Patient compliance estimated from pharmacokinetic (PK) sample: Application to imatinib

Emilie Hénin [1], Véronique Trillet-Lenoir [1,2], Brigitte Tranchand [1,3], Michel Tod [1], Pascal Girard [1]

[1] EA3738 CTO, Faculté de Médecine Lyon-Sud, Université de Lyon;
[2] Service d'Oncologie Médicale, Hospices civils de Lyon; [3] Centre Léon Bérard, Lyon

Introduction

- In a previous study[1], we proposed a methodology to estimate patient compliance to an oral anticancer chemotherapy from a single PK sample taken on day 10, sparse sample taken on day 1 and a population PK model
- The method was evaluated *in silico* with the capecitabine/FBAL example (ratio $t_{½}$ / τ = 0.25 †) and adherence to doses given up to 5 t½ could be correctly estimated

† $t_{½}$ is the drug plasma elimination half-life, τ is the interdose interval

Objectives

Evaluate further our methodology on an anticancer oral drug, imatinib (Glivec®)

Methods

Idea of the compliance estimation method

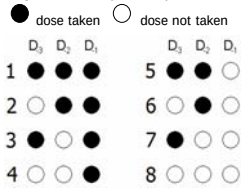
Extract the compliance information from a single PK sample and compare it to corresponding concentration Bayesian predictions and given a pop PK model

- 8 compliance patterns were defined as the sequence of last 3 doses taken or not (Figure 1)

2 types of information are needed:

- population PK model describing the evolution of plasma conc. and parameter statistical distributions
- individual conc. predictions derived from Bayesian *posthoc* estimates

Figure 1: Compliance patterns



Simulation procedure

- 1000 PK parameter sets drawn according to *a priori* population distributions and each simulated patient is assumed to have a given compliance pattern
- Simulation of sparse conc. on day 1 and one conc. on day 10
- Re-estimation of individual Bayesian PK parameters based on day 1 sparse samples
- Comparison of the actual concentration versus the predicted ones computed according to each pattern
- Choice of the compliance profile which minimise the distance between actual and predicted value

Performance of the compliance estimation

Evaluation at several time points after last taking on day 10

- Last1T: % patients for which last taking is well predicted
- Last2T: % patients for which last 2 takings are well pred.
- Last3T: % patients for which last 3 takings are well pred.

Impact of the error model on performance

Quantification by simulating various magnitude of the residual error CV (1, 5, 10, 20, 30, 40 and 50%)

In silico evaluation

Imatinib ($t_{½}/\tau$ = 0.625)

- One compartment pop PK model published by Widmer et al[2] with first order absorption and elimination
- Residual variability modelled with an exponential error model with CV 31%
- 500 mg once daily
- 4 PK samples taken on day 1 at 0.1, 1.6, 7.1 and 18 h
- 1 PK sample taken on day 10

Results

The best estimation is obtained 5 hours after last dose taking on day 10:

- but performance is quite stable through time
- compliance over the 2 last takings is correctly estimated (Table I – CV 31%)

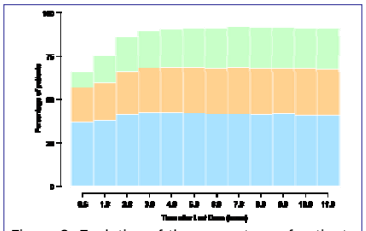


Figure 2: Evolution of the percentage of patients whose compliance is well estimated
Last1T (blue), Last 2T (blue+orange), Last 3T (blue+orange+green)

Impact of the CV of the residual error model

Table I: Performance of the estimation method at the best sampling time

CV	Sampling time at day 10	Last 1T	Last 2T	Last 3T
31%	5 hours	91.8	69.6	44.4
1%	Any	100	100	100
5%	2 hours	99.8	99.1	89.0
10%	3 hours	99.1	92.9	70.5
20%	5 hours	94.4	77.6	51.0
30%	5 hours	90.9	68.9	42.6
40%	5 hours	87.1	63.3	37.8
50%	5 hours	83.9	58.9	34.5

Comparison with Capecitabine/FBAL example (CV~20%)

Table II: Performance of the estimation method in both examples

Run	$t_{½}$ / τ	Sampling time at day 10	Last 1T	Last 2T	Last 3T
Imat. 20%	0.625	5 hours	94.4	77.6	51.0
FBAL	0.25	5 hours	99.8	71.9	44.6

Conclusion and perspectives

- 2 parameters have an effect on the method performance
  - ratio $t_{½}$ / τ
  - σ the magnitude of the error model
- PK method is not informative enough and should be associated to electronic monitoring in a future clinical study (*OCTO – Compliance to an oral chemotherapy*)

References

1. Hénin et al, PAGE 16-Abstr 1193, 2007, Copenhagen
2. Widmer et al, *Br J Clin Pharmacol* 62: 97-112, 2006