Modelling chemotherapy induced haematological toxicity AUC-effect and K-PD model

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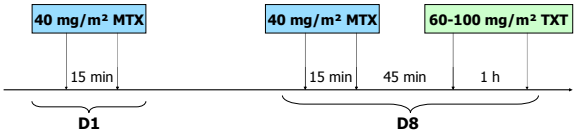
Objective of the study : Haematotoxicity is the major adverse effect of most of the anticancer drugs. This limits dosage intensification and may jeopardize the continuation of treatment.

The aim of this work is to find a model connecting haematological toxicity (neutropenia, lymphocytes, leucocytes, platelets) for two anticancer drugs administered in combination : methotrexate (MTX) and docetaxel (TXT) to drug exposure and dose administered.

The last model[1] may be interesting in clinical practice to adjust dosage regimen without necessity of having blood samples for doing PK analysis.

Patients :The study included 28 patients receiving several cycles of two drugs, MTX and TXT. For each cycle, administrations were made at day one and eight as following :

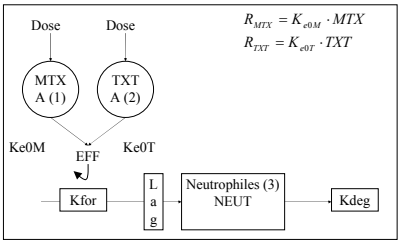


Data : MTX : 944 observations for 77 kinetics, and TXT : 449 observations for 38 kinetics, 747 haematological values for each of neutrophils, platelets, lymphocytes.

Method : 1) A pharmacokinetic model for both drug MTX and TXT was determined using NONMEM[2]. FO and FOCEI methods were used. FOCEI predicted concentrations better than FO.

2)Several relationships have been explored between AUC and haematological parameters

3) K-PD model was built according to the following scheme



$$EFF = E\max \cdot \frac{\left(\frac{R_{MTX}}{ED_{50}M} + \frac{R_{TXT}}{ED_{50}T} + \alpha \cdot \frac{R_{MTX}}{ED_{50}M} \cdot \frac{R_{TXT}}{ED_{50}T}\right)^{\gamma}}{1 + \left(\frac{R_{MTX}}{ED_{50}M} + \frac{R_{TXT}}{ED_{50}T} + \alpha \cdot \frac{R_{MTX}}{ED_{50}M} \cdot \frac{R_{TXT}}{ED_{50}T}\right)^{\gamma}} \qquad \begin{array}{l} \alpha = 0 \text{ additive} \\ \alpha > 0 \text{ synergism} \end{array}$$

Results: 1) Data for each drug were best fitted with a 3 compartment model **figure 1** shows for MTX that FOCEI improves the fitting.

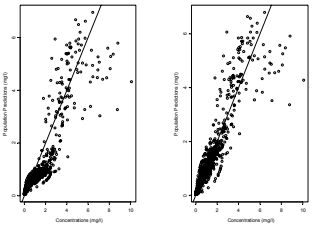


Figure 1 shows population prediction vs observation for both methods: clearly, this plot shows a biased fit for lower concentration (<4mg/l) with FO which is corrected by the use of FOCEI.

Figure 1 : MTX model without covariates, FO (left) and FOCEI (right)

Final model included different covariates; results are shown in **Table 1**.

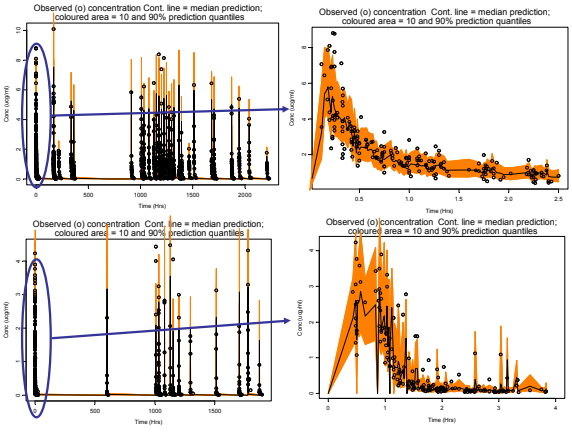
Nonmem Analysis	TXT	MTX
CL (L/h)	$36.8 \cdot \left(\frac{AGE}{56.5}\right)^{-0.835} \cdot \left(\frac{ALAT}{23}\right)^{0.0568} \cdot \left(\frac{AAG}{1.455}\right)^{-0.115}$	$7.03 \cdot \left(\frac{CREC}{84}\right)^{-0.702} \cdot \left(\frac{SURF}{1.72}\right)^{1.44}$
V1 (L)	8.5	$6.99 \cdot \left(\frac{SURF}{1.72}\right)^{2.65}$
V2 (L)	381	$17.9 \cdot \left(\frac{SURF}{1.72}\right)^{1.4} \cdot \left(\frac{ALAT}{14}\right)^{-0.155}$

Table 1 : Pharmacokinetic results with 3compartments model FOCEI

Table 2: decrease of inter-ind. Variability with covariates

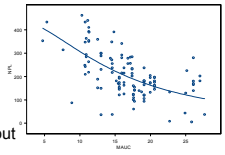
Ω	TXT		MTX	
covariables	No	Y	No	Y
CL (L/h)	37 %	34 %	30 %	18 %
V1 (L)	22 %	20 %	29 %	12 %
V2 (L)	45 %	45 %	16 %	21 %
σ	0.28	0.28	0.25	0.25

Qualification of the model was performed using a predictive check method
We simulated 200 new datasets where all dosage, measurements times, covariates were identical to observed dataset, except the concentration that was simulated. From those 200 simulated datasets, we computed the quantiles (10, 50 and 90 %) of concentrations.
The orange area represents 80% of the simulated data, and o are the observed concentrations, the black line is the median of the simulated data **(left panel)**.
In order to improve the graphical visualization we enlarged the first administration simulation (**right panel**).



A relationship with MTX AUC and platelets nadir with every cycle and the first cycle alone was found.

$$NPL \sim 453\left(1 - \frac{AUC^{1.9}}{\left(AUC^{1.9} + 15^{1.9}\right)}\right)$$



First result of KPD model: FO successful but no POSTHOC
Figure 2 shows Population prediction of neutrophils for 2 patients from FO with additive model.

Next steps
Switch to multiplicative or mixed error model.

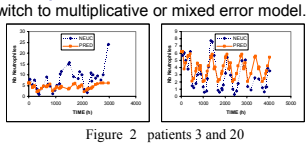


Figure 2 patients 3 and 20

- Try log transformation both sides
- Use FOCE method
- Implement a rebound effect model
- Consider transit compartment model rather than lag time
- Fit PK-PD model and compare with KPD
- Other suggestions?

References:
1: Jacqmin et al. Modelling drug induced changes in biomarkers without using drug concentrations : Introducing the K-PD model PAGE 2001
2: Beal SL and Sheiner LB. NONMEM users' guides. San Francisco : NONMEM Project Group, University of California. 1992.