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Population pharmacokinetics of erlotinib and its pharmacokinetic/pharmacodynamic relationships in head and neck squamous cell carcinoma

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ABSTRACT

A clinical study was conducted to determine the safety and efficacy of neoadjuvant erlotinib treatment in patients with head and neck squamous cell carcinoma [Thomas F, Rochaix P, Benlyazid A, et al. Pilot study of neoadjuvant treatment with erlotinib in non-metastatic head and neck squamous cell carcinoma. *Clin Cancer Res* 2007;**13**:7086–92]. The aim of the present analysis was to explore the impact of several covariates on the pharmacokinetics of erlotinib and its main metabolite (OSI-420) and to determine PK/PD relationships.

Patients and methods: Plasma concentrations of erlotinib and OSI-420 of 42 patients were analysed using the NONMEM program to evaluate the impact of patients' covariates on erlotinib pharmacokinetics. The presence of single nucleotide polymorphisms (SNP) in *ABCB1* (2677G > T/A and 3435C > T), *ABCG2* (421C > A) and *CYP3A5* (6986G > A) was investigated. Pharmacokinetic/pharmacodynamic relationships between plasma drug exposure (AUC) and early drug response or toxicity were also studied.

Results: The covariates retained to predict erlotinib clearance were ALAT (alanine amino transferase), age and *ABCG2* polymorphism. A significant link between drug exposure and the grade of skin rash was observed but early response to treatment was not correlated to the erlotinib AUC.

Conclusions: Erlotinib treatment may present criteria justifying dose individualisation but further studies, including more patients, are necessary to define the modalities of this adaptation.

1. Introduction

Erlotinib (OSI-774, Tarceva®) is a potent, orally active EGFR tyrosine kinase inhibitor that blocks EGFR-mediated intracellular signalling, approved for the treatment of patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen[2] and in combination with gemcitabine for locally ad-

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vanced unresectable or metastatic pancreatic cancer.[3] The clinical pharmacokinetics of erlotinib in a large number of patients participating in clinical trials has been studied with a population approach.[4] Erlotinib is metabolised by the CYP3A4, CYP3A5, CYP1A1 and CYP1A2 isoforms of the P450 enzymes.[5] The main circulating metabolites of erlotinib are products of the O-demethylation of the side chains (such as OSI-420 and OSI-413) and their *in vitro* cellular activity against EGFR is very similar to that of erlotinib. It has been suggested that erlotinib is a substrate of both ABCB1 (P-glycoprotein) and ABCG2 (BCRP) transporters.[6,7]

Regarding the pharmacokinetic/pharmacodynamic (PK/PD) relationships of erlotinib, most clinical studies show a correlation between drug exposure and toxicity,[4,8] while the relationship between clinical response and the area under the curve (AUC) of plasma erlotinib concentrations remains unclear.[8–10]

We carried out a study in which forty-two patients pending surgery with head and neck squamous cell carcinoma were treated with neoadjuvant erlotinib.[1] The aim of this pilot clinical trial was to assess the feasibility of using erlotinib in chemo-naïve patients and its pharmacodynamic effects. Despite the short duration of treatment (median: 20 days), some patients had an early clinical response. The present work aims to examine erlotinib pharmacokinetics in these patients with a population approach and then to evaluate the impact of different covariates on the pharmacokinetic parameters. As well as the biological and morphological covariates, the patients' genotypes for single nucleotide polymorphisms (SNP) in *ABCB1* (2677G > T/A and 3435C > T), *ABCG2* (421C > A) and *CYP3A5* (6986G > A) were determined. The secondary objective was to study the pharmacokinetic/pharmacodynamic relationships by considering the early clinical response, the biological response of the tumour and toxicity.

2. Methods

2.1. Patients, blood sampling and mass spectrometry analysis

The study design has been published previously.[1] Between November 2003 and October 2006, a total of 42 patients with non-metastatic head and neck tumours were included in the study. On day 1 of the treatment, three blood samples were collected from each patient: before erlotinib administration, 2 h and 4–8 h after the dose. Patients were clinically evaluated at a median time of 14 days after starting the treatment and one blood sample was obtained. On the day preceding, and the day of the surgery, two additional samples were collected (respectively, 6–8 h and approximately 24 h after the last administration of erlotinib). Blood samples were centrifuged (1500*g*, 15 min) within 1 h and the plasma frozen at –20 °C until analysis.

The determination of plasma erlotinib and OSI-420 was done by Advion BioServices, Inc. (Ithaca, NY, United States America) using a validated coupled liquid chromatography–mass spectrometry technique.[11] The calibration range was 1–3000 ng/mL for erlotinib and 1–1000 ng/mL for OSI-420.

The fraction of unbound erlotinib in plasma (f_u) was determined using equilibrium dialysis with C^{14}-erlotinib (Roche, Basel, Switzerland). Its radiochemical purity was >98%. Plasma samples collected before the administration of erlotinib were dialysed against an equal volume of Sorensen's buffer (pH 7.4) at 37 °C for 10 h. Preliminary experiments showed that the erlotinib f_u was constant within the range of concentrations found *in vivo*.

Clinical data such as body weight (BW), age, gender and smoking status were collected. All variables except smoking status were available for all patients and were tested as covariates.

2.2. Patients' genotyping

A blood sample was collected on day 1 for pharmacogenetic investigation. Genomic DNA was extracted using the QIAamp DNA Blood midi Kit (Qiagen). Patients were genotyped for *ABCB1* variants (G2677T, G2677A and C3435T) on genomic DNA by PCR-RFLP as previously described.[12]

The *ABCG2* 421C > A variant was determined by polymerase chain reaction (PCR) and sequenced from normal DNA. Forward and reverse PCR primers were: 5′-ACCTTAGTTATGTTATCTTTGTG-3′ and 5′-GAAACTTCTGAATCAGAGTCAT-3′. An M13 primer sequence was incorporated at the 5′ end of all the PCR primers to facilitate subsequent DNA sequencing. PCR reaction and sequencing were undertaken as previously described.[1] The presence of CYP3A5*1/CYP3A5*3 alleles was determined on genomic DNA with allele specific real time PCR as previously described by Yates and colleagues.[13]

KRAS status was determined for each patient in tumour DNA extracted as previously described.[1] Mutations in exon 2 (codons 12 and 13) were investigated using nested PCR followed by sequencing as described by Eberhard et al.[14]

2.3. Pharmacokinetic analyses

Plasma erlotinib and OSI-420 plasma concentrations were analysed according to a non-linear mixed effect approach using the NONMEM program (version VI, level 1.0, Icon Development Solutions, Ellicot City, MD, running on a Pentium 200 pro) with the first-order conditional estimation (FOCE) method. A proportional error model was used for both inter-patient and residual variability. The influence of the following 16 covariates on pharmacokinetic variables was examined: unbound fraction of erlotinib (f_u), alpha-1 acid glycoprotein (AAG), albumin (ALB), body weight (BW), age (AGE), serum creatinine (SCR), creatinine clearance (CRCL), total bilirubin (BILI), aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), alkaline phosphatases (PAL), total proteinemia (PROT), gender (SEX), ABCB1 (2677G > T/A and 3435C > T), ABCG2 (421C > A) and CYP3A5 (6986G > A). Smoking status was missing for 4 out of 42 patients and was therefore not tested as a covariate. However, given the proven effect of smoking status on erlotinib clearance, a univariate analysis was performed on *post hoc* clearance values to check the existence of this effect.

First, the influence of each covariate was tested according to the following equation using body weight (BW) and erlotinib clearance (CL), for example: $TVCL = \theta1*(BW/\text{mean BW})^{\theta2}$ where $\theta1$ is the typical value of CL (TVCL) for a patient with the mean covariate value, and $\theta2$ is the estimated influential

factor for the covariate. Full and reduced models (removing one parameter) were compared by using a χ^2-test of difference between their respective objective function values (OFV). This value is an indicator of the goodness of fit of the model. A decrease of at least 6.63 ($p < 0.01$, 1 degree of freedom) was required for a covariate to be considered significantly correlated with the pharmacokinetic parameter (log–likelihood test). Second, an intermediate model including all significant covariates was obtained. A stepwise backward elimination procedure was carried out. Covariates remained in the final population pharmacokinetic model when the removal of the covariate resulted in an increase of the OFV of at least 6.63 ($p < 0.01$).

Erlotinib data were analysed first and provided a model with covariates to describe erlotinib CL and volume of distribution. Second, a model predicting both erlotinib and OSI-420 CL and volume was developed. The covariates found at the first stage were kept for the prediction of erlotinib CL and volume while developing the global model. A bioavailability (F) of 1 was assumed in the absence of IV drug administration data and CL and V corresponded to apparent parameters (i.e. CL/F and V/F).

A visual predictive check (VPC) was performed by simulating from the final model 1000 concentrations at 2 h post-dose, 4 h post-dose and subsequently every 4 h on day 1 and every 4 h on day 15. The 50th percentile concentration (as an estimator of the population-predicted concentration) and the 5th and 95th percentile concentrations were processed using R (RfN, version 2007a) and then plotted with GraphPad Prism version 4. Observed erlotinib and OSI-420 concentrations were superimposed on the plots.

2.4. Pharmacokinetic/pharmacodynamic relationships

Systemic exposure to erlotinib and OSI-420 was calculated using individual *post hoc* clearance: AUC = dose/CL for erlotinib. Relationships between AUC at day 1 and toxicity were evaluated. For relationships between AUC and either clinical, or biological response, mean daily AUC was calculated by weighting daily AUC values by the number of corresponding days for patients for whom dose was reduced due to skin toxicity. Early tumour response was assessed using CT scans taken before and after treatment (on the day before surgery). The relative variation in tumour size (unidimensional measurement of longest diameter) was analysed as a quantitative variable [(size after treatment – size before treatment) / size before treatment].

Toxicity (i.e. skin rash) was evaluated at the mid-treatment visit (median time of 14 days) and graded using the National Cancer Institute Common Toxicity Criteria, version 2.0. The biological response was assessed by the modification of the expression of EGFR signalling proteins (i.e. phosphorylated EGFR, phosphorylated ERK, phosphorylated Tyrosine, p27, p21 and phosphorylated Akt) in tumour samples obtained before and after treatment, as previously described.[1] Protein expression was assessed using the ImmunoReactive Score (IRS), according to Remmele and colleagues.[15] For each of the proteins under study, the response was measured as the relative variation in IRS before and after treatment ((IRS after – IRS before) / IRS before).

2.5. Statistical methods

The relationship between early clinical response and mean daily AUC was examined using linear regression, as was the relationship between biological response and AUC. A four-level ordered logistic regression (with skin toxicity graded 0–3 as response variable) was used to examine the association between skin toxicity grade and initial daily AUC. Based on this model, the cumulative-predicted probabilities of side-effects according to AUC were obtained and represented as curves.

Finally, the impact of smoking status on clearance was assessed using Wilcoxon's non-parametric rank test.

All the analyses were performed using Stata version 10.0, Stata Co., College Station, TX, USA.

3. Results

3.1. Patients

The 42 patients were treated for a median time of 20 days (range 5–32 days) and were assessable for both pharmacokinetic and pharmacogenetic investigations. Only 30 patients out of the 42 had a complete course of treatment and were treated for a median time of 22.5 days (range 18–32 days). Indeed, 12 patients discontinued treatment, mostly because of skin toxicity. Among these, eight stopped the treatment definitively while the other four accepted to restart erlotinib at 100 mg/day. The patients' characteristics are summarised in Table 1.

3.2. Pharmacokinetic analyses

The pharmacokinetics of erlotinib were adequately described by a one-compartment model with first-order absorption and first-order elimination. This model was associated with a lower objective function value than that found with zero-order absorption from the depot compartment, however a typical value for the constant rate of absorption (K_a) could not be estimated because of the small number of PK samples during the absorption phase and so was fixed at 0.95 h^{-1}, which was the typical value obtained by Lu et al.[4] in a population analysis of erlotinib pharmacokinetics with 591 patients. As shown in Table 2, ALAT, AGE and ABCG2 were kept in the final CL model; an increase in ALAT and AGE was associated with a decrease in CL (negative θ coefficient) and the presence of a variant allele of ABCG2 was associated with a 24% decrease in CL. For the volume of distribution of erlotinib (V), BW was the only significant covariate associated with a decrease in inter-individual variability (IIV) from 35% to 22%.

Analysis of the plasma concentrations of both erlotinib and OSI-420 required an additional compartment with first-order elimination from the metabolite compartment and corresponding variables: Vm/fm (apparent volume of distribution of OSI-420) and CLm/fm (apparent total clearance of OSI-420), where fm is the fraction of erlotinib converted into OSI-420. Three covariates (i.e. BW, AGE and ALAT) were significantly ($p < 0.01$) correlated with CLm/fm. The stepwise backward elimination procedure was carried out on CL and on CLm/fm for the final model (Table 2).

Table 1 – Summary of patients' characteristics (n = 42).

	Abbreviation	Mean (SD)	Range
Demographic and morphological covariates			
Age (years)	AGE	55.7 (9.8)	39–83
Weight (kg)	BW	73.9 (13.6)	44–110
Sex (male/female)	SEX	39/3	
Biological covariates			
α1 Acid glycoprotein (g/L)	AAG	1.03 (0.42)	0.55–2.3
Serum Albumin (g/L)	ALB	37.7 (3.9)	30–45
Total Protein (g/L)	PROT	70.4 (6.4)	53–84
Serum Creatinine (μmol/L)	SCR	76.3 (12.0)	56–114
Creatinine clearance[a] (mL/s)	CLCR	1.68 (0.43)	0.83–2.88
Total bilirubin (μmol/L)	BILI	11.4 (4.7)	5.7–27
ASAT (UI/L)	ASAT	23.8 (16.1)	11–81
ALAT (UI/L)	ALAT	27.4 (17.4)	9–86
Alkaline phosphatases (UI/L)	PAL	81.3 (25.1)	42–165
Genetic data	Abbreviation	Frequency	Range
ABCB1 exon 21 – G2677T (W/H/V)[b]	G2677T	15/23/4	
ABCB1 exon 21 – G2677A (W/H/V)[b]	G2677A	42/0/0	
ABCB1 exon 26 – C3435T (W/H/V)[b]	C3435T	10/22/10	
ABCG2 exon 5 – C421A (W/H/V)[b]	ABCG2	34/8/0	
CYP3A5 (*3–*3/*1–*3)	CYP	38/4	
Others			
Smokers (yes/no/unknown)	SMOK	23/15/4	
Unbound fraction of erlotinib	f_u	3.8 (0.8)	1.9–5.4%

a Calculated using the Cockcroft and Gault formula.
b W, wild-type; H, heterozygous; V, homozygous variant.

This final model adequately described the erlotinib and OSI-420 pharmacokinetic profiles at both day 1 and at steady-state (day 15) as shown by the VPC (Fig. 1). Erlotinib and OSI-420 data obtained from blood samples taken on the day before and the day of surgery corresponded to steady-state concentrations and were mixed with the day 15 observed data in the VPC graph.

Erlotinib CL was significantly higher in smokers (median: 7.28 L/h; interquartile range IQR: 5.29–13.85) than in non-smoking patients (4.98 L/h; IQR: 3.89–6.74), $p = 0.008$).

3.3. *PK/PD relationships*

There was no significant relationship between early clinical response and mean daily AUC ($p = 0.39$), or between biological response and mean daily AUC (between $p = 0.24$ and $p = 0.84$ depending on the protein). Of note, none of the 42 patients were carriers of *KRAS* mutations in codons 12 and 13.

Similarly, the analyses performed on the 30 patients with complete treatment showed no significant relationship between early clinical response and mean daily AUC ($p = 0.77$), or between biological response and mean daily AUC (between $p = 0.52$ and $p = 0.80$ depending on the protein).

The relationship between drug exposure and the severity of skin toxicity was also examined. The box-plot in Fig. 2 shows an increase in AUC with increasing grade of toxicity. This positive association between exposure and toxicity was found to be significant in the four-level ordered logistic regression analysis ($p = 0.014$). Fig. 3 shows the cumulative probabilities of having skin toxicity according to AUC using the probabilities predicted by the ordered logistic regression model.

4. Discussion

The design of this study enabled us to obtain pharmacokinetic and pharmacodynamic data for 42 patients and the population approach was used to calculate the drug exposure for each patient (AUC), despite the small number of samples (<6 per patient).

We observed a high inter-individual variability of pharmacokinetic parameters that was only partially explained by patients' covariates. The significant covariates in the prediction of erlotinib clearance were ALAT, AGE and ABCG2 polymorphism. Of note, no covariates reflecting renal function (such as CRCL or SCR) were retained in the final model, which confirms the lack of incidence of renal dysfunction on erlotinib CL that has previously been published.[16] Although Lu et al.[4] who carried out a population analysis on erlotinib pharmacokinetic data, found CRCL as a pertinent covariate to predict clearance, the coefficient associated with the power of CRCL was small and probably not relevant. In our model, ALAT and AGE were negatively correlated with erlotinib clearance. Indeed, an increase of both covariates might be the reflection of hepatic dysfunction which leads to a decreased erlotinib CL. The impact of hepatic dysfunction on erlotinib clearance has been confirmed in a clinical study using a more conventional approach.[16] In the Lu et al.[4] population analysis, 6 covariates predicted erlotinib clearance: gender, albuminemia, total bilirubin, creatinine clearance, alpha-1 acid glycoprotein (AAG) and smoking status. The decrease in CL/F associated with high AAG is consistent with the extensive protein binding of erlotinib (92–95%). For this reason, we

Table 2 – Final and alternative covariate models for pharmacokinetic parameters (CL and V for erlotinib clearance and volume of distribution and CLm/fm and Vm/fm for OSI-420 apparent clearance and volume of distribution).

Model	Coefficient values	95% Confidence interval	CV[a]
Final model			
Erlotinib	θ1 = 4.96	[3.76; 6.16]	
	θ2 = –0.55	[–0.80; –0.30]	
CL(L/h) = θ1 × (**ALAT**/27)^{θ2} × (**AGE**/56)^{θ3} × θ4^{ABCG2}[d]	θ3 = –2.04	[–3.28; –0.80]	CL: 57%
	θ4 = 0.76	[0.55; 0.97]	
V (L) = θ5 × (**BW**/74)^{θ6}	θ5 = 165	[139; 191]	V: 32%
	θ6 = 0.73	[0.31; 1.16]	
Residual variability = ε1	*ε1 = 0.06*	*[0.03; 0.09]*	*ε1 = 25%*
OSI-420			
CLm / fm(L/h) = θ7 × (**ALAT**/27)^{θ8} × (**AGE**/56)^{θ9} × (**BW**/74)^{θ10}	θ7 = 78.5	[61.7; 95.3]	CLm: 58%
	θ8 = –0.51	[–0.83; –0.18]	
	θ9 = –1.81	[–3.12; -0.50]	
Vm / fm (L) = θ11	θ10 = 0.84	[0.14; 1.54]	Vm: 0%[b]
	θ11 = 19.1	[8.22; 30.0]	
Residual variability = ε2	*ε2 = 0.16*	*[0.08; 0.23]*	*ε2 = 39%*

Alternative models		ΔOFV[c]	*p*	CV[a] (%)
Covariate deletion on CL				
CL = θ1 × (**ALAT**/27)^{θ2} × (**AGE**/56)^{θ3}	θ1 = 4.60 θ2 = –0.62 θ3 = –2.28	+7	<0.01	56
CL = θ1 × (**ALAT**/27)^{θ2} × θ4^{ABCG2}	θ1 = 5.12 θ2 = –0.36 θ4 = 0.72	+26	<0.001	64
CL = θ1 × (**AGE**/56)^{θ3} × θ4^{ABCG2}	θ1 = 4.90 θ3 = –1.81 θ4 = 0.59	+29	<0.001	69
CL = θ1	θ1 = 4.02	+63	<0.001	78
Covariate deletion on V				
V = θ2	θ2 = 177	+9	<0.01	42
Covariate deletion on CLm				
CLm / fm = θ5 × (**ALAT**/27)^{θ8} × (**AGE**/56)^{θ9}	θ5 = 75.6 θ8 = –0.54 θ9 = –2.04	+14	<0.001	60
CLm / fm = θ5 × (**ALAT**/27)^{θ8} × (**BW**/74)^{θ10}	θ5 = 81.9 θ8 = –0.35 θ10 = 0.96	+20	<0.001	61
CLm / fm = θ5 × (**AGE**/56)^{θ9} × (**BW**/74)^{θ10}	θ5 = 84.8 θ9 = –1.46 θ10 = 0.91	+18	<0.001	63
CLm / fm = θ7	θ7 = 84.4	+48	<0.001	67

a Coefficient of variation for inter-individual variability (not explained by the covariate, if any) or residual variability.
b Variability on Vm was arbitrarily fixed to zero because analyses led to a very low value.
c Change in objective function by comparison with the final covariate model.
d ABCG2 = 0 for wild-type patients and ABCG2 = 1 for heterozygous or homozygous variant-type patients.

expected AAG and f_u to be significant covariates. One explanation could be that in our patient group, the mean AAG is lower than that in Lu et al.'s study,[4] probably due to the fact that their data came from patients included in phases 2 and 3 clinical trials, who are generally in poor condition, with inflammatory signs leading to an increase in AAG. In the present study, the inter-individual variabilities of AAG and f_u were limited, which may have reduced the impact of these covariates on CL.

Because of missing data, smoking status could not be included in the final model and was examined with univariate analysis only. The effect of smoking on erlotinib clearance is consistent with a previously published study[17] on smokers and non-smoking healthy volunteers. Recently Hughes et al.[18] suggested 300 mg/day as the maximum tolerated dose in NSCLC patients who smoke instead of 150 mg/day. The contribution of CYP1A1 and CYP1A2 to erlotinib metabolism has been well established[5] and the increased clearance in smokers is the clinical consequence of CYP1A1 and CYP1A2 induction by active smoking. The pharmacogenetic evaluation showed that the *ABCG2* polymorphism (421C > A) had a significant impact on erlotinib CL. Indeed, patients carrying at least one variant allele (421A) showed a 24% decrease in erlotinib CL compared with wild-type patients. This result concurs with a previous study describing the effect of this particular polymorphism on gefitinib disposition, in which patients carrying the variant genotype had a significantly higher drug accumulation factor, consistent with a lower clearance.[6] Moreover, it has also been shown that this *ABCG2* SNP (421C > A) had a similar impact on imatinib clearance,[19] showing a 22% decrease in patients carrying at least one variant allele. The final model generated a *post hoc* clearance for each patient that provided information concerning drug exposure (i.e. AUC). We did not identify any PK/PD relationships regarding the early response to treatment, either clinical or biological, and to our knowledge, no other study has ever shown a clear correlation between AUC and response. In a phase 2 study,[10] the median trough concentrations of both erlotinib and OSI-420 seemed to predict improved survival. More recently Calvo et al.[9] studied a subgroup of 25 patients enrolled in the Soulieres' phase II trial in order to assess erlotinib PK/PD relationships. Neither overall survival (OS) nor categorical response was related to erlotinib plasma levels. The design of our study did not enable us to consider TTP

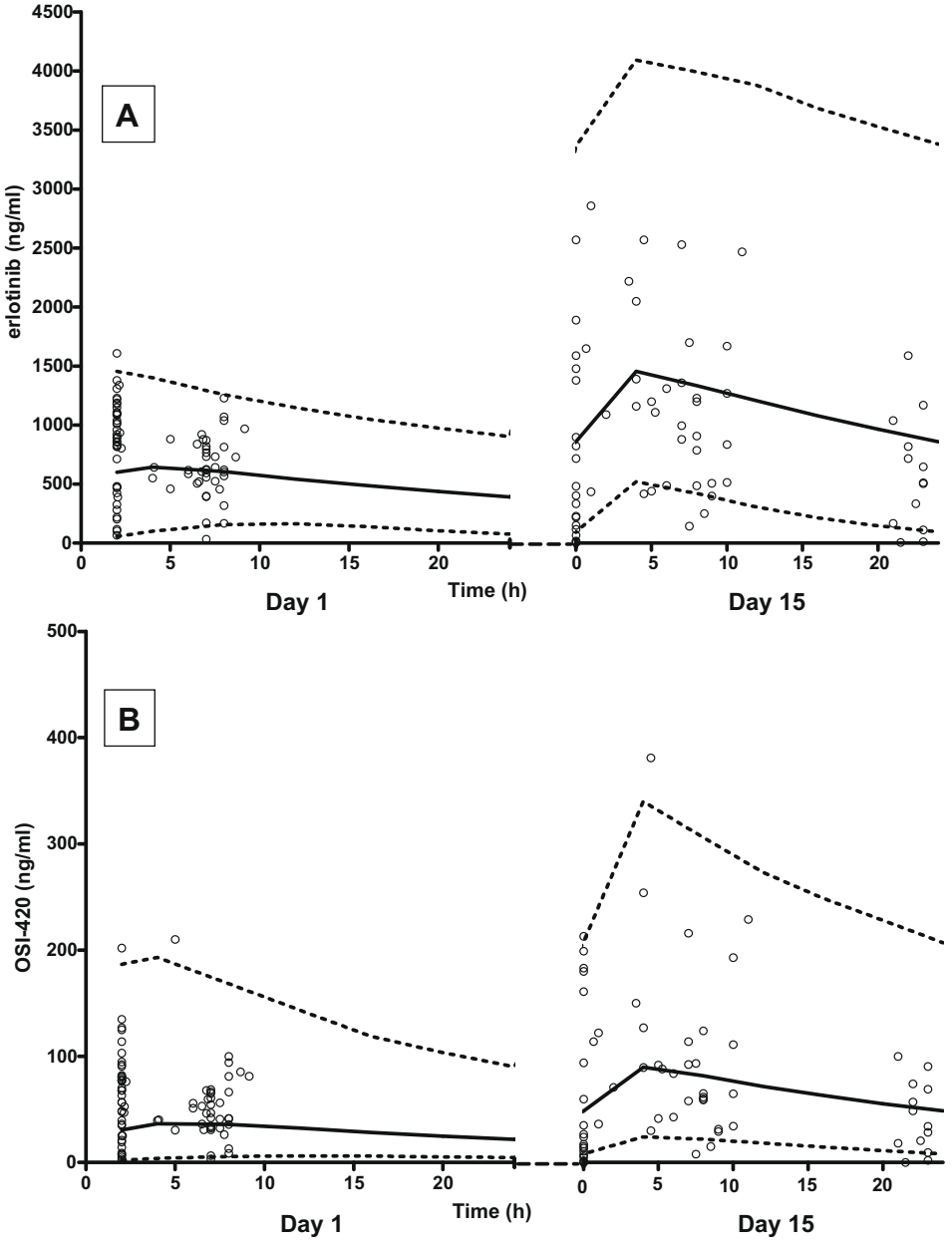

Fig. 1 – Visual predictive check of the final population model for erlotinib (A) and OSI-420 (B). Observed data are represented by circles. The population-predicted profile (50th percentile) is shown by the solid line and the 90% prediction intervals by the broken lines.

and OS and our PK/PD results refer to early evaluation because of the short duration of treatment and therefore may not be comparable to studies evaluating long term response. However, the originality of our study lies in the evaluation of the biological response as defined by the decrease in the expression of EGFR signalling proteins. We have already published the absence of correlation between clinical early response and this biological response.[1] In this paper, the relationship between exposure and the biological response was assessed but surprisingly, the relative variation of protein expression was not correlated with exposure. To our knowledge, this is the first study showing that a higher exposition to erlotinib does not result in better cellular response within the tumour. This observation raises the question of the optimal dose and circulating level of erlotinib required to obtain a response to treatment. However, as in previous studies,[4,8] a positive association was observed between AUC and the severity of skin toxicity. Moreover, it is now known that patients with skin rash (and probably high erlotinib plasma AUC) have an improved survival[20] and it has been hypothesised that rash may be a surrogate marker for favourable outcome. Authors of this meta-analysis based on results from two phase 2 studies[20] suggested that future studies randomising patients to erlotinib maintenance or different therapies depending on the occurrence of a rash during a 2 or 3 week lead-in period should be driven to compare OS between both groups. As it is highly probable that most of the patients without rash are underexposed to the drug, we think that

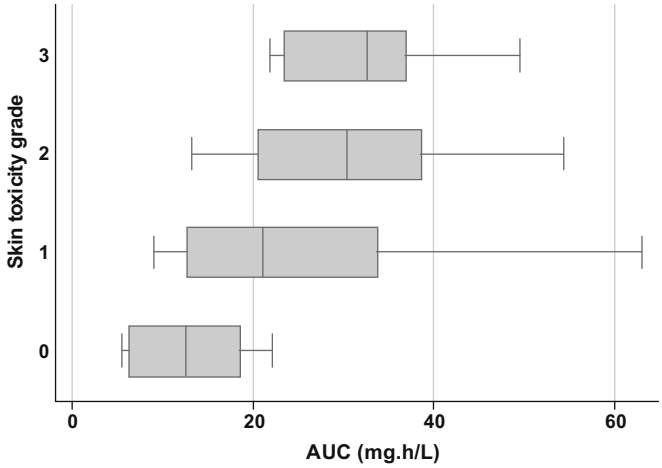

Fig. 2 – Box plot of severity of skin rash versus erlotinib AUC.

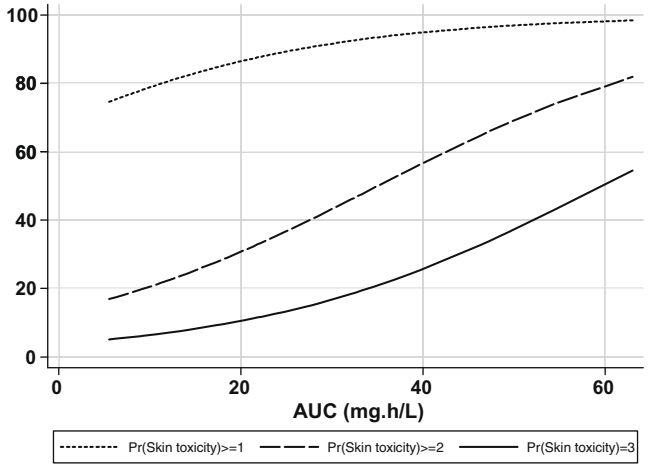

Fig. 3 – Relationship between skin toxicity and drug exposure (AUC). Curves show the cumulative probability (%) of having skin toxicity greater than or equal to a certain grade according to AUC, using the probabilities predicted by the four-level ordered logistic regression model.

such future studies should include drug monitoring to determine the cut-off AUC or concentration associated with a 'sufficient' rash and better outcome. Both the population approach (to determine the AUC from few blood samples) and the ordered logistic regression curves between AUC and toxicity used in the present work could help to define the necessary AUC to obtain the rash grade that leads to better OS or PFS. Moreover, such pharmacokinetic investigations would definitively solve the issue of the lack of response in patients with no rash, i.e. underexposure or other resistance mechanisms.

In conclusion, we observed a high inter-individual variability in erlotinib pharmacokinetic parameters that was partly explained by patients' age, hepatic function, ABCG2 genetic polymorphism and smoking status. A dose reduction or increase should therefore be considered for patients with such characteristics. However, the uncertainty concerning the relationship between erlotinib AUC and the response to treatment limits the application of dose individualisation. There is now a need to clarify erlotinib PK/PD relationships and to identify the subset of patients that could benefit from dose individualisation.

Conflict of interest statement

None declared.

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