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ORIGINAL ARTICLE

Pharmacokinetic evaluation of the vinorelbine–lapatinib combination in the treatment of breast cancer patients

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Abstract
Purpose The objectives of this study were to investigate the pharmacokinetics of intra-venous vinorelbine combined with lapatinib as well as the effect of covariates in breast cancer patients.
Methods Women with HER2 + locally advanced or metastatic breast cancer progressing after ≤2 lines of trastuzumab-based treatment were treated with lapatinib per os starting 7 days (D) (D-7 to D0) before adding vinorelbine on a D1 & D8 every 3 weeks intravenous schedule. Lapatinib was given everyday. Dose levels [DL, lapatinib (mg)/vinorelbine (mg/m^2)] ranged from 750/20 to 1,250/25. A total of 29 patients, 37–76 years old, were treated with the combination of lapatinib + vinorelbine. For pharmacokinetic analysis, 7 time point samples were collected on D1 of cycle 1 for lapatinib and vinorelbine assays. For vinorelbine and lapatinib, respectively, whole blood and plasma concentrations were measured using ultra performance liquid chromatography with tandem mass spectrometry validated methods. Data analysis was performed using a non-linear mixed effect model program (Monolix version 3.1 s).
Results A three-compartment open model adequately described vinorelbine pharmacokinetics. Body weight (BW) and platelet count significantly influenced blood vinorelbine clearance (CL). BW significantly influenced volume (V) and CL terms. Platelet count influenced vinorelbine elimination CL. The final parameter estimates were as follows: CL = 24.9 L/h, V1 = 8.48 L, Q2 = 50.7 L/h, V2 = 1,320 L, Q3 = 66.1 L/h, and V3 = 62.4 L (Qi and Vi denote inter-compartmental clearance and peripheral volume of distribution, respectively), normalized for a 70-kg patient according to BW allometric scaling (CL is normalized for a 250,000 platelet count). A one-compartment model with linear elimination adequately fitted the lapatinib plasma concentration–time data. The population pharmacokinetic parameters were CL = 27.7 L/h, V = 357 L, and the absorption constant, $ka = 0.44\ h^{-1}$. The between-subject variabilities (BSV) could be well estimated for CL, V but not for *ka*. No covariate effect, including body surface area and vinorelbine dosage, could be identified for lapatinib.
Conclusions The pharmacokinetic modeling of vinorelbine and lapatinib was consistent with the results previously reported. BW and platelet count were confirmed as

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influencing blood CL of vinorelbine. A pharmacokinetic interaction occurred between vinorelbine and lapatinib probably due to lapatinib inhibition of CYP450-3A4. The combined lapatinib administration decreases statistically significant the vinorelbine CL. The maximal tolerated dose for the combination of lapatinib with vinorelbine on a q3w schedule is as follows: lapatinib 1,000 mg/day continuously and vinorelbine 22.5 mg/m^2 D1 & D8.

Keywords Vinorelbine · Lapatinib · Drug-interactions · Population pharmacokinetics · Anti-cancer agents

Introduction

Vinorelbine is a semisynthetic vinca alkaloid which is marketed under the brand name of Navelbine® for its activity against non-small cell lung and advanced breast cancer. Vinorelbine blocks cell mitosis by interfering with microtubule assembly and by depolymerisation of microtubules [1]. Vinorelbine also promotes apoptosis in cancer cells [2].

Lapatinib (Tykerb®) is a potent orally active small molecule that reversibly inhibits ErbB1 and ErbB2 tyrosine kinases leading to inhibition of MAPK and PI3 K signaling pathways. Lapatinib is approved in many countries for the treatment of advanced or metastatic breast cancer with HER2-overexpressing tumors either in first combination with aromatase inhibitors or after trastuzumab in combination with capecitabine for patients who have progressed after treatment regimens containing anthracyclines, taxanes, and trastuzumab [3]. Lapatinib is clinically active as a single agent or in combination with various antineoplastic agents in patients with HER2-overexpressing breast cancer or other solid tumors [4]. Lapatinib-related hepatotoxicity has been reported [5].

A novel combination of oral lapatinib as a selective dual ErbB1/ErbB2 targeted drug + intravenous (IV) vinorelbine as a cell-cycle inhibiting agent could provide a high-potential novel treatment for locally advanced or metastatic HER2 overexpressing breast cancer. Lapatinib is extensively metabolized by cytochrome P450 enzymes, in particular CYP3A4/5. Lapatinib has been shown to be a strong inhibitor of CYP3A4 by undergoing biotransformation to form reactive electrophilic species [6]. CYP3A4 is also principally involved in the metabolism of vinorelbine. Mechanism-based inactivation of CYP3A4 may lead to accumulation of coadministrated drugs in clinical practice. Lapatinib is a potent mechanism-based inactivator [6], which could modify the pharmacokinetics of vinorelbine.

GEP01 is a phase I pharmacokinetic study of oral lapatinib and IV vinorelbine in the treatment of HER2-overexpressing locally advanced or metastatic breast cancer patients.

Our objectives were to develop a population pharmacokinetic model for vinorelbine and lapatinib and to examine the potential pharmacokinetic interactions given the shared metabolic pathway through CYP3A4 for both compounds.

Methods

Patients

Women were eligible if they were ≥18 years of age with HER2 overexpressing locally advanced or metastatic breast cancer progressing after ≤2 lines of trastuzumab-based treatment. Patients were required to be off treatment at least 4 weeks since their last radiotherapy course and at least 3 weeks since their last cycle of chemotherapy or treatment with trastuzumab.

The study was approved by a central national ethic committee, the protocol was reviewed by the local committees of all participating institutions, and written informed consent had to be obtained from patients before inclusion. Appropriate information had to be given to patients before study initiation.

Drug administration

Patients were treated with lapatinib starting 7 days (D7 to D0) before adding vinorelbine on a day 1 (D1) and day 8 (D8) every 3 weeks (q3w) IV infusion over 15 min schedule, until disease progression, unacceptable toxicity, or intercurrent conditions precluding the continuation of treatment. Lapatinib was given orally and continuously. Dose levels (DL) of lapatinib (mg)/vinorelbine (mg/m^2) ranged from 750/20 to 1,250/25.

Vinorelbine assay

Whole blood samples were collected on day 1 of cycle 1, before and at approximately 12 min, 1, 3, and 24 h following the start of infusion, according to a validated limited sampling strategy for estimation of vinorelbine clearance (CL) [7]. Vinorelbine blood concentrations were measured by a validated ultra performance liquid chromatography method coupled with tandem mass spectrometry detection (UPLC-MS/MS) [8]. The lower limit of quantification of this method was 10.0 ng/mL. The within-assay precision and accuracy were 11.7 and 89%, respectively. The between-assay precision and accuracy were 11.1 and 92%, respectively.

Lapatinib assay

Blood samples for pharmacokinetics of lapatinib were collected on day 1 of cycle 1 and at approximately 12 min,

1, 3, 6, 12, and 24 h after lapatinib administration. Blood samples were immediately centrifuged to yield plasma. Lapatinib plasma concentrations were measured by a validated UPLC-MS/MS method [9]. The lower limit of quantification of this method was 10.0 ng/mL. The within-assay precision and accuracy were 12.8 and 109%, respectively. The between-assay precision and accuracy were 19.1 and 118%, respectively.

Pharmacokinetic modeling

Data were analyzed using the nonlinear mixed effect modeling software program Monolix version 31 s [10] (http://wfn.software.monolix.org). Parameters were estimated by computing the maximum likelihood estimator of the parameters without any approximation of the model (no linearization) using the stochastic approximation expectation maximization (SAEM) algorithm combined to a Markov Chain Monte Carlo (MCMC) procedure. The number of MCMC chains was fixed to 10 and 20 for all estimations of vinorelbine and lapatinib, respectively. A proportional model was used to describe the residual variability, and the between-subject variabilities (BSV) and η were ascribed to an exponential model. Parameter shrinkage was calculated as $\{1 - \mathrm{sd}(\eta)/\Omega\}$, where $\mathrm{sd}(\eta)$ and Ω are the standard deviation of individual, η_i, parameters and the population model estimate of the BSV, respectively. Specific tests comparing the log-likelihood, the Akaike information criterion (AIC) and the bayesian information criterion (BIC) were performed to test different hypotheses regarding the final model, covariate(s) effect on pharmacokinetic parameter(s), residual variability model (proportional versus proportional plus additive error model), structure of the variance–covariance matrix for the BSV parameters. Diagnostic graphics and other statistics were obtained using the R program [11]. They included predictions (PRED) and individual predictions (IPRED) versus observations (OBS) data, and the normalized prediction distribution errors (NPDE) metrics was used for residuals [12]. The predictive performance of the model was measured using the visual predictive check, drawn using 400 simulations of the final population model.

Results

Population characteristics

From the 29 patients investigated, 115 blood vinorelbine and 169 lapatinib plasma concentrations were available for analyses. No concentration was reported below the limit of quantification (BLQ). The patient's characteristics on entry into the studies are summarized in Table 1.

Table 1 Characteristics of the 29 patients

Parameter	Mean	Median	Range
Age (year)	59	57	37–76
Height (cm)	160	161	142–176
Bodyweight (kg)	65	62	45–110
Lean body mass (kg)	44	44	34–60
Ideal bodyweight (kg)	53	53	36–66.5
Body mass index (kg/m^2)	25.1	24	18.7–39
Body surface area (m^2)	1.67	1.62	1.40–2.22
Serum creatinine (μM)	62	62	47–80
Platelets count ($\times 10^3$/mm^3)	294	271	151–539

Vinorelbine population pharmacokinetic modeling

A three-compartment open model adequately described blood vinorelbine time-concentration courses, for which CL, Q2, and Q3 denote the clearance of elimination and inter-compartmental clearances, and V1, V2, and V3 denote the central and peripheral volumes of distribution, respectively. BSV could be estimated for CL, V1, and V3 only. Also, a covariance term between CL- and V1 BSVs was significant. Residual variability was described by a proportional error model. At this step, V1 and CL estimates (% relative standard error or %rse) were 19.7 L h^{-1} and 5.15 L (22 and 30%) and the corresponding BSVs were 0.673 and 0.964 (9 and 10%).

The main covariate effects were related to body size descriptors and platelet counts. Since there was a wide range in the patients body mass index, different body size descriptors were investigated, i.e., Body Weight (BW), Ideal Body Weight (IBW), and Lean Body Mass (LBM). As shown in Table 2, BW was the best size descriptor. Thus, CL and volume terms were normalized after a 70-kg patient body weight according to allometric scaling rule. This reduced the global BSV and the goodness-of-fit criteria (Table 2). The inclusion of platelet counts in the CL covariate model again reduced the global BSV. Lapatinib was also considered as either a categorical or a continuous covariate influencing clearance. No significant difference was observed between 750 mg of lapatinib (reference dose group) and 1,000 and 1,250 mg of lapatinib as other groups. Also when the effect of lapatinib was modeled as $\mathrm{CL} = \mathrm{TVCL} \times (\text{platelet effect}) \times (\text{BW effect}) \times (1 - \mathrm{LAPDOSE}/(\mathrm{LAPDOSE} + \mathrm{lapdose50}))$, a significant lapdose 50 of 1,890 mg (15%) was estimated, but the BIC/AIC criteria values and BSV increased. So the lapatinib effect was not retained in the final model. Table 2 summarizes the model building steps. The improvement of fit from the covariate-free model to the final model is illustrated in Fig. 1. The final covariate model for clearance was then

Table 2 Pharmacokinetic model building for blood vinorelbine

Model	Details	AIC/BIC
A. Classical three-compartment covariate-free	CL, V1, Q2, V2, Q3, V3 η_{Q2}, η_{V2}, η_{Q3} fixed to 0 Correlation between η_{CL} and η_{V1} $\eta^2(CL + V1 + V2) = 2.24$	−458/−443
B. Effect of ideal body weight	CL terms = TVP × $(IBW/70)^{0.75}$ V terms = TVP × $(IBW/70)^{1}$ $\eta^2(CL + V1 + V2) = 1.71$	−459/−444
C. Effect of lean body mass	CL terms = TVP × $(LBM/60)^{0.75}$ V terms = TVP × $(LBM/60)^{1}$ $\eta^2(CL + V1 + V2) = 1.49$	−468/−453
D. Effect of body weight, BW	CL terms = TVCL × $(BW/70)^{0.75}$ V terms = $(BW/70)^{1}$ $\eta^2(CL + V1 + V2) = 1.38$	−475/−460
E. Effect of BW + Effect of platelets on CL	CL = TVCL*$(PLAT/250)^{\beta}$ × $(BW/70)^{0.75}$ $\eta^2(CL + V1 + V2) = 1.06$	−478/−461
F. Effect of BW + Effect of platelets on CL + a. Effect of platelets on V1	CL = TVCL × $(PLAT/250)^{\beta CL}$ × $(BW/70)^{0.75}$ V1 = TVV1 × $(PLAT/250)^{\beta V1}$ × $(BW/70)^{1}$	−478/−460 −476/−459
b. or V2	or V2 = TVV2 × $(PLAT/250)^{\beta V2}$ × $(BW/70)^{1}$	
G. Effect of BW + Effect of lapatinib, categorial effect	Reference TVCL for 750 mg lapatinib and 70 kg BW CL = TVCL × β_{LAP} 1,000 mg CL = TVCL × β_{LAP} 1,250 mg	−477/−459

η, between-patients variability, *AIC* akaike information criterion/*BIC* bayesian information criterion, *BW* bodyweight in kg, *LBM* lean body mass in kg, *IBW* ideal body weight in kg, $\eta^2(CL + V1 + V2)$ denotes the sum of between-patients variances (η^2s) for the clearance and volume parameters. For all models, the residual variability was proportional

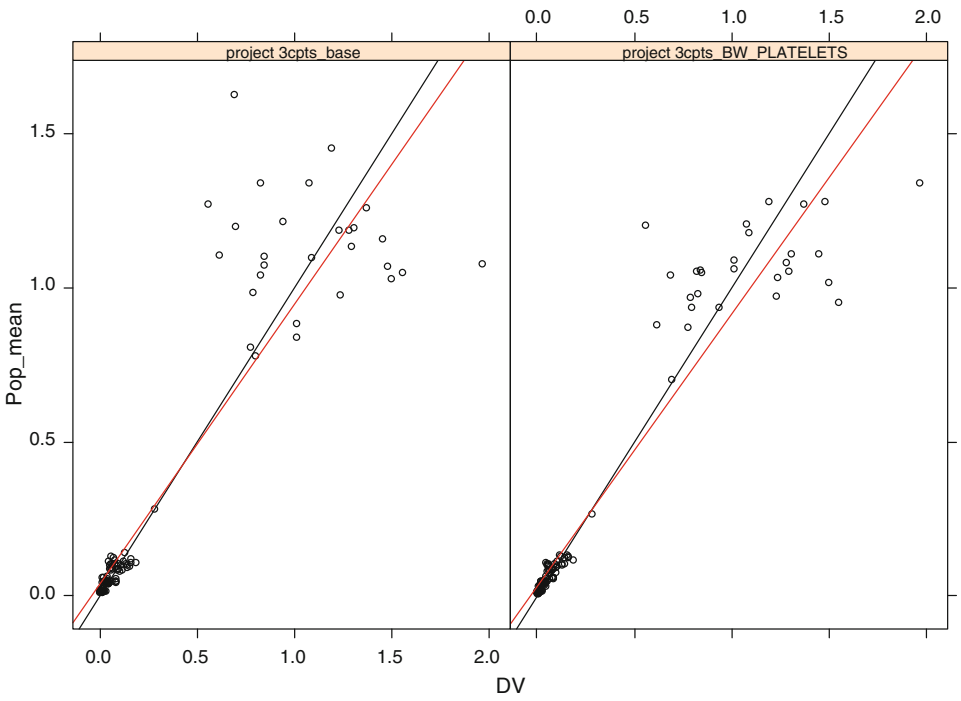

Fig. 1 Observed vinorelbine concentrations, DV, versus model predictions, Pop_mean on a log scale for the covariate-free versus the final model. *Left panel* covariate-free model; *Right panel* final model including the effect of body weight on clearance and volume terms based on allometric rule plus the effect of platelets on elimination clearance (correlation 0.915 and 0.954, bias −0.01 and 0.005, precision 0.194 and 0.142 for left and right panels, respectively)

$$CL = 24.9 \times (PLAT/250,000)^{-1.1} \times (BW/70)^{0.75}$$

where 24.9 denotes the population typical value (TV) of CL and corresponds to the CL of a patient weighing 70 kg with a platelet count of 250,000/mm^3. Table 3 summarizes the results and Fig. 2 depicts the diagnostic plots for the final population model.

The results of the visual predictive check (VPC) for the final blood vinorelbine population model at the 22.5 mg/m^2 dose level are depicted in Fig. 3. The observed concentrations were centered about the model-predicted median, and the proportion of observations out of the model-predicted 5th and 95th percentile curves were not significantly different from 10%.

Table 3 Pharmacokinetic parameters of vinorelbine combined with lapatinib 750–1250 mg in 29 patients

Parameter	Covariate effect	Estimate (%rse)	BSV (%rse) [shrinkage]
CL, L h^{-1} 70 kg^{-1}	(BW/70)$^{3/4}$	24.9 (22)	0.506 (18) [0.17]
Per 250,000 platelets/mm^3	(PLATELETS/250,000)$^{\beta}$	−1.1 (42)	
V1, L 70 kg^{-1}	(BW/70)^{1}	8.48 (24)	0.458 (31) [0.18]
Q2, L h^{-1} 70 kg^{-1}	(BW/70)$^{3/4}$	50.7 (8)	NA
V2, L 70 kg^{-1}	(BW/70)^{1}	1320 (32)	0.874(18) [0.16]
Q3, L h^{-1} 70 kg^{-1}	(BW/70)$^{3/4}$	66.1 (10)	NA
V3, L 70 kg^{-1}	(BW/70)^{1}	62.4 (10)	NA
Residual var., proportional	NA	0.236 (9)	NA

Parameters are normalized after a 70-kg patients body weight (BW) according to allometric scaling

%rse, percent relative standard error, *BSV* between-patients variability (η), *CL* and *Q*, elimination and inter-compartmental clearances, *Vn* central and peripheral volumes of distribution, *NA* not applicable

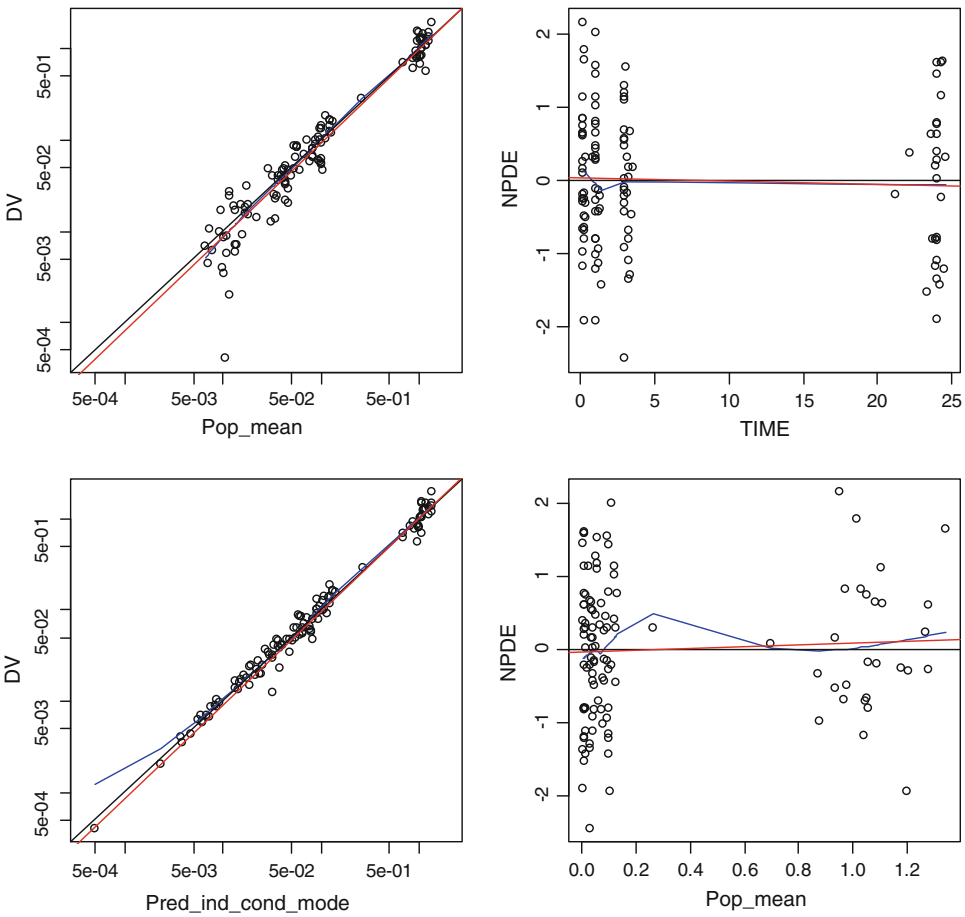

Fig. 2 Diagnostic plots for the final vinorelbine population model. Observed vinorelbine concentrations, DV, versus model predictions (Pop_mean) and individual predictions, (Pred_ind_cond_mode) on a log scale and normalized prediction distribution errors (NPDE, mean = 0, variance = 1) versus time and model predictions. The mean and variance of the NPDE distribution were not significantly different from 0 and 1 (Wicoxon signed rank and Fisher variance tests, $P = 0.99$ and $P = 0.51$) and the distribution was normal (Shapiro–Wilk normality test, $P = 0.77$)

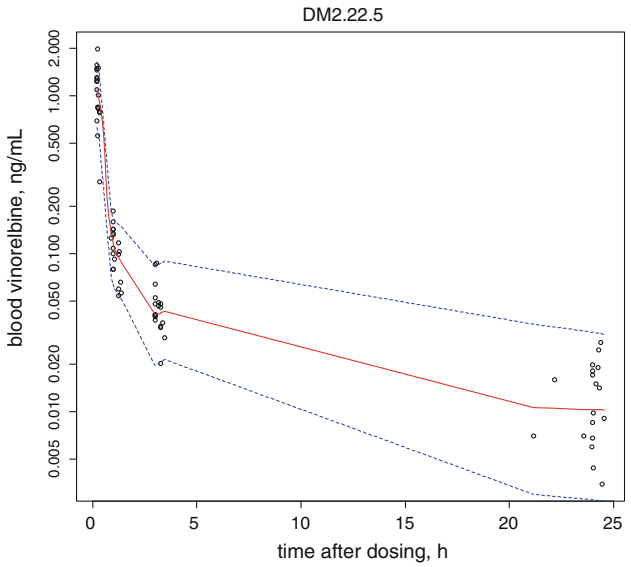

Fig. 3 Visual predictive check for the final blood vinorelbine population model at the 22.5 mg/m^2 dose level. (*open circle*) Observed data. The *solid lines* denote the 5th, median, and 95th percentiles from *bottom* to *top* of 400 Monte Carlo-simulated predictions. The *dashed lines* stand for the 5th, median, and 95th percentiles of the observed concentrations. The *bottom* and *top lines* include the 90% confidence interval

Table 4 Parameter estimates of the final lapatinib population model in 29 patients

Parameter	Estimate (%rse)	BSV (%rse) [shrinkage]
CL/F, L h^{-1}	27.7 (18)	0.63 (9) [0.06]
V/F, L	357 (13)	0.37 (19) [0.10]
Ka, h^{-1}	0.44 (18)	NA
Residual var., prop.	0.412 (7)	NA

%rse, percent relative standard error, *BSV* between-patients variability (η), *CL/F* and *V/F* apparent clearance and volume of distribution, F being the unknown bioavailability, *NA* not applicable

Lapatinib population pharmacokinetic modeling

A one-compartment open model adequately described lapatinib time-concentration courses, for which pharmacokinetic parameters included apparent clearance (CL/F), apparent volume of distribution (V/F), and absorption rate constant (Ka), F being the unknown bioavailability. BSV could not be estimated for Ka. The residual variability, proportional error model, was 0.412 (rse 7%). No covariate effect was significant, including a BW effect based on allometric rule. Table 4 summarizes the parameter estimates of the final lapatinib population model, and Fig. 4 depicts the diagnostic plots.

The results of the VPC for the final plasma lapatinib population model at the 1,000 and 1,250 mg DL are depicted in Fig. 5. The proportions of observations out of the model-predicted 5th and 95th percentile curves were not significantly different from 10%.

Tolerance and determination of maximum tolerated dose

No dose-limiting toxicity (DLT) occurred at DL1, DL2, and DL3. Two DLT were observed at DL4 (vinorelbine 25 mg/m2 + lapatinib 1,000 mg) out of 3 patients. One patient presented with febrile neutropenia; the other one had a grade 4 neutropenia for more than 7 days. Both DLT observed at DL4 were hematological and suggested that they were related mostly to vinorelbine, warranting the exploration of an immediate higher dose for lapatinib with the vinorelbine dose used in DL3. This led to an extra DL3 (vinorelbine 22.5 mg/m^2 + lapatinib 1,250 mg) to the original design. Of 9 patients eventually enrolled at DL3, 2 developed a DLT: one grade 4 neutropenia $>$ 7 days and 1 grade 4 neutropenia and diarrhea with confusion, multivisceral failure, and pancreatitis. Thus, DL3 (1,000/22.5) was further validated as the maximum tolerated dose with a total of 11 patients. Clinical details have been submitted for publication (REF DU PAPIER CLINIQUE SOUMIS).

Discussion

As previously observed, the pharmacokinetics of blood vinorelbine was satisfactorily described by an open three-compartment model with linear elimination. The vinorelbine pharmacokinetic parameters were significantly influenced by BW using an allometric scaling. Over the range body size predictors observed in these patients, IBW and LBM were also tested in the model but were not superior to BW in explaining the pharmacokinetic variability. Moreover, CL was specifically influenced by the platelet count: the greater the platelet count was, the lower the CL. These covariate effects are reasonable because of the high affinity binding of vinorelbine to platelets [13] and because BW is usually identified as influencing both volume and CL terms. This final model was validated by the very conservative NPDE test and its good predictive performance was assessed by the visual predictive check plot. The blood CL estimate, 24.9 L/h (19.7 L/h for the covariate-free model), was clearly lower than previously reported values: 39.4 L/h for the covariate-free model in a large pharmacokinetic population analysis including 64 patients, 20–45 mg/m^2 vinorelbine infusions, 99 pharmacokinetic courses, and 1228 observations [7], 45–46 L/h in 52 elderly patients receiving 60 mg/m^2, using a limited sampling (1.5, 3, and 24 h) and a Bayesian estimation

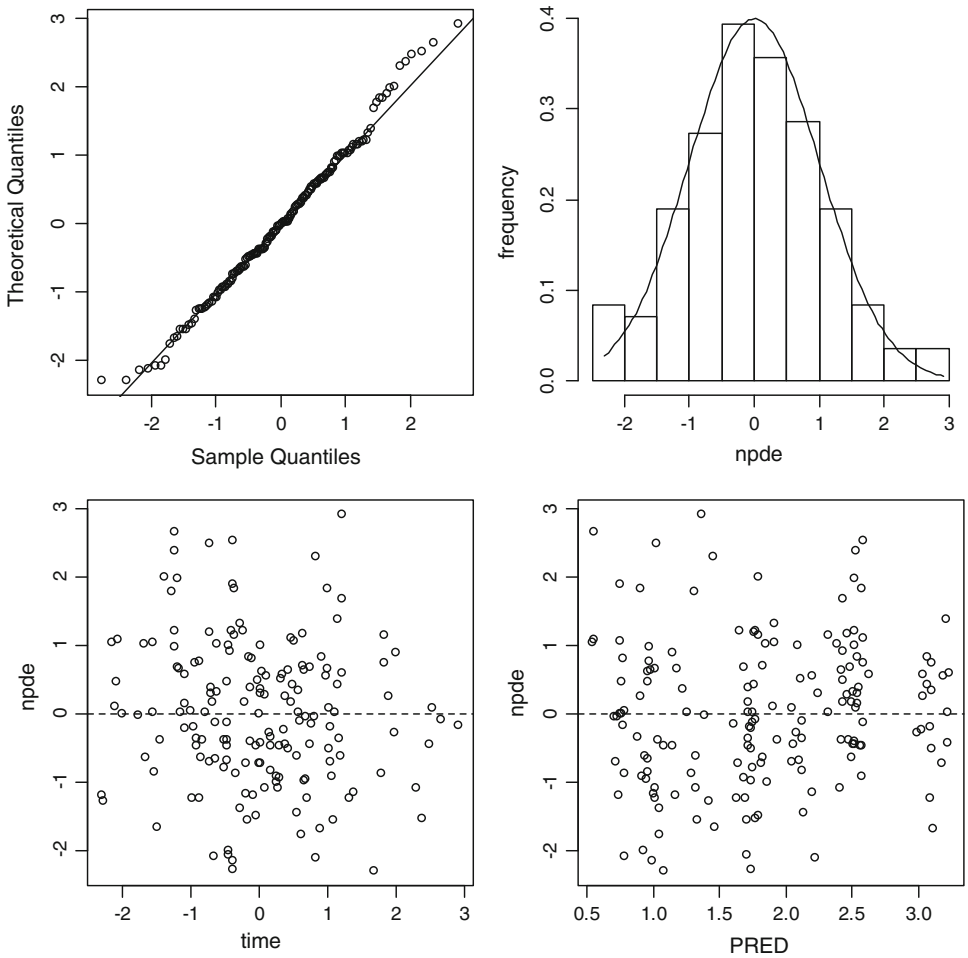

Fig. 4 Diagnostic plots for the final lapatinib population model. Observed lapatinib concentrations, DV, versus model predictions (Pop_mean) and individual predictions, (Pred_ind_cond_mode) on a log scale and normalized prediction distribution errors (NPDE, mean = 0, variance = 1) versus time and model predictions. The mean and variance of the NPDE distribution were not significantly different from 0 and 1 (Wicoxon signed rank and Fisher variance tests, $P = 0.79$ and $P = 0.22$) and the distribution was normal (Shapiro–Wilk normality test, $P = 0.36$)

[14], 41.5 L/h in 18 patients receiving 20–40 mg/m^2 with a rich sampling protocol, 12 concentration–time points after the start of infusion [15], and 33.1 L/h in 41 patients receiving 60 mg/m^2, using a limited sampling (0.33, 3, and 24 h) and a Bayesian estimation [16]. The lower CL value observed in this study could be due to the combined lapatinib administration since lapatinib and vinorelbine are metabolized by the CYP3A4 pathway and since lapatinib is known to inhibit this pathway. A statistically significant effect of lapatinib could not be shown in this study, likely because there was no patient group without lapatinib, and since the lapatinib doses (750–1,250 mg/24 h) were in a too narrow range to detect a significant effect between these dosage subgroups. A student's *t* test comparing our vinorelbine CL estimate to previously published ones [7, 16] showed a significant decrease in CL ($P < 0.001$) when vinorelbine was administered in combination with lapatinib (our study) compared with vinorelbine administered alone [7, 16].

The pharmacokinetics of plasma lapatinib was satisfactorily described by an open one-compartment model with linear elimination as reported in a previous study using a population analysis [17]. Our plasma CL/F estimate (16.5 L/h/m^2) was close to the previous reported value (12.1 L/h/m^2) in a phase I/II study including 16 patients with 80 samples. The observed inter-individual variability estimates 0.63 and 0.37 for CL, and volume are consistent with those reported in the same previous phase I/II study. Different covariates including BW, height, body surface area, IBW, LBM, and vinorelbine dosages were analyzed for their significance in the model. The lapatinib pharmacokinetic parameters were not significantly influenced by these covariates.

Conclusions

A one-compartment model described the pharmacokinetics of lapatinib without any covariate effect. The pharmacokinetics of vinorelbine was best described by an open three-compartment model with linear elimination. BW and platelet count were confirmed as influencing

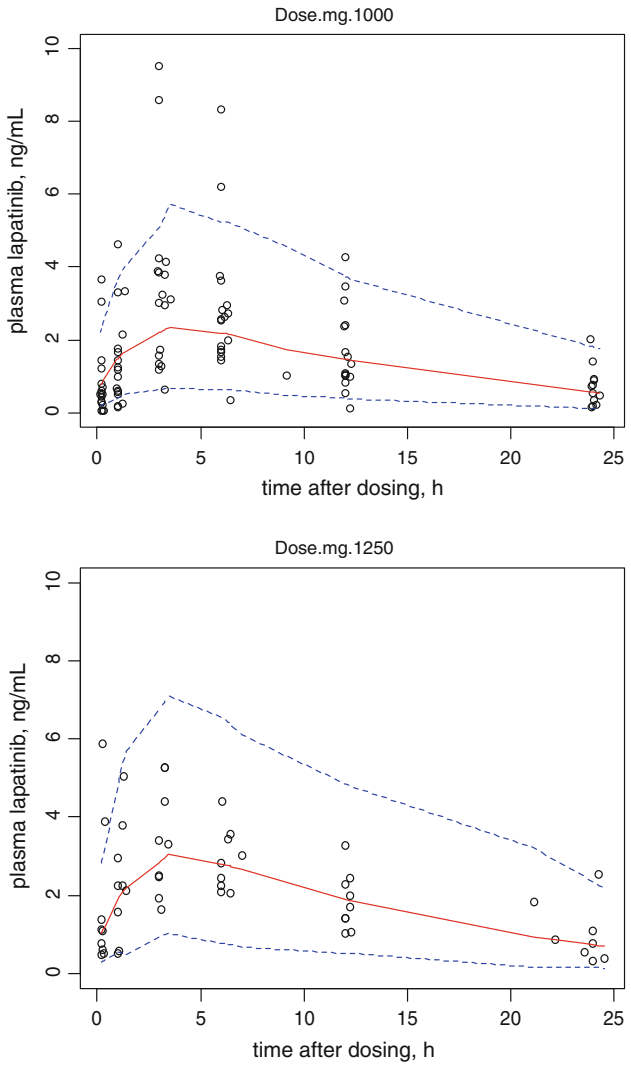

Fig. 5 Visual predictive check for the final plasma lapatinib population model at the 1,000 and 1,250 mg dose levels. *Circle* observed data. The *solid lines* denote the 5th, median, and 95th percentiles from bottom to top of 400 Monte Carlo-simulated predictions. The *dashed lines* stand for the 5th, median, and 95th percentiles of the observed concentrations. The *bottom* and *top lines* include the 90% confidence interval

blood CL of vinorelbine. The combined lapatinib administration (750–1,250 mg/day) decreased statistically significant the vinorelbine CL as compared with previous reports, strongly suggesting a pharmacokinetic interaction between vinorelbine and lapatinib due to CYP450-3A4 interaction.

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