

INTRODUCTION

Sorafenib is an oral multi-tyrosine kinase inhibitor, approved for the treatment of patients with diverse cancer pathologies: advanced unresectable renal cell carcinoma, gastrointestinal stromal advanced or metastatic tumor after failure with imatinib and sunitinib, liver unresectable carcinoma and thyroid cancer refractory to radioactive iodine.

High inter- (61-65%) and intra-individual (44-47%) variability in pharmacokinetics was observed during phase I studies, as well as in population pharmacokinetic (pop-PK) studies, which could explain the unstable response and the unintended toxicities that occur in some patients under a recommended dosage of sorafenib.

Therefore, we aimed to develop a sorafenib pop-PK model based on a large population of cancer outpatients treated by sorafenib during a long period. This pop-PK model will be used to predict sorafenib plasma pharmacokinetics based on sparse therapeutic drug monitoring using Bayesian approach, then to explore the relationship between sorafenib plasma exposure and toxicity outcome in patients from La Timone hospital.

METHODS

1- Population and samples collection

- Multicentric (10 French hospitals: Cochin hospital, CHU Nancy, Beaujon hospital ...), retrospective and observational study
- Sparse pharmacokinetic data available at steady state from 267 patients treated with sorafenib between 2008 and 2018, under a b.i.d regimen of 200-5200 mg sorafenib
- Lower limit of quantification (LLOQ): 0.5 mg/L (by HPLC method)

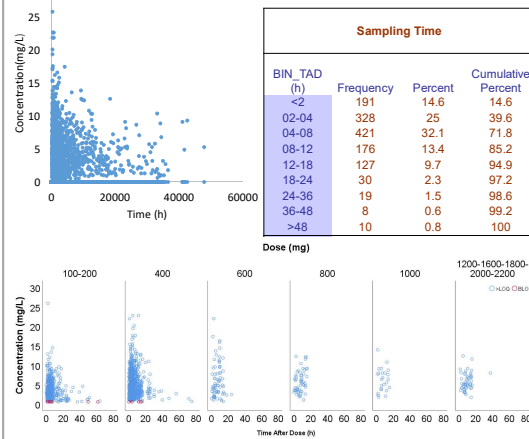
2- Model Development & Application

- Nonlinear mixed-effect modeling, using the NONMEM software version 7.3 (using FOCE INTERACTION algorithm)
- Several structural models tested: 1 or 2 compartments with first order elimination, first-order, zero-order, weibull or saturated absorption (Michaelis – Menten)
- Model evaluation was performed using standard goodness-of-fit plots, such as population predicted concentrations (PRED) and individual predicted concentrations (IPRED) versus observed concentrations (DV), and simulation-based tools such as visual predictive check (VPC).
- The case patient parameters were estimated using Bayesian method in NONMEM and used to simulate the exposure to sorafenib over the course of the treatment in R studio.

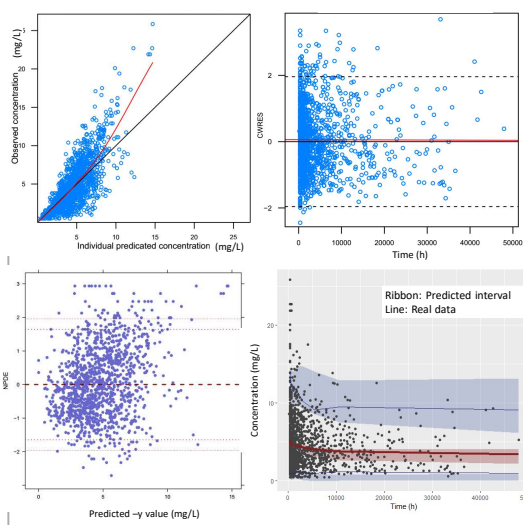
RESULTS

Data set

- 1310 steady-state samples collected/ 267 outpatients.
- 1 -2 samples per occasion (time after dose 0-187.92 h)
- 1 - 50 occasions/individual
- No covariate available



Goodness of fit (GOF) plots



Final model population parameters

- Structural model : 1-compartment with first-order absorption and linear elimination. Bioavailability (F1) varies as a function of the dose and declines over time on sorafenib treatment:

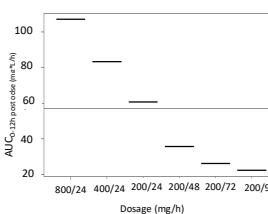
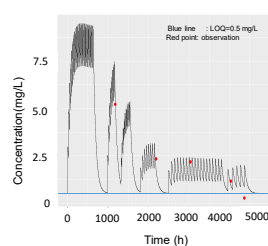
$$F1 = (F_{max} - \frac{F_{max} \cdot DOSE^n}{D50^n + DOSE^n}) * (1 - \delta * (1 - e^{-\lambda * TIME/720}))$$

Theta	Estimate	RSE (%)	95%CI
CL (L/h)	1.8	9.1	1.481-2.119
V (L)	72.4	16.6	48.88-95.92
KA (h ⁻¹)	0.767	29.3	0.326-1.208
Fmax (FIX)	0.44	-	0.44-0.44
n	1.4	7.8	1.186-1.614
Prop.RE (%)	42.7	3.2	0.400-0.454
Add.RE (mg/L)	0.504	30.2	0.206-0.802
lambda (month ⁻¹)	0.125	21	0.073-0.177
delta (%)	40.9	6.2	0.360-0.458
D50 (mg)	446	13.8	325.264-566.736

Omega	Estimate (CV%)	SE	RSE	Etabar	p val	Shrinkage
BSV ETACL	0.226 (47.5)	0.033	14.6%	0.014 (0.023)	0.5419	20.4%
BSV ETAV	0.821 (90.6)	0.195	23.8%	-0.102 (0.031)	0.0011	43.5%
BSV KA	1.64 (128.1)	1.23	75%	-0.022 (0.024)	0.3422	69.9%

Ka: absorption rate; V: Volume of distribution; CL: Clearance; F1: Bioavailability; Fmax: Maximum value of bioavailability; D50: Dose level with half of bioavailability; Prop.RE: Proportional residual error; Add.RE: Additive residual error; delta: maximum effect of time in bioavailability; lambda: first order decay constant; BSV: between subjects variability; CV: coefficients of variation; SE: Standard error; RSE: Relative standard error; CI: confidence interval

Case patient's simulation



- The individual PK parameters, the plasma concentration time curve and the steady-state AUC from 0 to 12h (AUC₀₋₁₂) post dose of this patient were estimated or simulated base on the final model POP-PK.

- The predicted AUC₀₋₁₂ values are particularly high when compared to the mean AUC₀₋₁₂ of 57.7±28.6 mg* h/L in patients experiencing grade 3-4 adverse events [4] and are consistent with the observed severe toxicities.

CONCLUSION

• Conclusion:

- ✓ A steady-state one-compartment structural model (with the bioavailability varying with dose and time) best described our sorafenib pharmacokinetic sparse data.
- ✓ The typical population parameters values and inter-individual variabilities were in line with previously published studies.
- ✓ However, some bias is still present in the current model, leading to under-prediction of extreme concentrations (over 12 mg/L). They might be ascribed to unavailable covariates.
- ✓ The final POP PK model was used to estimate PK parameters and simulate the exposure to sorafenib in one patient experiencing high toxicity at the La Timone hospital. These results document the decision to continue reducing the sorafenib dose by expanding the time between doses with the 200mg dosage.

• Perspectives:

- ✓ To overcome these bias, alternative random effects and more complex absorption models will be tested, using additional data from patients receiving alternate sorafenib treatment regimen.
- ✓ The final model will be used to estimate PK parameters from therapeutic drug monitoring data and to adjust the dose accordingly in the population of patients under sorafenib use at the Timone hospital.

REFERENCES

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