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M.C. Launay-Iliadis · R. Bruno · V. Cosson
J.C. Vergniol · D. Oulid-Aissa · M. Marty
M. Clavel · M. Aapro · N. Le Bail · A. Iliadis

Population pharmacokinetics of docetaxel during phase I studies using nonlinear mixed-effect modeling and nonparametric maximum-likelihood estimation

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Abstract Docetaxel, a novel anticancer agent, was given to 26 patients by short i.v. infusion (1–2 h) at various dose levels (70–115 mg/m^2, the maximum tolerated dose) during 2 phase I studies. Two population analyses, one using NONMEM (nonlinear mixed-effect modeling) and the other using NPML (nonparametric maximum-likelihood), were performed sequentially to determine the structural model; estimate the mean population parameters, including clearance (Cl) and interindividual variability; and find influences of demographic covariates on them. Nine covariates were included in the analyses: age, height, weight, body surface area, sex, performance status, presence of liver metastasis, dose level, and type of formulation. A three-compartment model gave the best fit to the data, and the final NONMEM regression model for Cl was $Cl = BSA(\theta 1 + \theta 2 \times AGE)$, expressing Cl (in liters per hour) directly as a function of body surface area. Only these two covariates were considered in the NPML analysis to confirm the results found by NONMEM. Using NONMEM [for a patient with mean AGE (52.3 years) and mean BSA (1.68 m^2)] and NPML, docetaxel Cl was estimated to be 35.6 l/h (21.2 l h^{-1} m^{-2}) and 37.2 l/h with interpatient coefficients of variation (CVs) of 17.4% and 24.8%, respectively. The intraindividual CV was estimated at 23.8% by NONMEM; the corresponding variability was fixed in NPML in an additive Gaussian variance error model with a 20% CV. Discrepancies were found in the mean volume at steady state (Vss; 83.2 l for NPML versus 124 l for NONMEM) and in terminal half-lives, notably the mean $t_{1/2\gamma}$, which was shorter as determined by NPML (7.89 versus 12.2 h), although the interindividual CV was 89.1% and 62.7% for Vss and $t_{1/2\gamma}$, respectively. However, the NPML-estimated probability density function (pdf) of $t_{1/2\gamma}$ was bimodal (5 and 11.4 h), probably due to the imbalance of the data. Both analyses suggest a similar magnitude of mean Cl decrease with small BSA and advanced age.

Key words Pharmacokinetics · Population · NONMEM · NPML · Docetaxel · Taxotere

M.C. Launay-Iliadis[1] · A. Iliadis
INSERM U 278, 27 bd Jean Moulin, F-13385 Marseille Cédex 5, France

R. Bruno (✉) · V. Cosson · J.C. Vergniol · D. Oulid-Aissa · N. Le Bail
Rhône-Poulenc Rorer, Drug Metabolism and Pharmacokinetics Box 58, 20 bd Raymond Aron, F-92165 Antony Cédex, France

M. Marty
Hôpital Saint-Louis, 1 av Claude Vellefaux, F-75010 Paris, France

M. Clavel[†]
Centre Léon-Bérard, 28 rue Laënnec, F-69373 Lyon Cedex 08, France

A. Aapro[2]
C.H.U.G., 24 rue Micheli du Crest, CH-1211 Genève, Switzerland

Present address:
[1] Laboratoire de Pharmacocinétique et Toxicocinétique, Faculté de Pharmacie, 27 bd Jean Moulin, F-13385 Marseille Cédex 5, France
[2] European Institute of Oncology, Via Ripamonti 99, Milano, Italy

Introduction

The population approach permits observational data obtained from patients during clinical trials (pharmacokinetic screen) to be used to assess the pharmacokinetic/pharmacodynamic (PK/PD) variability in patient populations, find those covariates associated with significant changes in PK, and relate PK parameters to clinical outcome [17].

The feasibility and the timing of this approach during drug development are currently being evaluated [9]. The approach has been fully integrated into the clinical development plan of docetaxel (RP 56976, Taxotere), a new anticancer agent [3] presently undergoing phase II clinical trial. To design and implement a

Table 1 Summary of patients' characteristics

Covariate	Mean	(SD/CV)	Range	Symbol
Age (years)	52.3	(8.0/15.3%)	35–65	AGE
BSA (m^2)	1.68	(0.16/9.5%)	1.3–2.02	BSA
Height (cm)	168.0	(6.2/3.7%)	153–181	HGT
Weight (kg)	61.4	(10.7/17.4%)	40–84	WGT
		Number		Symbol
Sex (M/F)		9/17		SEX
WHO performance status (0/1/2)		8/17/1		PS
Presence of liver metastasis (Y/N)		8/18		META
Formulation (1/2)		14/12		FORM
Dose level ($>90\,mg/m^2$ or not)		15/11		DOS

limited sampling strategy for forthcoming trials, we needed to characterize docetaxel pharmacokinetics, i.e., determine the model structure and parameter estimates. To this end, a population analysis has been applied to pooled data obtained from two phase I studies [1, 5, 8], and covariates predictive of the interpatient variability of docetaxel clearance (Cl, in liters per hour) were preliminarily identified. We conducted this analysis using two different population analyses to pursue our methodological evaluation of population methods [4]: nonlinear mixed-effect modeling [18] implemented in the NONMEM software [2] and non-parametric maximum-likelihood [12] developed in the NPML software [13]. The results obtained with the two methods are compared. Preliminary results of these investigations have been presented elsewhere [6, 10].

Patients and methods

Patients

The data analyzed were obtained in two phase I trials. In the first trial, conducted in Paris and Lyon [8], docetaxel was given as 1- to 2-h infusions at ten dose levels ranging from 5 to 115 mg/m^2, the maximum tolerated dose. In the second abbreviated study conducted in Geneva [1], only two dose levels, 70 and 100 mg/m^2, given as 1-h infusions were studied.

Only the data from the 26 patients in both studies who received 70–115 mg/m^2, i.e., the dose levels encompassing those used in phase II studies, were considered in this analysis. Patients had breast, ovary, lung, or other histologically documented cancers. Written informed consent was obtained from all patients. Briefly, eligibility criteria included a WHO performance status of less than or equal to 2, a life expectancy of at least 12 weeks, and adequate renal and hepatic function. The demographic covariates selected for the population analyses were age, body surface area, height, sex, weight, and WHO performance status. In addition, eight patients had hepatic metastases. The patients' characteristics are summarized in Table 1.

Doses given were 70 (5 patients), 85 (6 patients), 100 (11 patients), and 115 mg/m^2 (4 patients). Note that 100 mg/m^2 is the standard dose proposed for phase II trials [8]. Moreover, two formulations were tested; in formulation 1, docetaxel was formulated as a 15-mg/ml solution in dehydrated alcohol/polysorbate 80 (50/50), whereas in formulation 2 the docetaxel concentration was 40 mg/ml in polysorbate 80 alone.

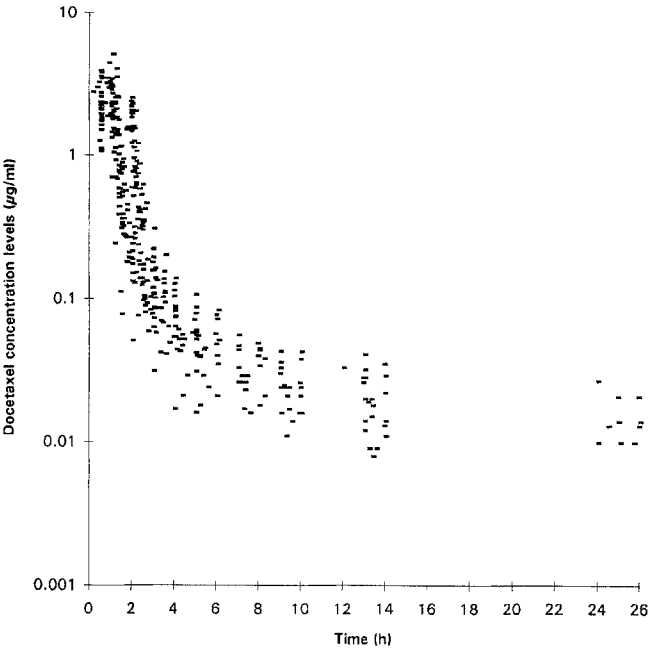

Fig. 1 Docetaxel pooled data (26 patients, 389 plasma levels)

A total of 389 docetaxel plasma levels were available for the 26 patients (9–17 per patient for 2–24 h after the end of the infusion). They were assayed by a semiautomated high-performance liquid chromatography (HPLC) analysis involving solid-phase extraction and UV detection. The limit of quantitation of the assay is 10 ng/ml, validated within the range of 10–5000 ng/ml with a coefficient of variation of $< 11\%$ [19]. The concentration-time profile of the pooled data is illustrated in Fig. 1.

Of the 26 patients, only 11 had measurements available at 24 h after the end of the infusion. At this time, plasma levels were below the limit of quantitation for 8 patients, whereas data were missing for the 7 remaining patients.

Population analysis

The two population analyses rely on different methods (one being parametric and the other being nonparametric) and, therefore, on different distribution assumptions regarding interindividual variability in PK parameters. Basic features are recalled below. In both population analyses, the PK model structure (two or three compartments with a first-order pattern of elimination) was tested in preliminary analyses and the two-compartment model was definitely rejected (see Table 2 for NONMEM). Since the NONMEM approach is the reference approach, the NONMEM analysis was done first.

NONMEM analysis

The analysis was performed using the NONMEM program (double precision, version III, level 1.2) [2] with the NMTRAN preprocessor running on a Digital DEC workstation 5000/240 under the Ultrix operating system (Rhône-Poulenc Rorer, Antony, France). Basically,

NONMEM can model nonlinear mixed effects and produces approximate maximum-likelihood estimates of the model parameters, assuming a parametric (normal) distribution for the random effects [18]. The three-compartment kinetic model was expressed as a function of Cl (in liters per hour), V_1 (in liters), and intercompartmental rate constants ($K_{12}, K_{21}, K_{13}, K_{31}$; per hour) using the PREDPP package (subroutines ADVAN5, TRANS1). Interindividual variability in Cl was modeled according to a proportional error (constant CV) model:

$$Cl_j = Cl(1 + \eta_{jCl}),$$

where η_{jCl} denotes the proportional difference between the true parameter (Cl_j) of individual j and the typical value of the parameter in the population (Cl). This error, η_{jCl}, is assumed to be normally distributed with zero mean and variance ω^2_{Cl}.

Intraindividual variability was also expressed as proportional:

$$Cp_{ij} = \tilde{C}p_{ij}(1 + \varepsilon_{ij}),$$

where Cp_{ij} and $\tilde{C}p_{ij}$ are the ith measured and "true" concentrations, respectively, and ε_{ij} denotes the intraindividual error randomly (normally) distributed with zero mean and variance σ^2.

The influence of covariates on docetaxel Cl was investigated in three steps. Comparison between two alternative regression models was done using the log-likelihood ratio test based on the asymptotically χ^2-distributed difference in the objective functions (δ) obtained from the fits to the two models; the number of degrees of freedom corresponds to the number of parameters tested. Step 1 consisted of screening one by one the influence of covariates (fixed effects) on pharmacokinetic parameters; step 2 evaluated the objective function of the full model expressing Cl as a function of all the influential covariates ($P < 0.05$, i.e., $\delta > 3.8$ for 1 df) found at step 1; and step 3 elaborated the final model by testing the full model against restricted models by removing each covariate from the full model in turn. At this step, a P value of 0.005 (i.e., $\delta = 7.8$ for 1 df) was used to compensate for the effect of multiple comparisons. Similarly, the final model was tested against the full model at $P < 0.005$ (i.e., $\delta > 16.7$ for 5 df).

NPML analysis

This analysis was performed using the NPML program (version 1, January 1989, completed April 1989) developed by Mallet [13] and running on a VAX 11/780 system (Service d'Informatique Médicale, Faculté de Médecine, Marseille, France). As for NONMEM, NPML relies on the maximum-likelihood principle and provides population characteristics (mean and variance of the model parameters) [12]. NPML estimates the entire probability distribution of the parameters without any a priori assumption on the distribution and incorporates covariates without specifying parametric relationships, an interesting feature during drug development [14]. The (population) distribution is the so-called joint probability density function (joint pdf) of the parameters from which the pdf of each parameter (marginal pdf) and the conditional pdfs (pdf of a parameter given one or more covariate values) can be calculated. Visualization of these distributions was made possible using the graphical software TRACE-REG, which was developed concurrently with NPML and included in the package. To run the NPML program, it was necessary to write some additional FORTRAN 77 code to read the data and specify the pharmacokinetic model expressed as a function of Cl, K_e (per hour), and intercompartmental rate constants (per hour). Then, the main program NPML and the new subroutines were compiled and linked to create an executable version of NPML.

We decided in this study that only the most influent covariates found in NONMEM (AGE and BSA) would be involved in the NPML analysis as a preliminary evaluation and to confirm the results obtained with NONMEM. A standard deviation (SD) was required for each covariate because NPML assumes that they are noisy; Gaussian functions with an SD of 0.1 m^2 and 3 years for BSA and AGE, respectively, were defined in the fixed variance error models. The residual error was assumed to be additive with a zero-mean Gaussian distribution and a constant CV fixed to 20% in the variance model, a value consistent with the final intraindividual NONMEM-estimated variability (23.8%). This variability is meant to capture assay reproducibility, model misspecification, and other sources of variability, e.g., varying infusion rate (assumed to be constant) and error in recording actual sampling times. No measure of the accuracy of the estimates can be obtained with NPML.

NPML estimates the discrete joint pdf of the pharmacokinetic parameters and the covariates obtained for the minimized log-likelihood value; it is characterized by a set of admissible values, termed the locations of the distribution, each associated with a probability, termed its weight. The number of locations is no greater than the number of patients included in the data set; each location is characterized by its weight, six model parameter values, and two covariate values. The pdf of any parameter, even those not estimated directly by NPML (e.g., V_1, Vss, and half-life of the three different phases), can be calculated from the locations and the estimated parameter values of the joint pdf by the use of standard formulas. The interindividual variability is estimated on all parameters through the covariance matrix and is expressed as CVs (%). Graphs of the distributions of all parameters and covariates, either marginal or conditional, can be displayed. Conditional means and variances are also easily computed. The shapes of the pdfs of the parameters obtained for different values of the covariates are informative about the distribution itself. However, they cannot afford a direct comparison between results obtained by NONMEM versus NPML, in particular the effect of a covariate on the mean Cl. Thus, for NPML results, the mean Cl was evaluated conditionally on known covariate values, and these Cl values were plotted as a function of the covariate. This graph was superimposed on the plot representing the relationship obtained using NONMEM. More specifically, the latter was obtained by varying one covariate and fixing the other one to the mean value.

Results

NONMEM analysis

All steps are summarized in Table 2. The three-compartment model fitted the data better than the two-compartment model. Among the nine covariates tested at the screening step, five (BSA, WGT, AGE, FORM, and PSS) provided highly significant ($P < 0.005$) improvements in the fit when individually entered in the Cl model, especially BSA, AGE, and WGT ($|\delta| \geq 39$). Sex (SEX) and the presence of liver mestastases (META) also had an influence on docetaxel Cl ($P < 0.025$), whereas the dose given and the height of patients did not prove to be significant. Since BSA and WGT were highly correlated ($r = 0.947, P < 0.0001$) and induced effects of the same magnitude, only one was used in the full model; BSA was chosen rather than WGT because of its preference by clinical oncologists (expression of Cl in liters per hour per square meter of BSA). Therefore, the six significant covariates ($P < 0.05$) other than WGT were entered in the following

Table 2 Summary of the NONMEM analysis (– not appropriate, *NS* not significant— $P > 0.05$ at the screening step and $P > 0.005$ at the destruction step)

	δ	ω_{CL}(%)	σ(%)	*P*
Basic model:				
2 compartments[a]	–	20.3	36.2	–
3 compartments	−333	21.7	25.1	<0.0005
Screening[b]: Cl =				
θ1 + θ2 × BSA	−44	–	–	<0.0005
θ1 + θ2 × WGT	−44	–	–	<0.0005
θ1 + θ2 × HGT	0	–	–	NS
θ1 + θ2 × AGE	−39	–	–	<0.0005
θ1(1 − θ2 × FORM)	−15	–	–	<0.0005
θ1(1 − θ2 × DOS)[c]	0	–	–	NS
θ1(1 − θ2 × SEX)	−7	–	–	<0.025
θ1(1 − θ2 × META)	−7	–	–	<0.025
θ1(1 − θ2 × PSS)[d]	−9	–	–	<0.005
Full model[e]	−77	16.9	23.6	–
Cl = (θ1 + θ2 × BSA + θ3 × AGE)(1 − θ4 × FORM)(1 − θ5 × SEX) (1 − θ6 × META) (1 − θ7 × PSS)				
θ1 = 0	+5	–	–	NS
BSA (θ2 = 0)	+9	–	–	<0.005
AGE (θ3 = 0)	+17	–	–	<0.0005
FORM (θ4 = 0)	+1	–	–	NS
SEX (θ5 = 0)	0	–	–	NS
META (θ6 = 0)	0	–	–	NS
PSS (θ7 = 0)	+4	–	–	NS
Final model 1: Cl = θ1 × BSA + θ2 × AGE	+12	18.7	23.7	NS
Final model 2: Cl = BSA × (θ1 + θ2 × AGE)	−3[f]	17.4	23.8	–

[a] Rejected model; reference fit for evaluation of the three-compartment model
[b]For the screening step the reference fit is that of the three-compartment model
[c]DOS = 1 when DOSE/BSA > 90 mg/m^2; otherwise, DOS = 0
[d]PSS = 1 when PS > 1; otherwise, PSS = 0
[e]Reference fit for destruction of the full model and evaluation of final model 1
[f]In reference to final model 1; statistical comparison is not possible

full regression model:

$$Cl = (\theta 1 + \theta 2 \times BSA + \theta 3 \times AGE)\,(1 - \theta 4 \times FORM) \times (1 - \theta 5 \times SEX)(1 - \theta 6 \times META)(1 - \theta 7 \times PSS),$$

where FORM = 0 if formulation 1 was given to the patient and *FORM* = 1 if it was formulation 2; SEX = 1 if the patient is male, otherwise SEX = 0; META = 1 if the patient had hepatic metastases, otherwise META = 0; and PSS = 1 if PS = 1 or 2, otherwise PSS = 0.

The full model was tested against restricted models. At this step, AGE was the most important determinant of Cl in the full model, whereas it was BSA at the screening step. Finally, AGE and BSA were the only two remaining significant covariates kept in the final step ($P < 0.005$), leading to final model 1:

$$Cl = \theta 1 \times BSA + \theta 2 \times AGE. \quad (1)$$

This model was not significantly different from the full model which involved five more parameters. An alternative final model allowing Cl to be expressed in liters per hour per square meter of BSA [Cl(l h^{-1} m^{-2})], as in clinical oncology, was proposed:

$$Cl = BSA(\theta 1 + \theta 2 \times AGE). \quad (2)$$

Although not statistically evaluable (final model 2 is not a reduced version of model 1), final model 2 fitted the data slightly better and, since it made sense in clinical practice, adjusting the effect of AGE to BSA in the expression for Cl (l h^{-1} m^{-2}), it was retained with only interindividual variability on Cl. Modeling the interindividual variability in the other PK parameters (K_{12}, K_{21}, K_{13}, K_{31}, and V_1) was attempted with the final model, but doing so resulted in no modification of the parameter estimates, and final model 2 was therefore left unchanged.

Parameter estimates are given in Table 3. For a patient with mean covariate values (AGE = 52.3 years, BSA = 1.68 cm^2), Cl was estimated to be 21.2 l h^{-1} m^{-2} or 35.6 l/h. Other parameters were also calculated, notably $t_{1/2\gamma}$ = 12.2 h and Vss = 124 l. Cl had a low interpatient variability (CV = 17.4%) after accounting for effects of BSA and AGE. Intraindividual variability was estimated at 23.8%. All error CVs estimating the accuracy of the NONMEM estimates

Table 3 Summary of the NONMEM and NPML analyses: estimated and calculated parameters. Numbers in parentheses represent the CV estimation (accuracy) for NONMEM, expressed in percent. Bold face characters represent estimated parameters; all others were calculated from the estimated values

	NONMEM (final model 2)	NPML
V_1(1)	**5.74** (17.6)	3.47
K_{12}(h^{-1})	**1.35** (25.5)	**5.56**
K_{21}(h^{-1})	**1.31** (19.4)	**3.73**
K_{13}(h^{-1})	**1.37** (14.1)	**2.69**
K_{31}(h^{-1})	**0.0699** (13.5)	**0.16**
ωCl (%)	**17.4** (34.8)	**24.8**
σ(%)	**23.8** (11.8)	20 (fixed)
Cl (l/h)	**BSA (34.5-0.254 × AGE)**/35.6[a]	**37.2**[b]
K_e(h^{-1})	6.2[a]	**13.3**
Vss(1)	124[a]	83.2
$t_{1/2\alpha}$(min)	4.5[a]	2.2
$t_{1/2\beta}$(min)	38.3[a]	20.4
$t_{1/2\gamma}$(h)	12.2[a]	7.89[c]

[a]Computed for mean BSA and AGE
[b]Mode: 34.8 h
[c]Two modes: 5 h and 12.4 h

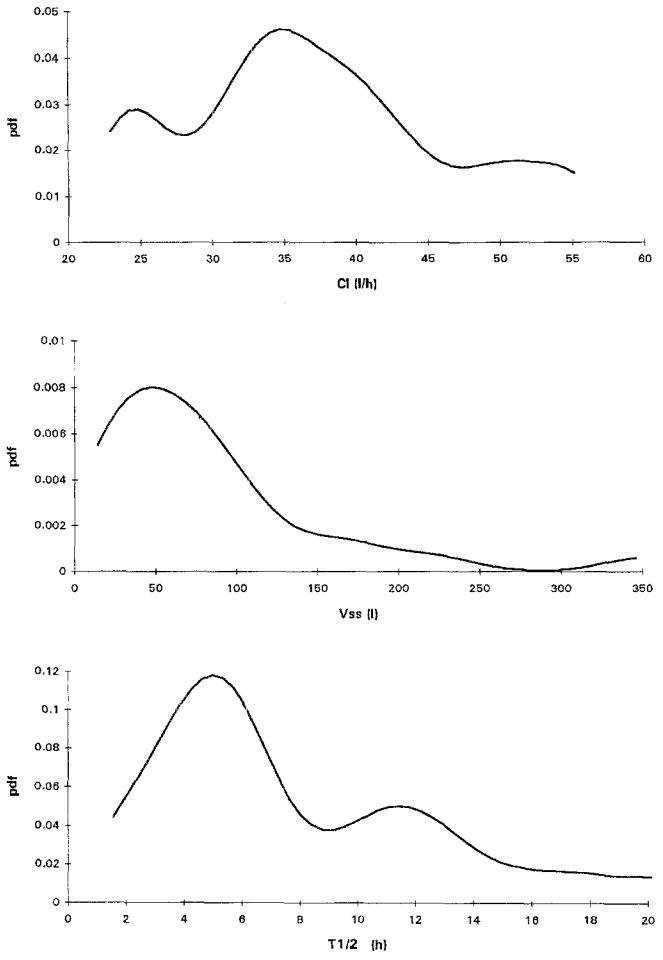

Fig. 2 Estimated NPML pdf of Cl (smoothing parameter, 2.5), Vss (25), and $t_{1/2\gamma}$ (1.3)

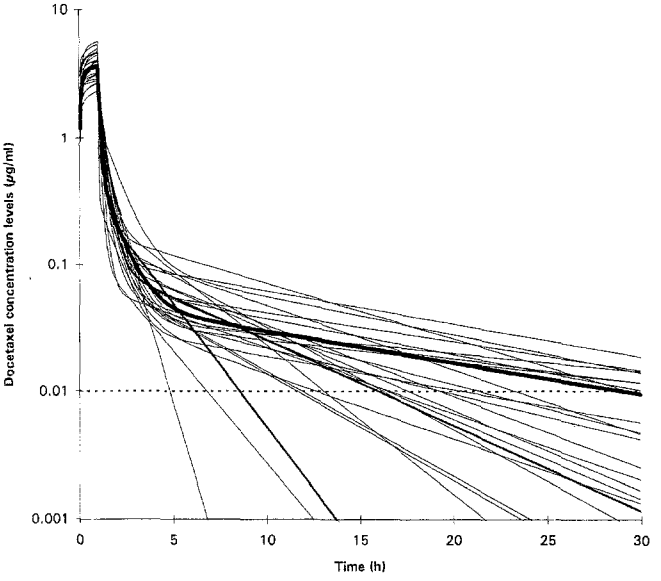

Fig. 3 Simulated profiles obtained for a 1-h, 100-mg/m^2 infusion using the NONMEM estimates (*thick line*) and the 25 discrete sets of NPML parameter estimates; the limit of quantitation of the assay (10 ng/ml) is indicated by the *broken line*

(Table 3) were low (13.5–25.5% for the PK parameters). According to this model, the predicted docetaxel exposure for a patient with mean covariate values following a dose of 100 mg/m^2 given over 1 h is: peak plasma level 3.6 µg/ml; AUC, 4.7 µg h^{-1} ml^{-1}. Varying BSA within the extreme values of the data base (1.3–2.02 m^2) would result in a ± 20% variation of Cl around the mean (35.6 l/h). Extreme Cl values for AGE varying from 35 to 65 years are predicted to be 25.6 and 18.0 l h^{-1} m^{-2}, respectively; that is, a + 21% and a − 15% change in the mean.

NPML analysis

The NPML estimation algorithm reached the minimum-likelihood value of 570 with 25 discrete admissible parameter values for the population distribution. The discrete distributions obtained by NPML were smoothed by assuming a Gaussian distribution in the neighborhood of each point of support for the distribution. The pdfs of Cl, Vss, and $t_{1/2\gamma}$ are displayed in Fig. 2 using a smoothing parameter of 2.5, 25, and 1.3, respectively. The shape of the pdf of Cl is roughly Gaussian, skewed slightly downward, with a mode (34.8 l/h) rather close to the mean population value (37.2 l/h). Two secondary modes can be observed at low (24.8 l/h) and high (51.4 l/h) Cl values. The distribution of Vss is rather log-normal, whereas that of $t_{1/2\gamma}$ looks clearly bimodal (modes at 5 and 11.4 h). However, there was evidence that patients with few data points, if any, during the terminal phase generated locations with a short $t_{1/2\gamma}$ as indicated by the correlation observed between posterior estimates of individual $t_{1/2\gamma}$, calculated with NPML parameters as prior and final observation times ($r = 0.777$, $P = 0.0005$). Estimated and derived population parameters are presented in Table 3 and compared with those of NONMEM. The population mean Cl was estimated at 37.2 l/h with an interindividual CV of 24.8%. All other CVs characterizing the interindividual dispersion were around 50% except that of K_{31} (72.8%). The terminal half-life, $t_{1/2\gamma}$, and total volume of distribution, Vss, with their corresponding interpatient CV(%) were 7.9 h (62.7%) and 83.2 l (89.1%), respectively.

Simulated profiles obtained for a 1-h, 100-mg/m^2 infusion using the 25 discrete sets of parameter values are drawn in Fig. 3 for comparison with the prediction for NONMEM. Graphs of conditional pdfs are not shown; however, mean Cl values evaluated conditionally on known covariate values were calculated. Conditionally to AGE, Cl decreased from 38.2 to 33.1 l/h, i.e, a variation of − 3% and + 11% around the mean. For BSA varying between 1.3 and 2 m^2, Cl changed more: − 27.7% and + 13.2% around the mean. These variations of Cl were plotted for either

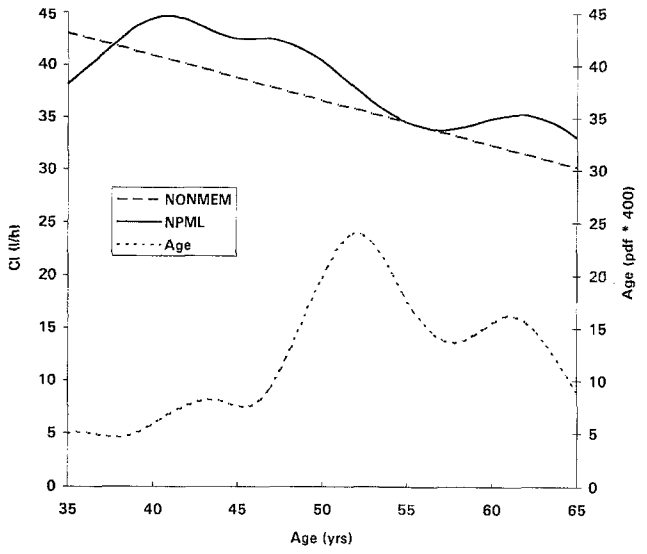

Fig. 4 Variations of mean Cl (1/h) as determined using NPML and NONMEM and the corresponding actual distribution of AGE (pdf)

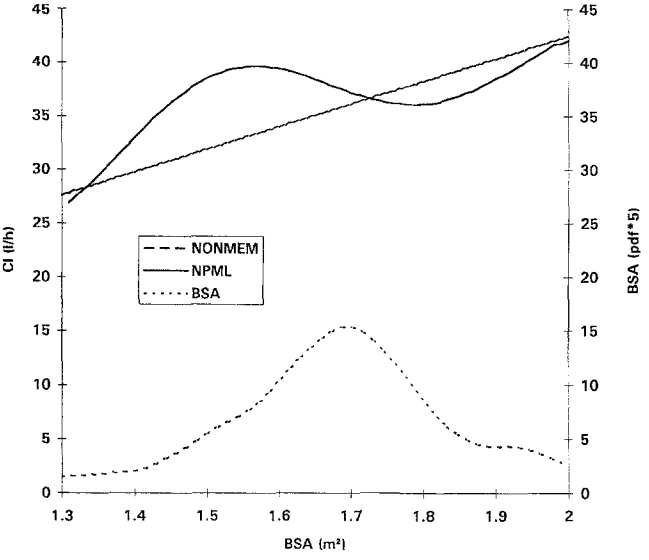

Fig. 5 Variations of mean Cl (1/h) as determined using NPML and NONMEM and the corresponding actual distribution of BSA (pdf)

AGE (Fig. 4) or BSA (Fig. 5) with corresponding NONMEM Cl so as to appreciate the variations in Cl predicted by both analyses. Figures 4 and 5 also provide plots of the smoothed histograms [11] of the actual covariate values in the population. This is useful to interpret the NPML results and evaluate the reliability of extrapolations on the borders, which may depend on the number of patients with such characteristics. BSA was regularly distributed, whereas for AGE there were only two patients under 45 years and a group of five over 60 years, which distorts the distribution. This indicates that in extrapolating Cl for young people we should be all the more careful, since the initial rise in Cl observed between the ages of 35 and 40 years is likely to be spurious.

Discussion

We report on docetaxel population pharmacokinetic data from two phase I studies using the administration schedule selected for phase II trials: short i.v. infusion given every 3 weeks. As usual, a standard pharmacokinetic analysis was conducted using the conventional approach based on nonlinear weighted regression analysis of individual concentration-time data [1, 8]. However, estimation of some parameters [e.g., terminal half-life ($t_{1/2\gamma}$) and steady-state volume of distribution (Vss)] by this individual analysis was difficult because of the imbalance of concentration-time data across patients, which resulted in high apparent variability of estimates. This was due either to the variation in actual infusion duration and sampling times, or to missing samples, or to the limit of sensitivity of the assay, which precluded full observation of the terminal elimination phase for patients receiving low doses and/or with high Cl. This last point induced confounding intercorrelations between the number of observation times in the terminal phase and both the dose (study design) and the pharmacokinetic outcome (Cl).

Nonlinear mixed-effect modeling has been advocated to handle such data [15, 16], and the pooled data were analyzed using the NONMEM program to obtain the best estimates of structural pharmacokinetic parameters. NONMEM estimates are in good agreement with values estimated using individual weighted least squares [1, 8] when the data permitted (i.e., when enough data points were in the terminal elimination phase). In addition, the analysis was performed using an alternative nonparametric approach to mixed-effect modeling, NPML. This method, previously applied to three drugs in routine clinical use [14], was performed for the first time in the context of drug development and, for this purpose, was used after NONMEM, although both methods are completely independent.

As far as the estimation of structural parameters is concerned, similarities and differences were observed with the two approaches. First of all, it was shown in preliminary analyses that the three-compartment model was, with both methods, the only one adequate to fit the data. Next, with this structural model, the population Cl was found to be very similar: 35.6 (NONMEM) and 37.2 l/h (NPML). The interindividual variability of Cl estimated by NONMEM (21.7%, overall estimate in the basic model not taking into account the covariates) was similar to that estimated by NPML (24.8%). Concerning the other PK

parameters (mean half-lives and Vss), some discrepancies between the two methods, leading to different profiles (Fig. 3), were observed. In particular, the NPML estimate of the $t_{1/2\gamma}$ pdf was clearly bimodal. We speculate that the reason for bimodality is due to a subset of patients (from among those lacking late data points) whose data can mainly be fitted with a biexponential model. Those patients generated NPML locations with a short $t_{1/2\gamma}$. This would give rise to the apparent bimodality of $t_{1/2\gamma}$ because of the lack of a prior hypothesis on parameter distribution in the NPML method, in contrast to NONMEM, which assumes unimodal ones. A similar problem was encountered with individual analysis [1, 8]. Further studies are presently ongoing to assess the performance of NPML in a more conventional situation for population analysis involving sparse data on a large population of patients. However, in the particular case of docetaxel, the problems in estimating $t_{1/2\gamma}$ had little influence on the estimation of Cl because of the slight contribution of the terminal phase to the overall AUC.

Concerning the effect of covariates, NONMEM was first used to find those with significant effects on Cl; these were BSA and AGE. The variability due to BSA should not be of clinical significance since it is accounted for by adjusting the dose to BSA. However, the effect of AGE deserves further investigation on a larger population to estimate its magnitude and determine whether it has any clinical significance. This will be studied on data from ongoing phase II trials. The results of both methods were in reasonable agreement. The general trends found by NONMEM and NPML (Figs. 4, 5) are comparable: Cl decreases with AGE and increases with BSA. Moreover, the estimated magnitude of the effects of the two covariates is also similar. As NPML estimates the full conditional pdfs, it should be more precise than NONMEM in describing a covariate effect because NONMEM modeling is based on regression, which has an averaging effect. However, in this particular case, the shapes of the relationship estimated in the NPML analysis confirmed those selected in the NONMEM analysis.

In conclusion, the NONMEM analysis of this experimental data set allowed the optimal estimation of structural pharmacokinetic parameters, which were used to define a limited sampling strategy for the phase II trials with a view to performing a large-scale, prospective, population pharmacokinetic/pharmacodynamic evaluation of docetaxel [7]. Concerning NPML, we believe that the lack of a prior hypothesis on parameter distribution might have been a problem in this particular case, generating bimodal distribution of the terminal half-life. Concerning the effects of covariates on Cl, the results of both methods are in good agreement. Also it should be emphasized that NPML can detect smooth effects of the covariates on the mean clearance. Both approaches will be used on phase II data to pursue our methodological evaluation.

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