Estimation of patient compliance to an oral anticancer chemotherapy from pharmacokinetic samples

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Purpose

- More and more oral anticancer chemotherapies ⟶ new problems in treatment management
- Non-compliance: deviance of the actual way patients take their treatment with the prescription
- Measure methods: pill count, patient interview, electronic monitoring, ... estimation from serum drug levels[1,2,3]

Objectives

Estimate compliance according to a single PK concentration value measured on one dosing interval at steady state **and** sparse samples taken after first dose

Methods

Assumptions:

- Prescribed doses are taken or not ("all-or-nothing" approach) and dosing times are known exactly
- Only the previous *n* doses can be assessed
- There is no inter-occasion variability
- Individual PK profiles can be derived from POSTHOC parameters estimated using sparse data sampled after first dose.

PK model and individual parameters:

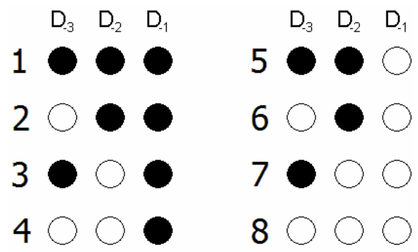
- Estimation of individual parameters from empirical Bayes estimates based on population PK model
- Predicted concentrations according to superposition principle and compliance patterns

Compliance patterns considered:

Compliance = sequence of *n* doses preceding a PK sample

For example, if n=3, there exists 8 compliance patterns

Figure 1: Compliance patterns



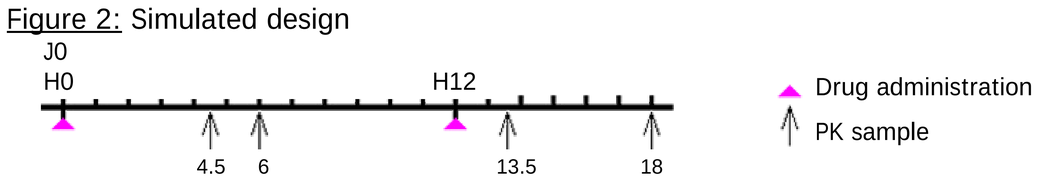
Pattern discrimination criteria:

- Euclidian distance between observed PK value and predicted ones
- Probability to observe a concentration value between the observed one and the predicted one (to be implemented)

In silico evaluation

- *In silico* study based on population PK model of capecitabine and its metabolites[4]
- Concentrations of FBAL (α-fluoro-β-alanine – capecitabine metabolite with the longest plasmatic half-life – 3 hours) simulated according to metabolite cascade's model
- FBAL kinetics were correctly modelled by a one compartment model with 1st order absorption and elimination
- 1000 PK parameter sets were randomly drown according to their population distribution and FBAL concentrations simulated following the 8 compliance patterns (last 3 doses taken or not)

Figure 2: Simulated design



- Individual PK parameters re-estimated on sparse data (4 samples optimally chosen after first 2 doses)

Results:

Table 1: Proportion of preferred pattern chosen (out of 1000 patients)

‰		Predicted pattern							
		1	2	3	4	5	6	7	8
Simulated pattern	1	354	110	97	419	15	4	1	0
	2	371	105	98	412	13	1	0	0
	3	253	90	104	496	39	12	3	3
	4	231	84	90	516	56	11	6	6
	5	1	3	8	18	516	287	162	5
	6	1	0	3	20	506	283	184	3
	7	0	0	0	2	21	32	620	325
	8	0	0	0	2	3	8	172	815

- Last 2 dose adherence well predicted
- 3rd past dose adherence badly predicted
- PK method is not informative enough

⟶ to be associated to electronic monitoring

Clinical application: future OCTO study

c**O**mpliance to oral **C**hemo**T**herapy in **O**ncology

- impact of non-compliance on efficacy and toxicity in cancer patients treated with an oral chemotherapy
- capecitabine (Xeloda®, Roche) prescribed to metastatic breast and colorectal cancer patients. First administrations supervised in the hospital
- building of population PK model of FBAL (capecitabine metabolite with longest half-life) – determination of individual PK parameters
- compliance estimated on PK sample and measured by electronic monitoring (EM)

Conclusion and perspectives

- Method allows to correctly characterize adherence up to 5 t½ in the past as long as dosing times are known (*e.g.* determined by EM)
- Develop a method to estimate amount (number of pills) taken for each EM system opening

References

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2. Lim LL, *Biometrics* 1992
3. Mu S *et al*, *J Pharmacokinet Pharmacodyn* 2003
4. Gieschke R *et al.*, *J Pharmacokinet Pharmacodyn* 2002