Population Pharmacokinetics/Pharmacodynamics of Docetaxel in Phase II Studies in Patients With Cancer

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Purpose: **The population pharmacokinetic/pharmacodynamic (PK/PD) approach was prospectively integrated in the clinical development of docetaxel to assess the PK profile in a large population of patients and investigate systemic exposure as a prognostic factor for clinical outcome.**

Patients and Methods: **PK analysis was performed at first course in 24 phase II studies of docetaxel monotherapy using four randomized limited-sampling schedules. Bayesian estimates of clearance (CL), area under the concentration-time curve (AUC), and peak and duration of plasma levels greater than threshold levels were used as measures of exposure. PD data included for efficacy, response rate, time to first response, and time to progression (TTP) in breast cancer and non-small-cell lung cancer (NSCLC), and for toxicity, grade 4 neutropenia, and febrile neutropenia at first course and time to onset of fluid retention. PK/PD analysis was conducted using logistic and Cox multivariate regression models.**

Results: **PK protocol implementation was successful. Most of the patients registered (721 of 936, 77%) were sampled and 68% were assessable for PK (640 patients). First-course docetaxel AUC was a significant predictor ($P = .0232$) of TTP in NSCLC (n = 151). Docetaxel CL was a strong independent predictor ($P < .0001$) of both grade 4 neutropenia and febrile neutropenia (n = 582). Cumulative dose was the strongest predictor ($P < .0001$) of the time to onset of fluid retention (n = 631). However, the duration of exposure over 0.20 μmol/L (0.16 μg/mL) at first course was an independent predictor ($P = .0029$). Few patients (n = 25, 4%) received the recommended dexamethasone premedication.**

Conclusion: **First-course docetaxel PK is a predictor of first-course hematologic toxicity, but also of fluid retention, which is cumulative in nature. Patients with elevated hepatic enzymes have a 27% reduction in docetaxel CL and are at a higher risk of toxicity. A starting dose of 75 mg/m² is currently being evaluated in this population. Prospective implementation of large-scale population PK/PD evaluation is feasible in early drug development and this approach generates clinically relevant findings.**

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IMPLEMENTATION OF pharmacokinetic/pharmacodynamic (PK/PD) studies is increasingly seen as an essential tool for new drug development. The usefulness of this approach has recently been discussed.[1-3] One of the expected benefits of this approach is more informative labeling to assist clinicians in optimizing drug use.[2,4] Specifically, this approach allows one to (1) assess the PK profile of the drug of interest over a large and representative population of patients (the target population); (2) estimate the magnitude of interpatient PK variability and relate it to pathophysiologic factors (ie, build a population PK model); (3) generate individual estimates of patient PK parameters (eg, plasma clearance [CL]) and systemic exposure (area under the plasma concentration-time curve [AUC], time over a threshold plasma level, etc) using the population PK model and Bayesian estimation; and (4) investigate PK estimates as prognostic factors for clinical outcome (PD), including efficacy and safety end points (PK/PD analysis).

The PK/PD analysis allows assessment of the clinical relevance of PK variability and identification of subpopulations of patients potentially at risk of unusual exposure because of altered PK.

Population PK/PD has been implemented prospectively in the clinical development of docetaxel (Taxotere; RP 56976, Rhone-Poulenc Rorer, Antony, France) a new taxoid active in several tumor types.[5,6] We present here the study design (PK-sampling strategy) and implementation and PK/PD

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models developed for docetaxel. The population PK model, which includes technical aspects of model building and validation, has been presented elsewhere.[7]

PATIENTS AND METHODS

Patients/Treatment

Data were prospectively collected from patients entered onto 24 phase II open, nonrandomized studies conducted from May 1992 to March 1994 to assess docetaxel clinical efficacy in a variety of tumor types, including breast cancer,[8-15] non–small-cell lung cancer (NSCLC),[16-21] ovarian cancer,[22] head and neck cancer,[23] melanoma,[24] renal cancer,[25] colorectal cancer,[26-28] gastric cancer,[29] small-cell lung cancer,[30] and soft tissue sarcoma.[31] Detailed protocols and clinical results of these studies are described in the references given. Briefly, criteria for eligibility included histology, at least one bidimensionally measurable lesion, adequate bone marrow reserve (absolute neutrophil count $> 2{,}000/\mu L$), adequate renal function (normal creatinine level), and adequate liver function (total bilirubin level < 1.25 times upper limit of normal [ULN], ALT ≤ 2 times ULN or ≤ 3 times ULN in case of proven liver metastases). According to the tumor type, patients could have received various extents of prior treatment. Docetaxel starting dose was either 75 mg/m^2 or 100 mg/m^2 given as a 1-hour infusion every 3 weeks. Dose reduction (25%) or delay of subsequent courses was permitted, based on the degree of toxicity observed.

The studies were conducted at multiple centers in Europe and in the United States (see Appendix). Protocols were approved by local ethics committees or institutional review boards.

Design of PK-Sampling Strategy

There is no formal solution for the optimal design of population PK/PD studies (number and time of samples per patients, number of patients, etc),[3] especially when the goal (as here) is to estimate both population parameters and individual parameters. The aim of the sampling strategy is to define the full PK profile over the population, the so-called full-screen approach,[32] by drawing a few samples per patient and varying (randomizing) the sampling times[33] among patients.

Recognizing the goal of individual estimates, our sparse sampling strategy design is based on optimal individual sampling times computed using preliminary population PK parameter estimates obtained from phase I data.[34] These sampling times are D-optimal[35] and were computed using the APIS package, version 3.03a.[36] Recognizing the goal of population estimates, separate sampling schedules, each consisting of early, mid-, and late time samples, were used to assure that the population PK samples were well spread across the available sampling time range.

There are six D-optimal sampling times (OST) for a three-compartment PK model (involving six parameters). OSTs were computed over a 0- to 24-hour observation interval. The estimated times (hours:minutes) are as follows: 0:30 (mid-infusion) or 1:00 (end of infusion), 1:15, 1:45, 3:45, 8:20, and 24:00.

The sampling strategy consists of four different sampling schedules (Table 1), which were randomly assigned to patients at study entry. Each schedule consists of three sampling times that ranged between mid-infusion and 6 hours (5 hours' postinfusion). The first sample is always taken during the infusion, either mid-infusion or just (5 minutes) before the end of the 1-hour infusion. The two other samples are drawn within 5 hours after the end of infusion. Six hours is the maximum observation time to comply with outpatient status. However, when possible (eg, for inpatients), one point could be replaced by a late sample drawn any time between 12 and 24 hours. A predrug sample (optional) is also requested to check the absence of analytic interference in patient plasma.

Table 1. Sampling Strategy Implemented in Phase II Studies

Sampling Schedule No.	Sampling Times: 1 During Infusion	2* After Infusion: Minutes	3 After Infusion: Hours
1	5 minutes before end	10	2
2	30 minutes after start	20	3
3	5 minutes before end	30	4
4	30 minutes after start	60	5

*When possible, this sample will be replaced by a blood sample obtained at a later time, ie, any time between 12 and 24 hours postinfusion.

A PK case report form (CRF) was designed to document actual sampling times, as well as actual time of beginning and end of infusion. In some patients who experienced infusion-related hypersensitivity reactions, administration was interrupted and then resumed shortly after (eg, 30 minutes). Actual times of starting and stopping the second infusion were also documented on the PK CRF. Docetaxel was assayed in plasma samples using high-performance liquid chromatography and UV detection after solid-phase extraction[37] in two different cross-validated centers.

PK Data Analysis

The collected data permitted elaboration and validation of a population PK model that related docetaxel CL to pathophysiologic factors. This analysis has recently been reported.[7] Population parameters from this analysis were used as prior information to estimate each individual's PK parameters from his plasma concentrations using Bayesian estimation as implemented in the NONMEM computer program (version IV, level 2.0).[38]

The PK model is a three-compartment structural model with first-order elimination. The basic parameters are elimination CL (liters per hour), volume of distribution of the central compartment, and intercompartmental rate constants. The interpatient variability of PK parameters is modeled as (eg, for CL): $CL_j = \hat{CL}_j \exp(\eta_{jCL})$, where η_{jCL} denotes the (proportional) difference between the true parameter (CL_j) of individual j and the typical value in the population ($\hat{CL}_j$) according to covariable values affecting $\hat{CL}$ for the j^{th} individual. Residual variability is modeled as proportional, consistent with the constant coefficient of variation of the assay measurement error.[37] Individual plasma CL_j, area under the plasma concentration-time curve (AUC_j), peak plasma level, and time that plasma levels were greater than given threshold levels are used as measures of drug exposure.

CL_j is directly estimated by the Bayesian CL after fitting. Based on the estimate of CL_j, the following clearance factor (CLf) is generated: CLf_j = (mean CL)/CL_j. Note that CLf_j is inversely proportional to CL_j: it takes values less than 1 for patients with CL greater than the mean, and values greater than 1 for patients with CL less than the mean (eg, 2.0 for a 50% decrease in CL). Use of this derived parameter facilitates the interpretation of PK/PD models in term of clearance changes, as will be seen later.

AUC_j is computed as follows: AUC_j ($\mu g \cdot h/mL$) = $Dose_j$ (mg)/CL_j (L/h). Peak plasma level is taken to be the model-predicted concentration at the end of infusion. Duration of exposure to plasma levels greater than 0.16 μg/mL (0.20 μmol/L) ($t_{0.20}$), 0.080 μg/mL (0.10 μmol/L) ($t_{0.10}$), and 0.040 μg/mL (0.05 μmol/L) ($t_{0.05}$) is computed from estimated

parameters using the implicit equation solver of EXCEL spread sheet, version 5 (Microsoft Corp).

PK/PD Analysis

PK/PD analysis was conducted using as independent variables individual estimates, CLf_j, other exposure parameters (see earlier), and several other covariables related to the patient's pathophysiologic status (demographics, disease spread) and extent of prior treatment. Docetaxel dose (milligrams per square meter), either given at first course or cumulative, was also considered as an independent variable measuring drug exposure.

Objective response rate, time to first response, and time to progression (TTP) were selected as the efficacy end points (dependent variables). Only data from patients with breast cancer and NSCLC were analyzed. Assessment of tumor response was made every 6 weeks according to World Health Organization (WHO) criteria. Objective responses (complete responses [CRs] and partial responses [PRs]) had to be confirmed after a minimum of 4 weeks and were reviewed by an independent panel. Time to first response was calculated from the first docetaxel infusion up to the date of the first objective response, either CR or PR, whichever occurred earlier. TTP was calculated from the first docetaxel infusion up to the date of progression.

For safety, the following end points were considered among all tumor types: (1) neutropenia (National Cancer Institute [NCI] grade) at first course; (2) Febrile neutropenia at first course. Febrile neutropenia was defined as fever greater than 38°C (NCI grade ≥II) with a concomitant NCI grade 4 neutropenia (neutrophil count <500/μL) that required antibiotics and/or hospitalization; and (3) time to onset of fluid retention calculated from the first docetaxel infusion up to the date of the first sign and/or symptom of fluid retention (peripheral edema, pleural or pericardial effusions, ascites, or weight gain).

Logistic regression was used to relate categorical end points, such as response rate and neutropenia grade, to the independent variables, while Cox regression was used for time to first response, TTP, and time to onset of fluid retention. Dose was the only time-dependent covariate in the Cox model. Model development involved stepwise inclusion and deletion of covariates. The significance level for variable entry or removal at each step was P less than .10; however, a final elimination pass, using P less than .05, was used to determine the covariates kept in the final model. The median time to onset of fluid retention was estimated using the Kaplan-Meier method. Analyses were performed using SAS software (SAS version 6.11; SAS Institute Inc, Cary, NC).

RESULTS

Study Implementation

The protocol was implemented at the first course of docetaxel treatment in 24 phase II studies conducted in more than 50 centers in Europe and three centers in the United States. Most of the patients registered (721 of 936, 77%) were sampled, and among them, 81 were not considered assessable for this analysis for the following reasons: not sampled at the first course (n = 12, 1.7%), lack of documentation of samples (n = 32, 4.4%), and samples lost during transfer from the clinical sites to the analytic laboratory (n = 18, 2.5%) or during assay procedure (n = 19, 2.6%). Overall, 640 patients (89% of patients sampled, 68% of patients treated) were assessable at first course. Compliance with the protocol was good, despite the unconventional

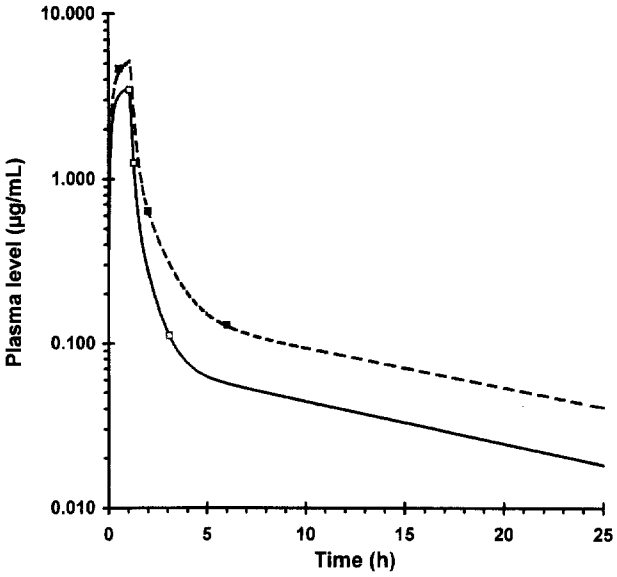

Fig 1. Docetaxel PK profile in representative patient with normal liver function (□) and patient with elevated hepatic enzymes (---■---). Lines denote model predictions after Bayesian estimation.

nature of the design and the multicenter and multinational setting of the studies. This could be attributed to the special attention paid to communication (investigators meetings, study initiation visits, etc) and monitoring to insure proper handling and documentation of plasma samples.

Typical individual PK profiles are shown in Fig 1, which illustrates two of the four sampling schedules. The full-population PK profile achieved by varying the sampling scheme across patients is illustrated in Fig 2 (data from a

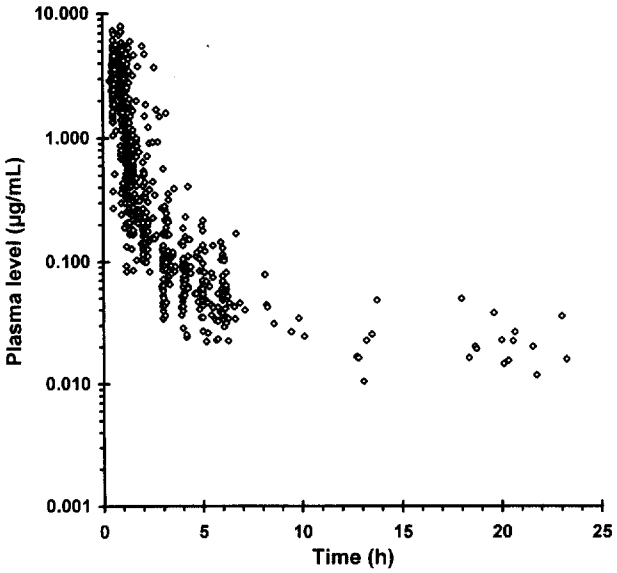

Fig 2. Docetaxel population PK profile in a subset of 254 patients.

subset of 254 patients). This profile comprises 716 data points, ie, a mean of 2.8 per patient (range, one to five). Overall, a fair number of late samples were obtained (67 samples from 50 patients).

Patient Characteristics at Baseline

Patient characteristics are listed in Table 2. The median age was 56 years; 42% were males and 58% females; 231 patients (36%) had breast cancer and 189 (30%) had NSCLC. Thirty-two percent of the patients were asymptomatic (WHO performance status, 0), whereas a performance status of 1 or 2 was reported in 54% and 14% of patients, respectively. Thirty-three percent of patients had ≥ three organs involved, 82% had visceral metastases, 35% had liver metastases, and 45% had previously been treated with chemotherapy. Most of the patients (95%) received 100 mg/m^2 as the initial dose. Initially, no premedication was used. Various premedication regimens (anti-H1 ± anti-H2 and/or corticosteroids either short-term [≤2 days] or long-term [≥3 days]) were subsequently given in some studies to prevent hypersensitivity reactions and fluid retention occurring during treatment. Few patients (n = 25, 3.9%) received the 5-day dexamethasone, presently recommended, premedication (8 mg orally twice daily starting the day before docetaxel).

Table 2. Patient Characteristics and Docetaxel Exposure (N = 640)

	Count			5% to 95%
	No.	%	Median	Percentile
Age, years			56	38-71
Sex				
Male	270	42		
Female	370	58		
WHO performance status				
0	202	32		
1	342	54		
2	90	14		
Total protein (g/L)			71	59-81
Albumin (g/L)			41	31-48
AAG (g/L)			1.34	0.76-2.59
Elevated liver enzymes	26	4.1		
Tumor type				
Breast	231	36		
NSCLC	189	30		
Other	220	34		
Disease spread				
No. of disease sites ≥3	214	33		
Visceral involvement (yes)	522	82		
Liver metastasis (yes)	221	35		
Prior treatments				
Chemotherapy (yes)	289	45		
No. of prior regimens (≥2)	110	17		
Taxotere treatment/exposure				
Initial dose (mg/m^2)				
75	31	5		
100	609	95		
CL (L/h)			36.3	17.5-59.3
CLf			1.02	0.622-2.11
AUC (μg · h/mL)			4.81	2.93-9.52
Peak (μg/mL)			3.26	1.93-5.76
$t_{0.20}$ (hours)			2.41	1.52-6.16 (0.858†)
$t_{0.10}$ (hours)			3.65	2.24-16.7 (0.856†)
$t_{0.05}$ (hours)			9.60	3.38-30.7 (0.838†)
Premedication				
None	252	39		
Recommended (5 days dexamethasone)	25	5		
Other	363	57		

*Patients with concomitant elevations of transaminases (>1.5 × ULN) and alkaline phosphatase (>2.5 × ULN).

†Correlation coefficient with AUC.

Individual PK Parameter Estimates

Individual estimates of PK and exposure parameters are listed in Table 2. The continuous lines in Fig 1 denote fits of patient data obtained using Bayesian estimation. In this large patient population, median clearance was 36.3 L/h, a value close to the value of 35.6 L/h previously estimated from phase I data,[34] and varied from 17.5 L/h to 59.3 L/h (5% to 95% percentile range). Representative exposure parameters were AUC 4.81 μg · mL/h and peak 3.26 μg/mL. Duration of exposure greater than threshold levels varied from 2.41 hours (0.20 μmol/L) to 9.60 hours (0.05 μmol/L). All of the measures of duration of exposure were strongly correlated with AUC ($r \geq .838$; Table 2).

PK/PD

Efficacy. No significant relationship was found between any estimate of docetaxel exposure and either objective response rate, time to first response, or TTP in breast cancer (201 assessable patients; response rate, 56%). The number of disease sites was a significant predictor of response for all end points ($P < .05$), baseline α-1-acid glycoprotein level (AAG), and number of prior chemotherapy regimens were additional predictors ($P < .005$) of TTP.

Regarding NSCLC (151 assessable patients; response rate, 29%), docetaxel AUC at first cycle was a significant predictor ($P = .0232$) of TTP after adjusting for other covariates (Table 3). AUC was the only measure of docetaxel exposure to reach statistical significance. The median TTP was 99 days (95% confidence interval, 84 to 121). According to this model, the risk of progression is decreased by 11% per unit AUC and by 43% for 5 AUC units (eg, from the median to approximately the 95th percentile in this population). In addition, duration of exposure over 0.10

Table 3. NSCLC: Cox Regression Model for TTP (N = 151)

Predictor	P	Risk Ratio	95% CI
Cumulative dose*	.0002	0.997	0.995-0.998
No. of disease sites	.0011	1.293	1.109-1.507
AAG	.0022	1.757	1.225-2.518
Performance status	.0177	1.483	1.071-2.055
AUC	.0232	0.891	0.807-0.984

NOTE. Progression occurred in 84% of patients (127 of 151).
Abbreviation: CI, confidence interval.
*Time-dependent covariate.

μmol/L was the only measure of exposure to reach borderline statistical significance ($P \simeq .10$) in predicting either response rate or time to first response. Of note, baseline AAG was a significant predictor of response for all end points ($P < .005$).

Neutropenia. Neutropenia was analyzed at first course in 582 patients. Most of the patients (375 of 582, 64%) experienced grade 4 neutropenia. Several strong predictors of grade 4 neutropenia were identified, including the various measures of docetaxel exposure, with Clf, AUC, and $t_{0.20}$ having the strongest effects ($P < .0001$). After adjustment for the other covariates in the model, dose no longer had a significant effect. CLf was retained in the final model (Table 4), since it greatly facilitates the interpretation of the model in terms of CL change. The incidence of neutropenia grade 4 was related to baseline neutrophil count ($P = .0002$) and the number of previous regimens ($P = .0002$) as expected. Baseline AAG level and first-course exposure were the most significant predictors ($P < .0001$). The higher the AAG level at baseline, the lower the odds of experiencing grade 4 neutropenia during the first course of treatment. According to the logistic regression model, a 1-g/L increase of baseline AAG (eg, from the median to approximately the 95th percentile in this population) results in an 83% decrease in the odds of experiencing grade 4 neutropenia. The effect of drug exposure change is the opposite, with a 430% (4.3-fold) increase of the odds of grade 4 for a 1-U increase in CLf. A 1-U increase in CLf corresponds to a 50% decrease of CL, which is also a change from the median to the 95th percentile in this population).

Febrile neutropenia was seen in 26 of 582 patients (4.5%) at first cycle. The model for this end point was similar to that for neutropenia grade 4, with exposure (CLf) and AAG

Table 4. Logistic Regression Model for Grade 4 Neutropenia (N = 582)

Predictor	P	Odds Ratio	95% CI
AAG	<.0001	0.17	0.10-0.29
CLf	<.0001	4.26	2.46-7.39
Baseline count	.0002	0.84	0.77-0.92
No. of previous regimens	.0002	1.72	1.30-2.29

NOTE. Incidence, 64% (375 of 582 patients).

Table 5. Logistic Regression Model for Febrile Neutropenia (N = 582)

Predictor	P	Odds Ratio	95% CI
CLf	.0012	3.03	1.55-5.93
AAG	.0056	0.28	0.12-0.69

NOTE. Incidence, 4.7% (26 of 582 patients).

being the only significant predictors (Table 5). In this model, change of exposure due to a 50% decrement in CL would result in a 300% (3.0-fold) increase in the odds of febrile neutropenia. The model-predicted probability of febrile neutropenia as a function of Clf (AAG fixed at the median) is illustrated in Fig 3.

Fluid Retention. Fluid retention occurred in 53% of 631 assessable patients. The median time to onset was 85 days (95% confidence interval, 81 to 92). Patients with breast and ovary carcinoma had disease-related baseline symptoms that resulted in a higher baseline risk than patients with other tumor types. The analysis was therefore stratified by tumor type with breast and ovary combined and other tumor types combined. Fluid retention incidence was 73% (172 of 236) in patients with breast or ovary tumors and 41% (163 of 395) in patients with other tumor types. Of note, few patients (n = 25, 4%) received the presently recommended 5-day dexamethasone premedication in this population, since this premedication was only recommended after the majority of these patients had been treated.

Owing to the cumulative nature of docetaxel-induced fluid retention, dose was treated as a time-dependent covariate in the analysis. Cumulative dose was the most important

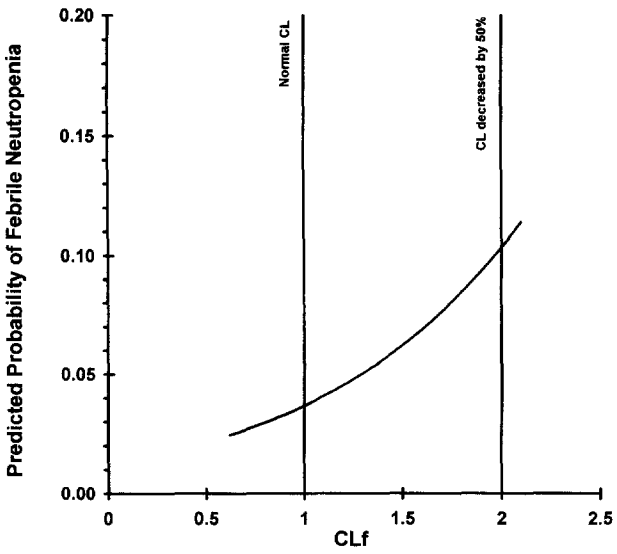

Fig 3. Model-predicted probability of febrile neutropenia as a function of CLf for a patient with median AAG. Reference vertical lines denote normal CL (CLf = 1) and 50% reduced CL (CLf = 2).

Table 6. Cox Regression Model for Time to Onset of Fluid Retention (N = 631)

Predictor	P	Risk Ratio	95% CI
Cummulative dose*	<.0001	1.005	1.003-1.007
$t_{0.20}$	.0029	1.087	1.029-1.148
Total protein	.021	0.980	0.964-0.997
AAG	.014	0.746	0.591-0.942

NOTE. Incidence, 53% (335 of 631 patients).

Stratification: breast/ovary—236 patients/incidence, 73%; other—395 patients/incidence, 41%.

*Time-dependent covariate.

predictor in the final Cox regression model (Table 6). However, several other baseline covariates had independent predictive power, including AAG and total protein levels. Drug exposure at first course was also highly significant in predicting the time to onset of fluid retention, after adjustment for the effect of cumulative dose. The duration parameter, $t_{0.20}$, was the most significant ($P = .0029$) measure of exposure for this regression.

According to the model, the risk of experiencing fluid retention at any time is increased by 64% for each additional cycle at 100 mg/m^2. An increase of $t_{0.20}$ by 4 hours, ie, roughly from the median (2.41 hours) to the 95th percentile (6.16 hours) at first course, increases the risk by 40% beyond the effect of cumulative dose.

DISCUSSION

Assessment of interpatient PK/PD variability early during drug development at the premarketing stage is thought to be of central importance to establish optimal and safe dosage recommendations for the clinician.[1,2,32] It is the reason why a large-scale prospective population PK/PD evaluation was fully and prospectively integrated early in the clinical development of docetaxel.

Study design in the context of population PK (ie, optimal number [and time] of samples, number of patients, etc) is still an open issue.[3] It is particularly complex when there are two goals: estimation of population parameters and estimation of individual parameters. Classical approaches to optimal (limited) sampling strategies for individual patient parameter estimation[40] are not optimal for all patients and particularly for patients with altered PK characteristics, ie, precisely those most critical to identify in a population study. The population parameter goal is best achieved when individual designs are varied to cover full PK profile (full PK screen).[32] Therefore, one must compromise between an individual-oriented fixed optimal sampling schedule and one that recognizes the population estimation goal. The way we chose to do so in this study was to vary the sampling strategy across patients while maintaining an informative design for each patient. Based on previous experience,[40] we decided to use three data points per patient. A major practical constraint was related to the fact that clinical phase II protocols did not require the patients to be hospitalized. Since we did not want to interfere with the clinical protocol, we had to limit our observation time to a 6-hour period for outpatients. However, it was possible to get a fair number of late samples and thus allow definition of the full kinetic profile of docetaxel in the population, as shown in Fig 2. Implementation of the protocol was successful, with 640 patients (68% of patients treated in 24 phase II studies) assessable for this analysis. However, it required considerable communication and monitoring effort.

The population PK analysis conducted in 547 patients showed important predictors of docetaxel CL and therefore exposure.[7] The three main predictors were body-surface area (BSA), plasma levels of AAG, and hepatic function. Age and albumin level had significant but minor influences on CL (eg, a 6.7% decrease for a 71-year-old patient). CL variability related to body size should not translate into variability in drug exposure, since the dose administered is already adjusted for BSA. This finding actually provides a justification for dose normalization to BSA for docetaxel, which has not been demonstrated for most anticancer agents.[41] The decrease in CL associated with high AAG level is consistent with the extensive protein binding of docetaxel.[42] High AAG levels results in lower docetaxel free fraction[42] and therefore decreased CL. However, there should be no change in the AUC of unbound docetaxel and therefore no clinical consequences are expected from the AAG effect on CL. The 27% decrease in CL observed in patients (23 of 547 patients; 4.2% of the population) with concomitant elevations of transaminases (ALT or AST $> 1.5 \times$ ULN) and alkaline phosphatase ($>2.5 \times$ ULN) is of more clinical relevance. Note that in the original analysis,[7] elevation of hepatic enzymes was based on international units that were subsequently adjusted to normal laboratory values. Of interest, docetaxel CL was unchanged in patients with hepatic metastases in the absence of concomitant elevations of enzymes[7] and in patients who had isolated elevations of transaminases or alkaline phosphatase (data on file). The docetaxel kinetic profile is illustrated in Fig 1 for a representative patient with elevated hepatic enzymes.

Population parameter estimates from the final population model[7] were used as prior information in subsequent Bayesian analysis to estimate individual PK parameters and exposure measures. A retrospective validation study demonstrated that the four sampling schedules implemented allowed accurate and precise estimation of individual CL (data on file). Actually, as few as two samples (end of infusion and 6 hours) allow unbiased and precise estimation of docetaxel CL using Bayesian analysis.[43]

A high docetaxel AUC at first cycle was found to reduce the risk of progression in patients with NSCLC after adjustment for other covariates, including the cumulative dose, whereas $t_{0.10}$, the duration of exposure to plasma levels greater than 0.10 μmol/L, was of borderline significance in predicting response rate. However, no significant relationships were found between any estimate of docetaxel exposure at first course and any efficacy end point for breast cancer. Our findings for NSCLC are consistent with the results reported by Huizing et al[44] for paclitaxel. PK/efficacy relationships are being further investigated by accruing new data.

The PK/safety analysis demonstrated that docetaxel exposure was a significant predictor of neutropenia grade 4 and febrile neutropenia at the same course. In particular, it was the main predictor of the occurrence of febrile neutropenia, with a 3.0-fold increase of the odds of febrile neutropenia for a 50% decrease in CL. Thus, the 27% CL decrease observed in patients with elevated hepatic enzymes is predicted to result in a 1.5-fold increase in the odds of febrile neutropenia, which indicates that decreases in CL of the magnitude observed in this population of patients might have clinical consequences. Recent studies with paclitaxel[45-47] after a 3-hour or 24-hour infusion demonstrate that neutropenia (percent decrease in neutrophil count) is not related to AUC, but to the duration of exposure over threshold levels (0.05 or 0.10 μmol/L). This finding is most likely related to the nonlinearity and the schedule dependence of paclitaxel PKs also evidenced in these studies. No clinically significant nonlinearity was seen for docetaxel from phase I data with varying infusion duration, (HL McLeod, submitted) and no schedule dependence was apparent in phase I studies.[5,6] Therefore, the 1-hour infusion was the only administration schedule tested in phase II studies. In our data base, all measures of exposure were highly correlated ($r > .8$) and duration of exposure over any threshold level was equivalently or less predictive than AUC or CL. A CL factor (reciprocal CL adjusted to the mean) was retained in the final models to facilitate clinical interpretation. Clinical end points such as grade 4 neutropenia or febrile neutropenia, rather than the percent decrease of baseline neutrophil count (which is more a PD end point), were chosen in this analysis for their clinical relevance.

The PK/PD findings for febrile neutropenia motivated a specific safety analysis conducted in 1,070 patients from the entire clinical data base.[48] An updated analysis on 1,366 patients recruited in 36 phase II studies of docetaxel monotherapy showed that 54 patients (4%) with baseline elevation of hepatic enzymes (as defined in the population PK analysis) had a threefold higher incidence of febrile neutropenia at first course compared with 1,312 patients with normal enzymes (22.6% *v* 6.2%, $P < .001$). This increase is consistent with the PK/PD findings. However, it is higher than predicted by the logistic regression model (1.5-fold increase). Some other safety parameters (eg, severe infections, mucositis, and toxic death) were also markedly impaired in these patients. These findings are consistent with preliminary observations in patients from four phase II studies.[49] Based on the population PK model, a 25% dose reduction should normalize the exposure of docetaxel in patients with elevated hepatic enzymes and improve the safety profile of docetaxel in this population. A 25% dosage reduction (from 100 mg/m^2 to 75 mg/m^2) is currently recommended in the European Summary of Product Characteristics (Commission of the European Communities, Brussels, Belgium, November, 27, 1995). A phase II study is currently ongoing in breast cancer patients with baseline impaired liver function to validate prospectively this dosage recommendation. However, these guidelines are only valid in the limit of the available data, ie, for enzyme elevations up to 3.5 × ULN for transaminases and up to 5 × ULN for alkaline phosphatase (95th percentile of our data). No data are currently available for patients with more severe hepatic impairment, including patients with elevated bilirubin levels. A specific phase I study is ongoing. A relationship between paclitaxel CL, liver disease, and toxicity was also reported in a limited number of patients in a phase I/II study of paclitaxel.[50] A lower paclitaxel dose was also necessary in patients with elevated transaminases.

Docetaxel exposure at first course was a significant predictor of the time to onset of fluid retention after adjustment for the effect of cumulative dose, although this effect was much less marked than that seen for neutropenia. This is expected, since neutropenia is a first-course response, while fluid retention is a consequence of the integrated response to multiple courses. Of interest, $t_{0.20}$, the duration of exposure over 0.20 μmol/L, was the best exposure-related predictor of fluid retention, which indicates that fluid retention might show some schedule dependency, with a short infusion duration lowering the risk of fluid retention relative to longer infusions. Dexamethasone premedication significantly delays the onset and reduces the severity of docetaxel-induced fluid retention.[51] This effect could not be assessed in this analysis, since only 4% of patients received the recommended premedication.

Baseline AAG level was a significant predictor of all the PD end points investigated in this study. AAG is an acute-phase protein, the level of which can vary considerably during several physiologic and pathologic conditions, including cancer.[52] Elevated AAG level has been shown to

be a predictor of disseminated breast cancer[53] and a sensitive marker of active lung cancer.[54] The finding that a high AAG level was a predictor of poor prognosis for response for both NSCLC and breast cancer, decreasing the odds of response and increasing the risk of relapse, is therefore not unexpected. However, the reasons for the association of high AAG level and decreased toxicity is currently unclear. The problem is complicated by the fact that AAG is a heterogeneous substance that presents genetic variants and a variable heteroglycan side chain.[52] Further investigations are therefore warranted to understand better the pathophysiologic role of AAG variants and the interaction of AAG with docetaxel PK/PD.

This study demonstrates for the first time that large-scale prospective implementation of population PK/PD early during the development of anticancer drugs is feasible. A large patient number was required for both the population PK analysis to validate the model in small patient populations with altered PK, and for the PK/PD analysis to maximize the power of multiple regression analyses conducted on poorly informative or rare clinical end points. This approach generated clinically relevant findings and provided information useful for the clinical use of docetaxel.

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APPENDIX

Principal Investigators and Institutions Participating in the Clinical Studies

European Organization for Research and Treatment of Cancer (EORTC), Early Clinical Trial Group
- Chairman: J. Verweij, Rotterdam, the Netherlands
- Past Chairman: S. Kaye, Glasgow, United Kingdom
- Study Coordinator: J. Wanders, Amsterdam, the Netherlands
- Study Chairmen: C.N. Stenberg, Rome, Italy; S. Amdal, Oslo, Norway; U. Bruntsch, Nurenberg, Germany; A. Sulkes, Petach Tikva, Israel; J.F. Smyth, Edinburg, United Kingdom; T.H. Cerny, Bern, Switzerland; M. Clavel, Lyon, France; W.W. ten Bokkel Huinink, Amsterdam, the Netherlands

EORTC Clinical Screening Group
- Chairman and Study Coordinator: B. Chevallier, Rouen, France
- Past Chairman and Study Coordinator: P. Fumoleau, Nantes, France

EORTC Soft Tissue and Bone Sarcoma Group
- Chairman: T. Tursz, Villejuif, France
- Past Chairman: H. Mouridsen, Copenhagen, Denmark
- Study Coordinator: D.J.T. Wagener, Nijmegen, the Netherlands

Hôpital Saint-Louis, Paris, France
- Study Chairman: M. Marty

The M.D. Anderson Cancer Center, Houston, TX
- Study Chairmen: F.V. Fossella; J. Kavanagh; R. Pazdur; V. Valero

The Memorial Sloan-Kettering Cancer Center, New York, NY
- Study Chairmen: N. Kemeny; J.R. Rigas; A.D. Seidman

The University of Texas Health Science Center, San Antonio, TX
- Study Chairman: P.M. Ravdin

The Cancer Therapy and Research Center, San Antonio, TX
- Study Chairman: H.A. Burris

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