

Growing evidence supporting therapeutic drug monitoring of erlotinib in non-small-cell lung cancer patients: a time-to-progression model.



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Background

Erlotinib is an epidermal growth factor receptor inhibitor used for the treatment of pancreatic cancer and non-small-cell lung cancer (NSCLC). Erlotinib pharmacokinetics (PK) is characterized by significant variability that may affect efficacy and tolerability. Some studies have demonstrated a relationship between exposure to erlotinib and clinical outcomes or skin toxicity.

Objectives

To develop a model describing the time-to-progression distribution of a sample of NSCLC patients treated with erlotinib. To identify covariates as progression-free survival predictors (including drug exposure).

Methods

Time-to-progression data and relevant covariates were available from 26 NSCLC patients treated with erlotinib at the University Clinical Hospital of Valencia. Erlotinib plasma concentration data were simulated for the 26 NSCLC patients using a previously published PK model [1]. Time-to-progression was characterized with a time-to-event (TTE) model. TTE modelling and PK simulation was performed in NONMEM v 7.1.0 [2]. Exponential and Weibull TTE distributions were tested. Covariates, such as age, gender, NSCLC subtype, presence and location of metastases and tumour mutations, were evaluated as progression-free survival predictors and inclusion was performed on basis of objective function value (OFV) decrease and graphical improvement of visual predictive check diagnostic graphics.

Results

Patients' characteristics are shown in tables 1-2. The Weibull distribution model (fig. 1a) fitted the observed data significantly better than the exponential distribution model ($\Delta\text{OFV}=-6.13$) (fig. 1b). Among the tested covariates, the following were included in the model in a stepwise manner: 1) epidermal growth factor receptor (EGFR) mutation on the shape parameter (α) ($\Delta\text{OFV}=-27.33$) (figure 1c); 2) erlotinib minimum plasma concentration on hazard (h) for patients with mutated EGFR ($\Delta\text{OFV}=-4.36$) (figure 1d); 3) presence of central nervous system metastases (CNSm) on the scale parameter (λ) ($\Delta\text{OFV}=-5.08$) (figure 1e). Equations and model parameters are shown in figure 1 and table 3, respectively.

Table 2. Categorical covariates.

Covariate	n
NSCLC subtype	
Adenocarcinoma	22
Squamous cell carcinoma	3
Other	1
Metastases	
CNS	6
Liver	4
Bone	5
EGFR	
Wild type	11
Mutation	11
Missing	4
Infiltration	
Yes	21
No	5

Table 1. Continuous covariates.

Covariate	Mean	Std. Deviation
Age (years)	62.73	11.45
Albumin (g/dL)	3.85	0.34
Cr Clearance (mL/min)	90.12	27.82
Bilirubin (mg/dL)	0.66	0.24

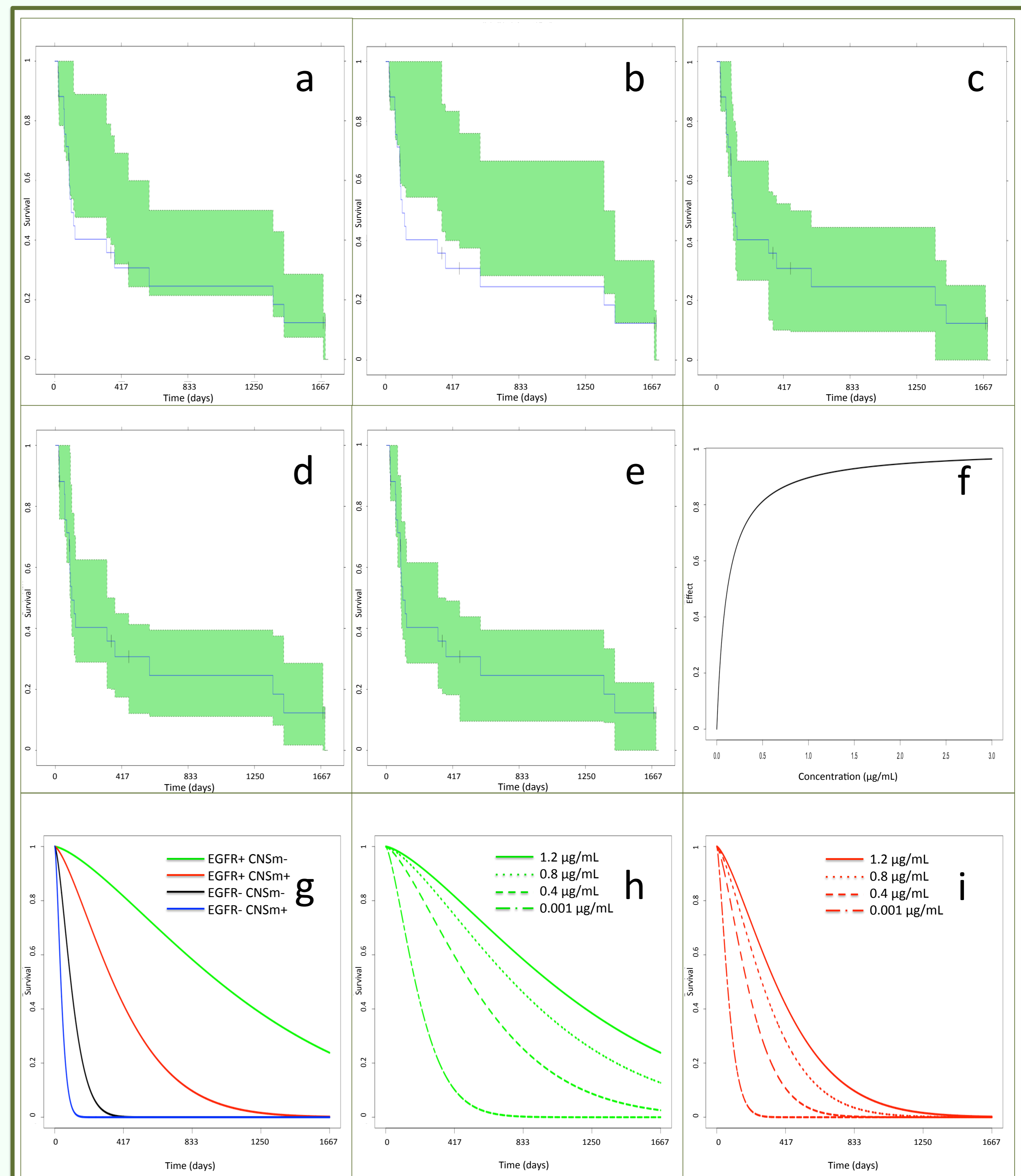


Figure 1. Figures a-e: Kaplan-Meier plots of progression-free survival data (blue line) and prediction intervals (green area, 100 simulations, $\alpha=1$) for each modelling step: (a) Weibull distribution; (b) Exponential distribution; (c) Inclusion of EGFR mutation on the shape parameter; (d) Inclusion of erlotinib minimum plasma concentration on hazard (h_0) for patients with mutated EGFR; (e) Inclusion of presence of central nervous system metastases (CNSm) on the scale parameter (λ). Figure f: Relationship between erlotinib minimum plasma concentration and drug effect. Figure g: Survivor function simulations for different patients characteristics (EGFR mutation and CNSm). Figures h and i represent survivor function simulations for EGFR+ and CNSm- (h) and for EGFR+ and CNSm+ (i) for different minimum concentration levels.

$$h_0(t) = \lambda \alpha (\lambda t)^{\alpha-1}$$

$$\text{if(EGFR=0)} \quad h_a(t) = h_0$$

$$\text{if(EGFR=1)} \quad h_a(t) = h_0 \cdot (1 - (C_{min}/(C_{min} + EC50)))$$

$$\lambda = \lambda_{CNSm=0} \cdot (1 + \theta_{CNSm=1} \cdot CNSm)$$

$$\alpha = \alpha_{EGFR=0} \cdot (1 + \theta_{EGFR=1} \cdot EGFR)$$

Figure 2. Model equations

Table 3. Model parameters.

Parameters	Value
$\lambda_{CNSm=0}$ (h^{-1})	$5.2 \cdot 10^{-6}$
$\alpha_{EGFR=0}$	1.520
$\theta_{CNSm=1}$	3.320
$\theta_{EGFR=1}$	-0.072
EC50 (mcg/mL)	0.116

Conclusions

The described model supports therapeutic drug monitoring of erlotinib based on the evidenced relationship between drug trough concentrations and progression hazard. It is concluded that TTE modelling of disease progression has the potential to improve the efficacy of NSCLC treatment with erlotinib.

References

- [1] Lu JF, Eppler SM, Wolf J, Hamilton M, Rakhit A, Bruno R and Lum BL. Clinical pharmacokinetics of erlotinib in patients with solid tumors and exposure-safety relationship in patients with non-small cell lung cancer. *Clin Pharmacol Ther* 2006; 80: 136-45.
 [2] Beal SL, Boeckmann AJ & Bauer RJ (Eds.) NONMEM Users Guides. Icon Development Solutions: Ellicott City, Maryland, USA, 1989-2011.