

## **Population pharmacokinetic analysis of erlotinib in cancer patients affected by NSCLC**

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**Type :** Clinical Applications

### **Objectives**

Erlotinib is an oral first-generation EGFR tyrosine kinase inhibitor approved in patients with non-small cell lung cancers (NSCLC) with EGFR activating mutations. Erlotinib is currently prescribed at fixed regimen of 150 mg once daily, and dose adjustments are proposed in case of severe acute toxicity. However, a large inter-variability in its pharmacokinetics was observed [1], which could explain the variability of clinical response (effect/toxicity). In particular, elderly patients are more subject to severe toxicities compared with younger patients [2, 3]. The aims of this study were to describe the pharmacokinetic profile of erlotinib in NSCLC patients, to identify influencing factors and to evaluate the risk of suboptimal exposure under standard dosage regimen, with a special focus on elderly patients.

### **Methods**

Multi-compartment models were compared to characterize erlotinib pharmacokinetics (PK) (NONMEM<sup>®</sup>). The effect of relevant covariates (age, sex, body weight, body mass index, smoking status, albumin, AST/ALT, C-reactive protein [CRP], sarcopenia, moderate/strong CYP3A4 inhibitors [INH3A4, INHP3A4] and inducers [INDM3A4, INDP3A4], moderate CYP1A2 inhibitors/inducers [INH1A2, INDM1A2], strong CYP1A2 inhibitors [INHP1A2], strong P-glycoprotein inhibitors/inducers [INHPPGP/ INDPPGP], Proton Pump inhibitors [PPI]) was explored using linear equations. The adequacy of the recommended dosage regimen (150 mg/day) was assessed in several age group through simulations in 1000 individuals based on the final model with inter-patient variability. Erlotinib minimal concentrations ( $C_{min}$ ) > 2000 ng/ml was used as the upper limit defining overexposure and potential toxicity [3]. The percentage of patients in each age category reaching this upper limit target was calculated after administration of standard and alternative dosage regimens.

## Results

The study population included a total of 482 erlotinib plasma concentrations collected from 91 cancer patients (25-91 years old) as part of a routine therapeutic drug monitoring program at the Cochin Hospital. A one-compartment model with first-order absorption and elimination provided the best model fit of erlotinib PK. Apparent clearance (CL/F) was 3.8 L/h (IIV, %CV 39%) and the apparent volume of distribution (V/F) was 165 L (%CV 47%). The absorption rate constant was 1.41 h<sup>-1</sup> (RSE 24%). Univariate analyses revealed a significant relationship between erlotinib CL/F and age, smoking, albumin, CRP, dual INHM3A4 and INHM1A2, moderate or strong IND3A4, INHPPGP, INDPPGP and PPI (p<0.05). Multivariate analyses with stepwise inclusion (p<0.05) and backward deletion (p<0.01) identified an increase of erlotinib CL/F in smokers by 44% and in presence of PPI (36%) or following the intake of an IND3A4 (69%). ALBU also increase CL/F by 7% when ALBU=36 (25th percentile, P25) compared to ALBU=41 (P75). In contrary, in presence of a dual INHM3A4 and INHM1A2, erlotinib CL/F decrease by 43%. Age was associated with a decrease in CL/F of 19% in 76 years old (P75) compared to 59 years old (P25) patients. The model-based simulations show that under 150mg daily, the percentage of patients with C<sub>min</sub> > 2000 ng/ml is 9% at 40 and increase to 15% at 60, 22% at 70 and 28% at 80 years old. Reducing the dose from 150 mg to 100 mg for 70 years old patients or older would decrease the risk of overexposure.

## Conclusions

This study confirms the large variability in erlotinib pharmacokinetics and the large influence of smoking and PPI intake on drug concentrations. As expected, medications modulating CYP3A4 and CYP1A2 activity modify erlotinib concentrations, which might lead to suboptimal exposure. Erlotinib CL decreases with age, increasing the risk of C<sub>min</sub> > 2000 ng/ml, which could explain the greater toxicity and more frequent discontinuation observed in elderly patients. A lower starting dose could be considered in this at risk population while accounting for the additive effect of co-medications and efficacy endpoints.

## References

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