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 levels1,2,3

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

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)

References
1. Lu J et al., J Pharmacokinet Pharmacodyn 2001
2. Lim LL, Biometrics 1992

In silico evaluation
• In silico study based on population PK model of capecitabine and its metabolites
• 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)

Results:

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<th>3</th>
<th>4</th>
<th>5</th>
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Clinical application: future OCTO study
Compliance to oral Chemotherapy in Oncology
• 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 % 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