Population Pharmacokinetics and Exposition-PFS Relationship of Cetuximab in Metastatic Colorectal Cancer

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Context

Cetuximab (Erbitux®) :

- is a chimeric *IgG1*κ monoclonal antibody targeted against Epidermal Growth Factor Receptor (*EGFR*).
- is used in metastatic colorectal cancer (mCRC) and head and neck cancer in association with chemotherapy or radiotherapy.

Pharmacokinetics of cetuximab is poorly known in mCRC. Concentration-effect relationship has not been described yet.

Objectives

- **To describe the pharmacokinetics of cetuximab and identify factors influencing its variability.**
- **To investigate the exposition-effect relationship of cetuximab in mCRC.**

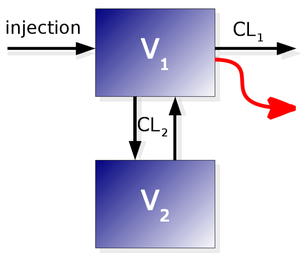
Patients and method

- Ninety-six mCRC patients were included in a multi-centric, non-comparative, open-label, phase II study.
- Cetuximab was combined with irinotecan and 5-FU.
- Cetuximab was administered as an infusion loading dose of $400\ mg/m^2$ followed by weekly $250\ mg/m^2$ infusions.
- Irinotecan dose was adjusted according to UGT1A1 genotype.

	Median	Range
Age (years)	63	(38 - 80)
Body weight (kg)	73	(34 - 113)
BSA (m^2)	1.795	(1.206 - 2.269)
	n	%
SEX		
Male	53	55.2%
Female	43	44.8%
KRAS		
wild-type	32	62.7%
muted	19	37.2%
Nonassessable	**45**	

Table 1: Patients caracteristics - BSA: Body Surface Area in m^2.

Pharmacokinetics model



Cetuximab concentrations were best described using a two-compartment model with both first-order and saturable (Michaelis-Menten) eliminations. V_1 and V_2 were central and peripheral volumes of distribution, respectively, CL and Q were systemic and distribution clearances, respectively. V_{max} was maximum elimination rate and K_M was concentration leading to half V_{max}. A population approach was applied using MONOLIX 3.1.

$$\begin{cases} \dfrac{dC_1}{dt} = -\dfrac{CL}{V_1}\cdot C_1 - \dfrac{Q}{V_1}\cdot C_1 + \dfrac{Q}{V_2}\cdot C_2 - \dfrac{V_{max}\cdot C_1}{K_m + C_1} \\ \dfrac{dC_2}{dt} = \dfrac{Q}{V_1}\cdot C_1 - \dfrac{Q}{V_2}\cdot C_2 \end{cases}$$

Progression free survival

Progression free survival (PFS) was calculated as the delay between the first cetuximab infusion and the first observation of disease progression or death from any cause. If a patient had not progressed or died, PFS was censored at the time of last follow-up.
Cetuximab dose-normalized AUC was used as a time-independant PFS prognostic factor.

Results

- A total of 1322 cetuximab concentrations were avaible in 96 patients.
- Cetuximab concentrations were satisfactory described by the PK model.
- V_1,V_2 and V_{max} were influenced by BSA. These values increased for increasing values of BSA.
- Time to progression is longer in KRAS wild-type patients with high cetuximab dose-normalized AUC.

Model Term	Parameter	Estimate	r.s.e.(%)	Wald test (p)
$V_1 = \theta_{V_1}\cdot\left(\frac{BSA}{1.795}\right)^{\theta_{BSA,V_1}}\cdot e^{\eta_{V_1}}$	$\theta_{V_1}\ (L)$	3.08	4	
	θ_{BSA,V_1}	0.407	41	0.014
$CL = \theta_{CL}\cdot e^{\eta_{CL}}$	$\theta_{CL}\ (L/d)$	0.451	4	
	$COV_{\theta_{V_1},\theta_{CL}}$	0.64		
$V_2 = \theta_{V_2}\cdot\left(\frac{BSA}{1.795}\right)^{\theta_{BSA,V_2}}\cdot e^{\eta_{V_2}}$	$\theta_{V_2}\ (L)$	4.05	7	
	θ_{BSA,V_2}	0.596	56	0.012
$Q = \theta_Q$	$\theta_Q\ (L/d)$	0.839	0	
$V_{max} = \theta_{V_{max}}\cdot\left(\frac{BSA}{1.795}\right)^{\theta_{BSA,V_{max}}}\cdot e^{\eta_{V_{max}}}$	$\theta_{V_{max}}\ (mg/d)$	12.4	7	
	$\theta_{BSA,V_{max}}$	1.17	23	2×10^{-5}
$K_M = \theta_{K_M}$	$\theta_{K_M}\ (mg/L)$	0.05	1	
$Y = e_1 + F(1+e_2)$	σ_{e_1}	3×10^{-11}	–	
	σ_{e_2}	0.22	2	

Table 2: Estimates of model parameters.

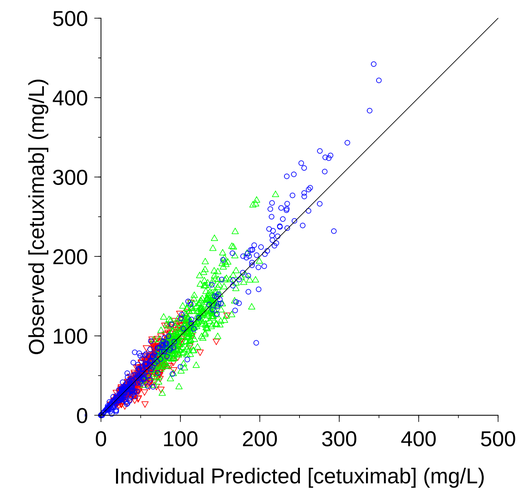


Figure 1: Individual model-predicted *vs* observed cetuximab concentrations.

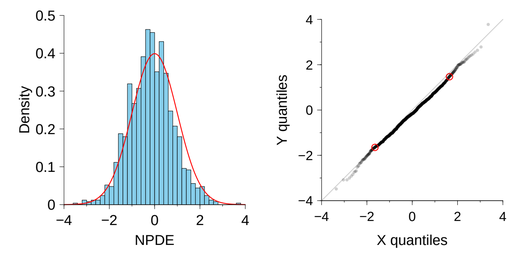


Figure 2: Histogram and QQ plot of normalised prediction distribution errors.

PK

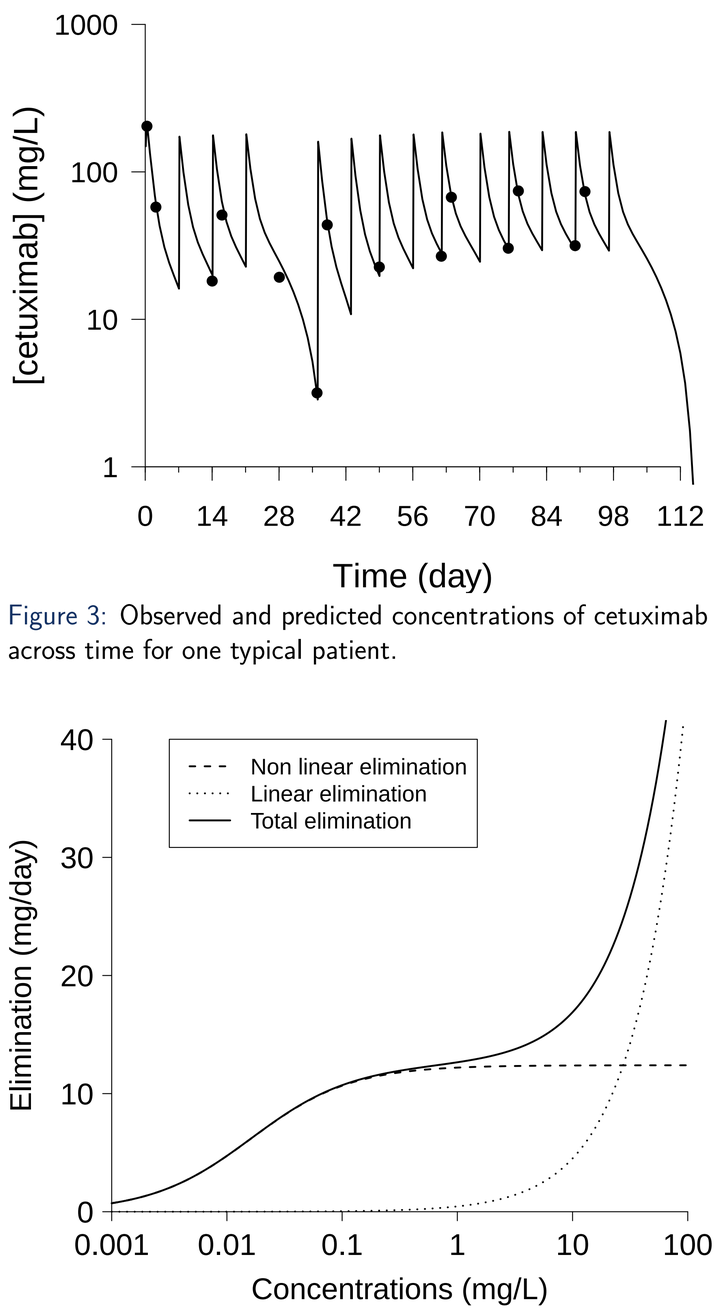


Figure 3: Observed and predicted concentrations of cetuximab across time for one typical patient.

Figure 4: Elimination *vs* cetuximab concentrations. Elimination increases at low concentrations.

PFS

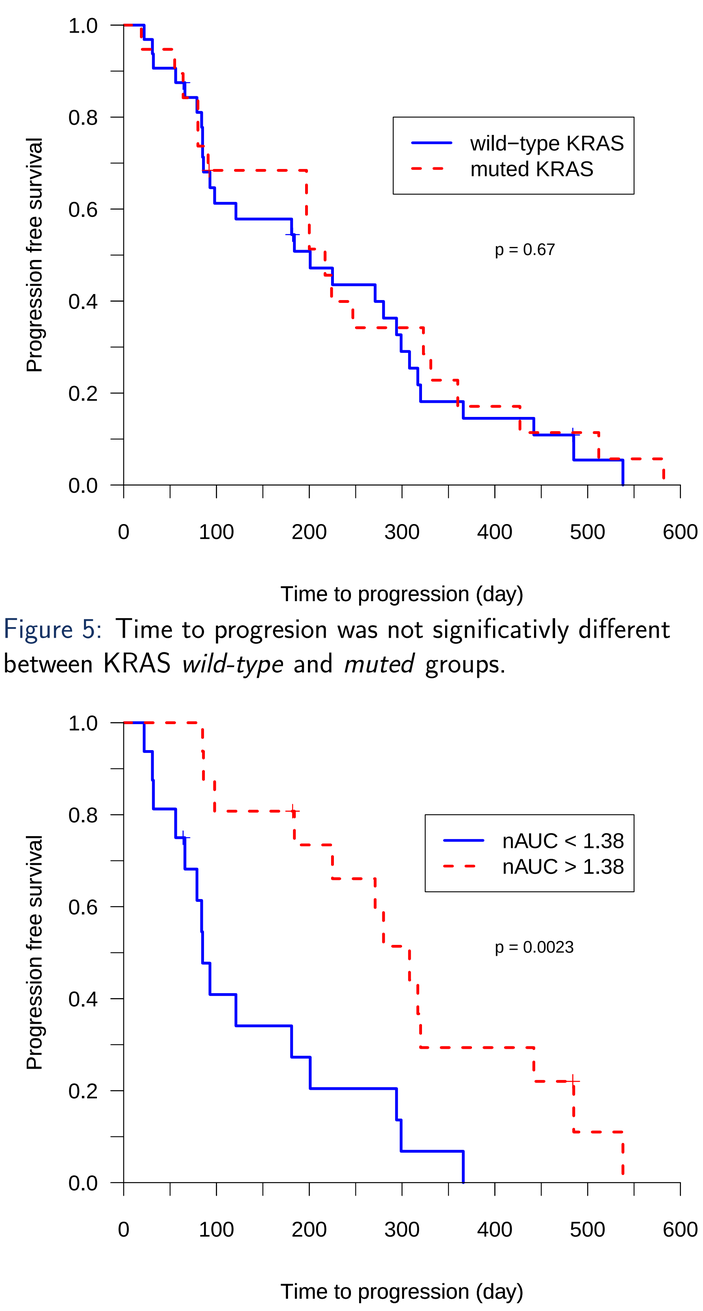


Figure 5: Time to progresion was not significativly different between KRAS *wild-type* and *muted* groups.

Figure 6: Influence of cetuximab dose-normalized AUC on PFS in KRAS *wild-type* patients.

Conclusions

- Cetuximab pharmacokinetics was satisfactorily described using a two-compartment model combining linear and nonlinear elimination rates.
- Time to progression is longer in KRAS *wild-type* patients with high cetuximab dose-normalized AUC.