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Pharmacokinetics and metabolism of docetaxel administered as a 1-h intravenous infusion

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Abstract Docetaxel, a taxane antitumor agent, was administered to 24 patients by a 1-h intravenous infusion at a dose level of 100 mg/m^2 with pharmacokinetic monitoring. The plasma concentration-versus-time data were fitted with a three-compartment model. The mean area under the curve (AUC) for docetaxel was 3.1 ± 0.9 h · mg/l and the clearance was 34.8 ± 9.3 l/h per m^2. There was considerable interpatient pharmacokinetic variability. In 33% of the patient population, metabolites were detected in plasma samples collected 5–30 min after the end of the infusion. The cyclized oxazolidinedione metabolite M4 was most frequently present and was detected in 8 out of 24 patients with maximal concentrations between 0.022 and 0.23 mg/l. Logistic regression analysis was performed to predict M4 docetaxel metabolism. In the final model, alanine aminotransferase and alkaline phosphatase levels were the strongest predictors. No relationship was found between M4 metabolism and percentage decrease in neutrophil count in this study. Three patients with high M4 concentrations in plasma during course 1 suffered from most pronounced fluid retention (grade 2–3) after two to five courses.

Key words Docetaxel · Taxotere · Metabolism · Pharmacokinetics · Pharmacodynamics

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Introduction

Docetaxel (Taxotere, RP 56976, NSC 628503, Fig. 1) is a semisynthetic drug obtained from a noncytotoxic precursor, 10-deacetyl baccatin III, extracted from the needles of *Taxus baccata* L [6]. The antitumor activity of this taxoid is related to the stabilization and promotion of the assembly of microtubules. The drug has shown activity in a variety of solid tumor types including breast cancer. The pharmacokinetics of docetaxel have been investigated in several phase I trials [1, 5, 7, 8, 12, 16]. The maximum tolerated dose is 80–115 mg/m^2 and the main dose-limiting toxicity is neutropenia. Other reported endpoints for safety are febrile neutropenia and fluid retention. These results have led to a recommended dosage schedule for phase II studies of 100 mg/m^2 given by intravenous infusion over 1 h every 3 weeks [7, 16]. The pharmacokinetics of docetaxel are linear, independent of the dose and schedule. The terminal half-life is approximately 11 h. Around 75% of the delivered dose is excreted in the feces and less than 5% of the unchanged drug is excreted renally [3, 7].

Population pharmacokinetics and pharmacodynamics of docetaxel have been studied in 24 phase II studies using four randomized limited sampling schedules [2, 4]. The area under the plasma concentration-versus-time curve (AUC) of the first course is a significant predictor of hematologic toxicity and time to onset of fluid retention. The plasma clearance in patients with impaired liver function is reduced (27%) compared to patients with normal liver function. These patients have a higher risk of toxicity [3, 4].

The drug is metabolized in the liver and four metabolites have been isolated from human feces and their

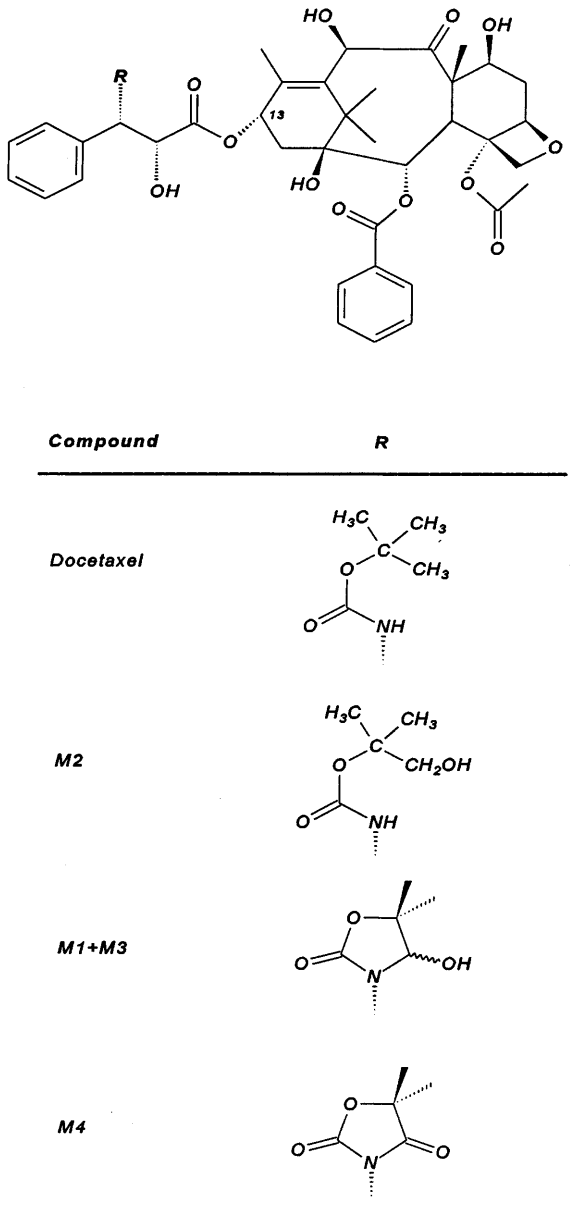

Fig. 1 Chemical structures of docetaxel and its four major human metabolites

structures have been elucidated [11]. The metabolites all originate from oxidation reactions of the *tert*-butyl moiety in the C-13 side chain of the parent compound (Fig. 1). An in vitro metabolism study with human liver microsomal fractions suggests the involvement of several cytochrome P450 isoenzymes in the human hepatic biotransformation of docetaxel [18].

Two methods for the quantification of docetaxel have been reported [9, 17], but it is not possible to quantify docetaxel metabolites using these methods. As a consequence there are no data so far available about docetaxel metabolism in plasma of treated patients. Recently we reported a bioanalytical high-performance liquid chromatographic (HPLC) method for docetaxel which includes the quantification of metabolic products [14]. The current study is focused on the analysis of docetaxel metabolites using this method in plasma samples of 24 patients treated in our hospital. Full pharmacokinetic profiles of the first course were fitted with a three-compartment model and the pharmacokinetic parameters were calculated and compared with those from other studies. Furthermore, we determined retrospectively the parameters that influenced the appearance of metabolites when docetaxel was administered as a 1-h infusion at a dose level of 100 mg/m^2.

Patients, materials and methods

Patient population, drug supply and treatment plan

The patients included in this study suffered from cancer and were not amenable to established therapies. All patients had acceptable bone marrow function (absolute neutrophil count (ANC) $\geq 2.0 \times 10^9$/l and platelets $> 100 \times 10^9$/l), serum bilirubin ≤ 1.25 times the upper limit of normal (ULN), serum creatinine ≤ 1.5 times ULN, WHO performance status ≤ 2, life expectancy ≥ 12 weeks, age > 18 years, and no symptoms of brain metastases. The study was part of a 'compassionate use' program for patients with different tumor types (Table 1) and was carried out with the approval of the hospital medical ethics committee. Written informed consent was obtained from all patients.

Docetaxel was supplied by Rhône-Poulenc Rorer (Anthony Cedex, France) as a concentrated sterile solution, containing 80 mg drug per vial in 2 ml of polysorbate 80 (Tween 80). The drug was prediluted with ethanol 95%/water (13/87, w/w) to obtain an intermediate solution of 10 mg/ml docetaxel. Thereafter, the appropriate amount of the drug was dissolved in a 5% dextrose solution to obtain a maximal concentration of 1 mg/ml. Docetaxel was administered intravenously as a 1-h infusion every 3 weeks. Routine prophylactic medication consisted of dexamethasone 8 mg orally and clemastine 2 mg orally, which were given 13 h, 7 h, and 1 h before the infusion. Dexamethasone was continued for 4 days twice daily at the same dosage.

Pharmacokinetic blood sampling

During the first course of docetaxel, blood samples (5 ml) were taken from each patient through a heparinized cannula in the opposite arm from the injection side before, at 30 min during, at the end of, and at 5, 10, 20, and 30 min, and 1, 2, 3, 4, 8, 18, 24 h after the end of the 1-h infusion. The samples were collected in EDTA tubes and centrifuged immediately (10 min at 2500 *g*). The plasma layer was then removed and stored at −30 °C until analysis.

Bioanalysis

The plasma levels of docetaxel and metabolites were determined using a validated high-performance liquid chromatographic (HPLC) method developed in our laboratory [14]. All plasma concentrations above the lower limit of quantitation (LLQ) of the assay (0.01 mg/l) were used.

Pharmacokinetic data analyses

The docetaxel concentration-versus-time curves were fitted using the MW\PHARM software program (Medi\Ware BV, Groningen, The Netherlands) [13]. The docetaxel kinetics were best described by a three-compartment model. The AUC was calculated by the integration of the plasma concentration-time curve with extrapolation to infinity. Elimination half-lives ($t_{1/2}$) were calculated from

Table 1 Patient characteristics ($n = 24$)

Gender (number of patients)	
Male	1
Female	23
Age (years)	
Mean	51
Median	48
Range	33–73
Weight (kg)	
Mean	66
Median	63
Range	49–89
Height (cm)	
Mean	169
Median	169
Range	152–188
Body surface area (m^2)	
Mean	1.75
Median	1.76
Range	1.46–2.14
Alkaline phosphatase (ALKPH, U/l)	
Mean	101
Median	84
Range	42–254
Alanine aminotransferase (ALAT, U/l)	
Mean	19
Median	13
Range	5–61
Aspartate aminotransferase (ASAT, U/l)	
Mean	21
Median	19
Range	5–55
Bilirubin (m*M*)	
Mean	7
Median	7
Range	4–15
Albumin (g/l)	
Mean	44
Median	44
Range	35–50
Serum creatinine (m*M*)	
Mean	83
Median	85
Range	63–105
Performance status (WHO)	
0	2
1	17
2	5
Tumor type	
Breast	19
Non-small-cell lung cancer	2
Other	3

the slopes of the exponential terms ($0.693/\lambda_i$). Plasma clearance (Cl) was calculated by dividing the delivered dose by the AUC. Volume of distribution at steady-state (V_{ss}) was calculated by the following equation:

$$V_{ss} = \frac{\text{dose}}{C_1 + C_2 + C_3} \times \left(1 + \frac{k_{1,2}}{k_{2,1}} + \frac{k_{1,3}}{k_{3,1}}\right)$$

where C_i is the initial concentration of the ith component of the curve and $k_{i,j}$ represents the rate constant between the compartments i and j. The maximal concentration (C_{max}) was generated from the experimental data and the duration above the threshold concentration of 0.1 mg/l ($T > 0.1$) were derived graphically.

The commercially available software package Statistical Product and Service Solutions (version 6.1 for Windows; SPSS, Chicago, Ill.) was used to execute logistic regression to relate metabolism (M4 concentrations >0.06 mg/l) to the following continuous variables: age, body surface area (BSA), length, weight, alkaline phosphatase (ALKPH), alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), ALAT plus ASAT, bilirubin, albumin, plasma creatinine, total docetaxel dose, AUC, C_{max}, Cl, $T > 0.1$, half-life of the terminal phase ($t_{1/2,\gamma}$), decrease in ANC and decrease in platelets. A Student's *t*-test was executed to compare the mean decreases in ANC of patients with (>0.06 mg/l) and without (less than LLQ) M4 metabolism. Bivariate correlations were calculated with one-tailed significance to determine whether Cl was related to age, ALKPH, ALAT and ASAT.

Results

Patient characteristics are listed in Table 1. Entered in the trial were 24 patients comprising 23 females and 1 male. The predominance of females is explained by the fact that most patients had advanced breast cancer. The median age was 48 years (range 33–73 years) and the median performance status was 1. All patients had received prior chemotherapy. The main observed toxicity was neutropenia. Most patients experienced grade 3–4 (14 patients, 58%) and the overall percentage decrease in neutrophil count was $68 \pm 28\%$ (grade 3, $80 \pm 7.8\%$, $n = 5$, and grade 4, $89 \pm 3.5\%$, $n = 9$) after the first course of docetaxel. Nonhematological toxicities following all courses of docetaxel are presented in Table 2. Most frequently scored nonhematological toxicities included alopecia. Edema, mainly affecting hands and ankles and significant weight gain, were observed in 7 of 24 patients. In this group of patients, edema appeared after a median of four courses (range one to five). Edema grade 2–3 was noted in patients 18, 23 and 24 with maximal M4 concentrations of 0.0384 (edema grade 3), 0.0673 (edema grade 2) and 0.230 mg/l (edema grade 3), respectively.

Table 2 Nonhematological toxicities following all courses (median five, range one to nine) of docetaxel

Toxicity	Number of patients with CTC			Total	Total (%)
	Grade 1	Grade 2	Grade 3		
Alopecia	5	18		23	96
Mucositis	6	6	3	15	63
Diarrhea	11	–	2	13	54
Fatigue	5	2	5	12	50
Myalgia	5	6	–	11	46
Neurological	10	–	–	10	42
Asthenia	2	6	2	10	42
Skin changes	8	–	–	8	33
Arthralgia	6	2	–	8	33
Nausea/vomiting	3	2	2	7	29
Edema/weight gain	2	3	2	7	29
Fever	–	6	–	6	25
Anorexia	5	–	–	5	21
Nail changes	5	–	–	5	21
Stomatitis	3	–	–	3	13

The docetaxel concentration-versus-time data for the population are presented in Fig. 2. Docetaxel concentrations were near the LLQ in most patients at 9 h after the start of the infusion. Pharmacokinetic analyses were conducted using nonlinear weighted regression analysis of individual concentration-time data. A three-compartment model was used to fit the data. Two extreme individual profiles are illustrated in Fig. 2. There was a significant interpatient pharmacokinetic variability in the docetaxel pharmacokinetics (Table 3). The total docetaxel AUC ranged from 1.4 to 5.2 h · mg/l (mean 3.1 h · mg/l). The initial half-life was short (about 5 min), followed by an intermediate phase with a 51 min half-life, and a terminal phase of 10.8 ± 14.1 h. The mean maximal plasma concentration was 2.6 mg/l. Plasma clearance was 34.8 ± 9.3 l/h per m^2 with a volume of distribution ranging from 12.4 to 340 l/m^2 with a mean value of 84.0 l/m^2.

Metabolites were detected in the plasma of 8 out of 24 patients and maximal concentrations were observed in the samples taken at 5 to 30 min after the end of the 1-h infusion (Table 4). M1 and M2 were not separated on the analytical column under the described conditions [14] and the sum of these concentration levels was determined. In general, the cyclized oxazolidinedione metabolite (M4) was the main metabolite detected in the plasma of these patients. Predictors for the presence of M4 at concentration levels of 0.06 mg/l or higher (patients 21–24) were determined (Table 5). The likelihood of M4 metabolism was strongly related to the ALAT level ($P = 0.0002$, see Table 5) and significant correlations were found for ALKPH, AUC, C_{max}, Cl and T > 0.1. Forward stepwise logistic regression revealed a model for M4 metabolism which included ALAT and ALKPH ($\chi^2 = 16.332$ and $P = 0.0003$) with an overall correct prediction of 95.8%:

$$P(\text{M4 metabolism}) = \frac{e^{-14.38+0.37\cdot ALAT+0.026\cdot ALKPH}}{(1+e^{-14.38+0.37\cdot ALAT+0.026\cdot ALKPH})}$$

No relationship was found between the percentage decrease in neutrophil count and the docetaxel AUC. Furthermore, the mean percentage decrease in neutrophil count was not significantly higher when M4 concentrations (> 0.06 mg/l) were detected in plasma or not ($P = 0.224$). Cl was related to ALAT (correlation coefficient −0.426, $P = 0.019$). No significant relationships were found between Cl and age, ALKPH or ASAT.

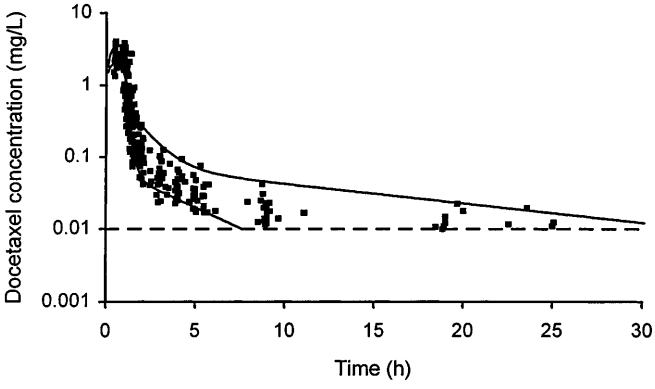

Fig. 2 Pooled concentration-versus-time data of 24 patients after a 1-h infusion of 100 mg/m^2 docetaxel. Two individual profiles with extreme plasma clearances are plotted and the lower limit of quantitation of the assay (0.01 mg/l) is indicated by the dotted line

Table 3 Pharmacokinetics of docetaxel after a 1-h intravenous infusion of 100 mg/m^2 with comparison to published data [3] (*NC* not calculated)

Pharmacokinetic parameter	Mean	SD	Range	Reference 3
Infusion duration (h)	1.00	0.13	0.85–1.40	1.0
C_{max} (mg/l)	2.6	0.5	1.8–4.0	3.7
$AUC_{0\rightarrow\infty}$ (h · mg/l)	3.1	0.9	1.4–5.2	4.6
Half-life $t_{1/2,\alpha}$ (min)	5.0	2.1	1.6–9.1	4
Half-life $t_{1/2,\beta}$ (min)	51	6.2	9–325	36
Half-life $t_{1/2,\gamma}$ (h)	10.8	14.1	2.1–69.3	11.1
Cl (l/h/m^2)	34.8	9.3	19.2–53.8	21
Vd_{ss} (l/m^2)	84.0	86.1	12.4–340	67.3
T > 0.1 (h)	1.8	0.7	1.0–3.6	NC

Discussion

In the study reported here we investigated the pharmacokinetics and metabolism of docetaxel administered as a 1-h intravenous infusion at a dose level of 100 mg/m^2. After HPLC analysis, full pharmacokinetic profiles were obtained for 24 patients. The estimations of the pharmacokinetic parameters were obtained using the conventional approach based on nonlinear weighted regression analysis of individual concentration-time

Table 4 Maximal metabolites and docetaxel concentrations in plasma of eight patients (patients 17 to 24) treated with a 1-h infusion of docetaxel at a dose level of 100 mg/m^2. In patients 1 to 16, metabolite concentrations (M1 + M2, M3 and M4) were below the lower limit of quantitation (– below the lower limit of quantitation, 0.01 mg/l)

Patient number	M1 + M2 (mg/l)	M3 (mg/l)	M4 (mg/l)	Docetaxel (mg/l)	Ratio M4/docetaxel
17	0.0331	–	0.0232	2.411	0.010
18	–	–	0.0384	2.712	0.014
19	–	–	0.0289	2.480	0.012
20	–	–	0.0221	2.493	0.009
21	–	–	0.0608	3.074	0.020
22	0.0827	–	0.0605	2.649	0.023
23	0.100	0.0370	0.0673	2.250	0.030
24	0.124	0.0777	0.230	1.879	0.122

Table 5 Predictors for the presence of M4 at concentration levels of 0.06 mg/l or higher (patients 21 to 24) identified with logistic regression

Predictor	*P*-value	Correlation coefficient
Age	0.9532	0.0000
BSA	0.5874	0.0000
Length	0.3144	0.0000
Weight	0.7518	0.0000
ALKPH	0.0116	0.4493
ALAT	0.0002	0.7508
ASAT	0.1947	0.0000
ASAT plus ALAT	0.0018	0.5972
Bilirubin	0.2605	0.0000
Albumin	0.6574	0.0000
Plasma creatinine	0.6019	0.0000
Total dose	0.5147	0.0000
AUC	0.0096	0.4661
C_{max}	0.0098	0.4649
Cl	0.0318	−0.3474
T > 0.1	0.0131	0.4384
$t_{1/2,\gamma}$	0.9927	0.0000
Decrease in ANC	0.2063	0.0000
Decrease in platelets	0.4679	0.0000

data. Using this approach, the apparent variability in parameter estimates such as the terminal half-life and the volume of distribution at steady-state will increase when a full observation of the terminal elimination phase is precluded (missing samples, variation in sample times, limit of sensitivity of the assay) [8]. To handle such data, nonlinear mixed-effect modeling (NONMEM) is superior [2–4, 8], but the estimates of the pharmacokinetic parameters obtained in this study are in good agreement with data evaluated using NONMEM (Table 3). Although the approach applied may result in higher apparent variability of the estimates, it is obvious that there was a considerable interpatient variability in the pharmacokinetics of docetaxel (Fig. 2).

Bruno et al. have demonstrated that docetaxel clearance, the most important parameter in analysing the pharmacokinetic variability, is related to α1-acid glycoprotein level, age, BSA and hepatic function [2, 4]. The latter was a strong, clinically relevant predictor, because patients with abnormal liver function (serum transaminase levels ≥1.5 times ULN and ALKPH levels ≥2.5 times ULN) had a 27% reduction in docetaxel clearance compared to patients with normal liver function [4]. A dose reduction to 75 mg/m^2 has been recommended in this group of patients. In our study, in a much smaller number of patients, the clearance was also related to ALAT, but no significant relationships were found with age, ALKPH or ASAT. The clearance was corrected for BSA. The α1-acid glycoprotein levels were not measured during the study.

Neutropenia, the dose-limiting toxicity in phase I, was experienced by most patients and the percentage decrease in neutrophil count was 68 ± 28% at a mean AUC of 3.1 h · mg/l, comparable with previously reported data [7]. However, the established relationship between the docetaxel AUC and the percentage decrease in ANC [1, 7] was not confirmed, despite the large pharmacokinetic and pharmacodynamic variabilities (decrease in ANC ranged from 15% to 95%). This may have been due to the heterogeneity of the patient population or the small number of patients in this study.

Docetaxel metabolites were quantified in plasma after the first course of docetaxel. Maximal metabolite concentrations were observed in the samples taken at 5 to 30 min after the end of the 1-h infusion (Table 4). The cyclized oxazolidinedione metabolite M4, the final product after successive oxidation reactions of the *t*-butoxy group of docetaxel (Fig. 1), was most frequently detected (8 out of 24 patients, 33%). In the liver the parent compound is oxidized into the primary alcohol (M2), leading then to a putative aldehyde giving the two cyclic hydroxyoxazolidinones (M1 and M3). Further oxidation of M2 leads to the unstable carboxylic acid derivative and finally to the cyclized oxazolidinedione metabolite (M4) [11]. The oxidative steps result from the involvement of P450 isoenzymes [18]. The presence of M4 was most strongly related to elevated liver enzymes, ALAT and ALKPH. Patients with an increase in these liver enzymes at baseline had a significantly higher frequency of febrile neutropenia, infections, severe stomatitis and even toxic death [4].

Although all metabolites were less cytotoxic and myelotoxic than docetaxel [15], detection of M4 metabolism might be used as an extra specific marker, along with the serum transaminase and ALKPH levels [2, 4], for an abnormal liver function resulting in an increased AUC and reduced plasma clearance. In this study, however, no relationship was found between M4 metabolism (as well as docetaxel AUC) and percentage decrease in neutrophils. As mentioned above, this may have been due to the heterogeneity of the patient population or the small number of patients in this study. Interestingly, patients with high M4 concentrations in the plasma during course one (patients 18, 23 and 24; Table 4) suffered from the most pronounced edema and weight gain (CTC grade 2–3) after two to five courses. The relevance of this observation is not yet clear. Other patients had received a median of five courses (range one to nine) with no signs or with only mild signs of fluid retention (Table 2).

For further (limited sampling) population studies, it is recommended that during all cycles an extra plasma sample be taken at 5 to 30 min after the end of the 1-h infusion for metabolite quantitation besides the plasma samples collected at 0.5 and 2 h after the start of the infusion to calculate the clearance [10]. These data may lead to a better insight into relationships between metabolic patterns and pharmacokinetics/pharmacodynamic outcomes. If such relationships can be confirmed, these models will facilitate the development of patient-tailored dosing strategies.

References

1. Bissett D, Setanoians A, Cassidy J, Graham MA, Chadwick GA, Wilson P, Auzannet V, Le Bail N, Kaye SB, Kerr DJ

(1993) Phase I and pharmacokinetic study of Taxotere (RP 56976) administered as a 24 hour infusion. Cancer Res 53: 523–527
2. Bruno R, Vivier N, Vergniol JC, De Philips SL, Montay G, Sheiner LB (1996) A population pharmacokinetic model for docetaxel (Taxotere®): method building and validation. J Pharmacokinet Biopharm 2: 153–172
3. Bruno R, Riva A, Hille D, Lebecq A, Thomas L (1997) Pharmacokinetic and pharmacodynamic properties of docetaxel: results of phase I and phase II trials. Am J Health Syst Pharm 54 [Suppl 2]: 16–19
4. Bruno R, Hille D, Riva A, Vivier N, ten Bokkel Huinink WW, van Oosterom AT, Kaye SB, Verweij J, Fossella FV, Valero V, Rigas JR, Seidman AD, Chevallier B, Fumoleau P, Burris HA, Ravdin PM, Sheiner LB (1998) Population pharmacokinetics/pharmacodynamics of docetaxel in phase II studies in patients with cancer. J Clin Oncol 16: 187–196
5. Burris H, Irvin R, Kuhn J, Kalter S, Smith L, Shaffer D, Fields S, Weiss G, Eckhardt J, Roderiguez G, Rinaldi D, Wall J, Cook G, Smith S, Vreeland F, Bayssas M, Le Bail N, Von Hoff D (1993) Phase I clinical trial of Taxotere administered as either a 2 hour or 6 hour intravenous infusion. J Clin Oncol 11: 950–958
6. Colin M, Guénard D, Guéritte-Voegelein F, Potier P (1989) Taxol derivatives, their preparation and pharmaceutical conditions containing them. Patent 4,814,470, 21 March 1989. U.S. Patent office, Washington, DC
7. Extra JM, Rousseau F, Bruno R, Clavel M, Le Bail N, Marty M (1993) Phase I and pharmacokinetic study of Taxotere (RP 56976; NSC 628503) given as a short intravenous infusion. Cancer Res 53: 1037–1042
8. Launay-Iliadis MC, Bruno R, Cosson V, Vergniol VC, Oulid-Aissa D, Marty M, Clavel M, Aapro M, Le Bail N, Iliadis A (1995) Population pharmacokinetics of docetaxel during phase I studies using nonlinear mixed-effects modeling and nonparametric maximum-likelihood estimation. Cancer Chemother Pharmacol 37: 47–54
9. Loos WJ, Verweij J, Nooter K, Stoter G, Sparreboom A (1997) Sensitive determination of docetaxel in human plasma by liquid-liquid extraction and reversed-phase high-performance liquid chromatography. J Chromatogr B 693: 437–441
10. Lustig V, Rosing H, van Warmerdam LJC, Huizing MT, ten Bokkel Huinink WW, Dubbelman AC, Beijnen JH (1997) Limited sampling models for the pharmacokinetics of docetaxel. Clin Drug Invest 13: 247–254
11. Monegier B, Gaillard C, Sablé S, Vuilhorgne M (1994) Structures of the major human metabolites of docetaxel (RP 56976 – Taxotere®). Tetrahedron Lett 35: 3715–3718
12. Pazdur R, Newman RA, Newman BM, Fuentes A, Benvenuto J, Bready B, Moore D Jr, Jaiyesimi I, Vreeland F, Bayssas MMG, Raber MN (1992) Phase I trial of Taxotere: five-day schedule. J Natl Cancer Inst 84: 1781–1788
13. Proost JH, Meijer DKF (1992) MW/PHARM, an integrated software package for drug dosage regimen calculations and therapeutic drug monitoring. Comput Biol Med 22: 155–163
14. Rosing H, Lustig V, Koopman FJ, ten Bokkel Huinink WW, Beijnen JH (1997) Bio-analysis of docetaxel and hydroxylated metabolites in human plasma by high-performance liquid chromatography and automated solid-phase extraction. J Chromatogr B 696: 89–98
15. Sparreboom A, van Tellingen O, Scherrenburg EJ, Boesen JJB, huizing MT, Nooijen WJ, Versluis C, Beijnen JH (1996) Isolation, purification and biological activity of major docetaxel metabolites from human feces. Drug Metab Dispos 24: 655–958
16. Tomiak E, Piccart MJ, Kerger J, Lips S, Awada A, de Valeriola D, Ravoet C, Lossignol D, Sculier JP, Auzannet V, Le Bail N, Bayssas M, Klastersky J (1994) Phase I study of docetaxel administered as a 1 hour intravenous infusion on a weekly basis. J Clin Oncol 12: 1458–1467
17. Vergniol JC, Bruno R, Montay G, Frydman A (1992) Determination of Taxotere in human plasma by a semi-automated high-performance liquid chromatographic method. J Chromatogr B 582: 273–278
18. Zhou-Pan XR, Marre F, Zhou XJ, Gauthier T, Placidi M, Rahmani R (1993) Preliminary characterisation of taxotere metabolism by using human liver microsomal fractions. Cell Pharmacol [Suppl] 1: 119