)	718 (671–754)
Number of patients that experienced FN	281 (240–329)	467 (431–514)**
Proportion of trials above each non-inferiority limit (NIL) (%)		
NIL$<$1.10		51
1.10$\leq$NIL$\leq$1.15		34.5
NIL$>$1.15		0.15

K-M, Kaplan-Meier. * Data are presented as medina (range). ** Significant difference ($p<0.05$) as assessed by Person's chi-square test in each trial simulation.

proportion of patients who experienced FN was 28.1 % and 46.7% in the reduced dose arm and the standard dose arm, respectively, and that at a two sided 5 % significance level, dose reductions due to FN were fewer in the reduced dose arm than the standard arm in all simulated clinical trials. Patients were able to receive a median cumulative dose of 168 mg/m^2 and 120 mg/m^2 in the arm with the standard dose and the arm with reduced dose, respectively; therefore, the reduced dose arm experienced an approximately 30% decrease in dose intensity, despite the lower toxicity rate and the resulting lower number of dose reductions. Nevertheless, the median overall survival time in the group that received the reduced dose of docetaxel was similar to the group that received the standard dose of docetaxel and the median 1-year survival rate was also similar in both docetaxel treatment groups. The non-inferiority limit, a 1.15 of hazard ratio of the reduced dose group to the standard dose group were met in 85.5% in the simulated clinical trials (totally 200 trials).

DISCUSSION

This study was aimed to perform clinical trial simulations to evaluate the dose reduction strategy of docetaxel for Japanese patients with liver dysfunction, which we previously proposed.[12] For this purpose, an LBR was performed for FN induced by docetaxel in these patients.

Fever occurring in neutropenic patients remains a common life-threatening complication of cancer chemotherapy.[18] FN requires treatment with broad-spectrum antibiotics[19,20] and the standard setting of care has required patient hospitalization with close monitoring until fever resolution and recovery from neutropenia. Therefore, FN is recognized to be a dose-limiting factor (DLF) of cancer chemotherapy and, is usually used as a criterion to drive dosage reduction in the clinical situation. In this sense, FN is more suitable as a criterion of dosage reduction than grade 4 neutropenia. Therefore, to drive dosage reduction by FN occurrence and to estimate each relative risk of risk factor in clinical settings, a model to predict FN occurrence was developed in this study. In the result of the present LBR, the relative risk of AUC was determined to be 1.64. This indicates that the risk of FN for cancer patients was increased 1.39 times as the AUC increases by 1 mg*h/l. The median cumulative AUC in the patients without liver dysfunction which received the standard dose (60 mg/m^2) was 8.58 mg*h/l, whereas the cumulative AUC in the patients with liver dysfunction, HEP2 and HEP3 which received the standard dose was simulated to be 13.3 mg*h/l and 15.9 mg*h/l respectively. An increase of median cumulative AUC in the patients with liver dysfunction was 1.55–1.85 in comparison with patients without liver dysfunction. In other words, the risk of FN occurrence may at least be doubled in the presence of liver dysfunction.

Bruno *et al.*[21] reported that AGP and docetaxel clearance are the significant covariates associated with FN occurrence, based on a stepwise logistic regression analysis for subjects enrolled in Phase II studies in Europe and United State. The odds ratio of each risk factor was calculated from the coefficients of a logistic regression model. However, the relative risk cannot be directly estimated from the results of a logistic regression analysis. In contrast, a log-binomial model produces an unbiased estimate of the adjusted relative risk.[22,23] Relative risk is clinically more intuitive than odds ratio for a measure of association between the exposure and the disease outcome. Therefore, in this study, an LBR was conducted using clinical data from Japanese cancer patients treated with docetaxel to develop a model of FN occurrence, and to estimate the relative risk of each factor to FN occurrence. The developed LBR model, which described the probability of FN occurrence, was used as a criterion to achieve a dosage reduction in a subsequent clinical trial simulation.

Clinical trial simulations were utilized by Veyrat-Follet *et al.*[17] for dosage optimization in NSCLC patients with high AGP. In this study clinical trial simulations were performed to evaluate alternative dosage regimens for liver dysfunction NSCLC patients treated with docetaxel. Reliable models were incorporated to predict toxicity (grade 4 neutropenia), time to progression (stop treatment) and drop-out, which were reported by Veyrat-Follet *et al.*[17] and Minami *et al.*[16] "Posterior predictive assessment,"[24] in which the percentiles and graphics of the posterior distributions of key statistics were reported after simulations, were used to validate the model. Using this approach, the overall simulation process was evaluated. To evaluate the simulation process, covariates (*i.e.*, AGP, ALB, BSA, HEP and disease sites), the dose intensity and the survival and toxic event (grade 4 neutropenia) were simulated. As the

result of the evaluation of the simulation process, similar time courses of death were observed in the Kaplan-Meier plots of the simulations and the observed phase II data (Fig. 1). The median number of patients who experienced grade 4 neutropenia was slightly higher in the simulation than in the phase II study, but the median overall survival time and 1-year survival rate were similar in the simulation and in the phase II study. The clinical trial simulation produced data patterns similar to the actual pattern, although the simulation process did not take into account all of the features of the phase II studies such as treatment delay and toxicities other than hematology (*i.e.*, nausea/vomiting, or alopecia).

The selection of the optimal dose of docetaxel for patients with liver dysfunction (HEP2 or HEP3) poses a challenge, because liver dysfunction is one of the dose-limiting toxicity of the anti-tumor drug. The simulation of safety endpoints enabled an evaluation of the possible doses for patients with liver dysfunction. The results of the trial simulation suggested that the arms with dose reductions of 50 mg/m^2 in patients with HEP2 and 40 mg/m^2 in patients with HEP3 may show the lower toxicity rates by 28.1% and 46.7%, respectively, than the arm with the standard dose. On the other hand, although there was an approximately 30% decrease in dose intensity in the reduced dose arm, the simulated trial showed a median overall survival time (11.25 months) in the dose reduction arm similar to the standard regimen of 60 mg/m^2 and the non-inferiority criteria of the hazard ratio of reduced dose group to the standard dose group were met in 85.5% cases of the simulated clinical trials. This implies that it may be possible to decrease toxicity, without loss of efficacy, by reducing the docetaxel dose in patients with liver dysfunction. Furthermore, clinical trial simulations may be useful to provide evidence of safety and efficacy and to quantitatively evaluate different scenarios of drug administration protocol when it is difficult to conduct a real clinical study.

In our clinical oncology practice with a short period (3-week), we did not observe the patients' survival. Therefore, the simulation model for the survival was adopted from Veyral-Follet *et al.*,[17] and therefore, the external validation of survival model was only performed by comparing between the simulated and the actual survival data of the clinical phase II trial in Japan, which showed reasonably overlapping patterns. The lack of robust validation, therefore, is the major limitation of this study, and further validation should be required to confirm the survival estimation in a long-term clinical monitoring. However, if it is possible for the physicians to appropriately reduce the docetaxel dose based on our proposed strategy to get the same AUC, the overall survival of the patients may not be significantly changed between the patients with normal and failed liver functions.

In conclusion, a model was developed to predict FN occurrence in Japanese cancer patients treated with docetaxel and clinical trial simulations were conducted for the first time to predict clinical outcomes of docetaxel for liver dysfunction patients and the results of this simulation study support the strategy that we had proposed to reduce the dose of docetaxel according to the extent of liver dysfunction.

Acknowledgements This study was supported in part by Grants-in-Aid from the Ministry of Health, Labor and Welfare, Japan, and the High-Technology Research Project of Showa University. We gratefully acknowledge the helpful contributions of the Pharsight Corporation in the development of the clinical trial simulation model. We also thank Drs. Y. Shyr and A. Shintani for helpful suggestions on statistics.

REFERENCES

1) Jones S. E., Savin M. A., Holmes F. A., O'Shaughnessy J. A., Blum J. L., Vukelja S., McIntyre K. J., Pippen J. E., Bordelon J. H., Kirby R., Sandbach J., Hyman W. J., Khandelwal P., Negron A. G., Richards D. A., Anthony S. P., Mennel R. G., Boehm K. A., Meyer W. G., Asmar L., *J. Clin. Oncol.*, **24**, 5381–5387 (2006).
2) Bear H. D., Anderson S., Brown A., Smith R., Mamounas E. P., Fisher B., Margolese R.,Theoret H., Soran A., Wickerham D. L., Wolmark N., *J. Clin. Oncol.*, **21**, 4165–4174 (2003).
3) Georgoulias V., Ardavanis A., Tsiafaki X., Agelidou A., Mixalopoulou P., Anagnostopoulou O., Ziotopoulos P., Toubis M., Syrigos K., Samaras N., Polyzos A., Christou A., Kakolyris S., Kouroussis C., Androulakis N., Samonis G., Chatzidaki D., *J. Clin. Oncol.*, **23**, 2937–2945 (2005).
4) Georgoulias V., Ardavanis A., Agelidou A.,

Agelidou M., Chandrinos V., Tsaroucha E., Toumbis M., Kouroussis C., Syrigos K., Polyzos A., Samaras N., Papakotoulas P., Christofilakis C., Ziras N., Alegakis A., *J. Clin. Oncol.*, **22**, 2602–2609 (2004).

5) Vasey P. A., Jayson G. C., Gordon A., Gabra H., Coleman R., Atkinson R., Parkin D., Paul J., Hay A., Kaye S. B., *J. Natl. Cancer Inst.*, **96**, 1682–1691 (2004).

6) Dreyfuss A. I., Clark J. R., Norris C. M., Rossi R. M., Lucarini J. W., Busse P. M., Poulin M. D., Thornhill L., Costello R., Posner M. R., *J. Clin. Oncol.*, **14**, 1672–1678 (1996).

7) Van Cutsem E., Moiseyenko V. M., Tjulandin S., Majlis A., Constenla M., Boni C., Rodrigues A., Fodor M., Chao Y., Voznyi E., Risse M. L., Ajani J. A., *J. Clin. Oncol.*, **24**, 4991–4997 (2006).

8) Petrylak D. P., Tangen C. M., Hussain M. H., Lara P. N. Jr., Jones J. A., Taplin M. E., Burch P. A., Berry D., Moinpour C., Kohli M., Benson M. C., Small E. J., Raghavan D., Crawford E. D., *N. Engl. J. Med.*, **351**, 1513–1520 (2004).

9) Tannock I. F., de Wit R., Berry W. R., Horti J., Pluzanska A., Chi K. N., Oudard S., Théodore C., James N. D., Turesson I., Rosenthal M. A., Eisenberger M. A., *N. Engl. J. Med.*, **351**, 1502–1512 (2004).

10) Muro K., Hamaguchi T., Ohtsu A., Boku N., Chin K, Hyodo I., Fujita H., Takiyama W., Ohtsu T., *Ann. Oncol.*, **15**, 955–959 (2004).

11) Bruno R., Vivier N., Vergniol J. C., De Phillips S. L., Montay G., Sheiner L. B., *J. Pharmacokin. Biopharm.*, **24**, 153–172 (1996).

12) Minami H., Kawada K., Sasaki Y., Tahara M., Igarashi T., Itoh K., Fujii H., Saeki T., Ozawa K., Sato H., *Cancer Sci.*, **24**, 144–149 (2009).

13) Holford N. H., Kimko H. C., Monteleone J. P., Peck C. C., *Annu. Rev. Pharmacol. Toxicol.*, **40**, 209–234 (2000).

14) Michelson S., Sehgal A., Friedrich C., *Curr. Opin. Biotechnol.*, **17**, 666–670 (2006).

15) Kunitoh H., Watanabe K., Onoshi T., Furuse K., Niitani H., Taguchi T., *J. Clin. Oncol.*, **14**, 1649–1655 (1996).

16) Minami H., Kawada K., Sasaki Y., Igarashi T., Saeki T., Tahara M., Itoh K., Fujii H., *Cancer Sci.*, **97**, 235–241 (2006).

17) Veyrat-Follet C., Bruno R., Olivares R., Rhodes G. R., Chaikin P., *Clin. Pharmacol. Ther.*, **68**, 677–687 (2000).

18) Bodey G. P., Buckley M., Sathe Y. S., Freireich E. J., *Ann. Intern. Med.*, **64**, 328–339 (1966).

19) Kojima A., Shinkai T., Soejima Y., Okamoto H., Eguchi K., Sasaki Y., Tamura T., Oshita F., Ohe Y., Saijo N., *Am. J. Clin. Oncol.*, **17**, 400–404 (1994).

20) Carlson J. W., Fowler J. M., Saltzman A. K., Carter J. R., Chen M. D., Mitchell S. K., Dunn D., Carson L. F., Adcock L. L., Twiggs L. B., *Gynecol. Oncol.*, **55**, 415–420 (1994).

21) Bruno R., Hille D., Riva A., Vivier N., ten Bokkel Huinnink W. W., van Oosterom A. T., Kaye S. B., Verweij J., Fossella F. V., Valero V., Rigas J. R., Seidman A. D., Chevallier B., Fumoleau P., Burris H. A., Ravdin P. M., Sheiner L. B., *J. Clin. Oncol.*, **16**, 187–196 (1998).

22) McNutt L. A., Wu C., Xue X., *Am. J. Epidemiol.*, **157**, 940–943 (2003).

23) Robbins A. S., Chao S. Y., Fonseca V. P., *Ann. Epidemiol.*, **12**, 452–454 (2002).

24) Gelman A., Carlin J. B., Stern H. S., Rubin D. B., ''Bayesian data analysis,'' Chapman & Hall, London, 1995.