PK/PD model extension to characterise bone marrow exhaustion in cancer patients making use of a prior paclitaxel PK model

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Background and Objectives

Dose individualisation and therapeutic drug monitoring are indicated for paclitaxel due to its complex non-linear pharmacokinetics (PK), the high inter-individual variability and a considerable risk of severe toxicity, especially neutropenia (pharmacodynamics (PD)). A population PK/PD model [1] was externally evaluated using data from a clinical trial (CEPAC-TDM) [2]. Thereby, worsening of neutropenia over repeated chemotherapy treatment cycles was observed, and hypothesised to be due to bone marrow exhaustion (BME). The aim of this work was to refine the previous PK/PD model by implementing BME in order to describe neutrophil concentrations in cancer patients over several cycles in a mechanistically plausible approach.

Methods

Patients (n = 183) received PTX (doses adjusted according to a published algorithm [1]) in combination with carbo- or cisplatin every 3 weeks for up to a maximum of 6 cycles. PTX plasma concentrations were measured ~ 24 h after PTX administration, while neutrophil concentrations were obtained on day 1 and day 15 ± 2 of each cycle.

A stepwise analysis was performed to develop the final model (Figure 1):

1) Prior information from the published PK model [1] was utilised applying the frequentist approach (normal–inverseWishart distribution) for re-estimating PK parameters.
2) To implement BME in a mechanistic way, an additional compartment was added to the Friberg *et al.* model [3] accounting for slowly proliferating stem cells (“Stem”), while the proliferation compartment (“Prol”) mimicked rapidly dividing progenitor cells. Both cell types were assumed to replicate with different proliferation rate constants, but influenced by the same drug effect and feedback mechanism.

NONMEM 7.3, PsN 4.4 and Xpose4 4.5.3 were used in the present work.

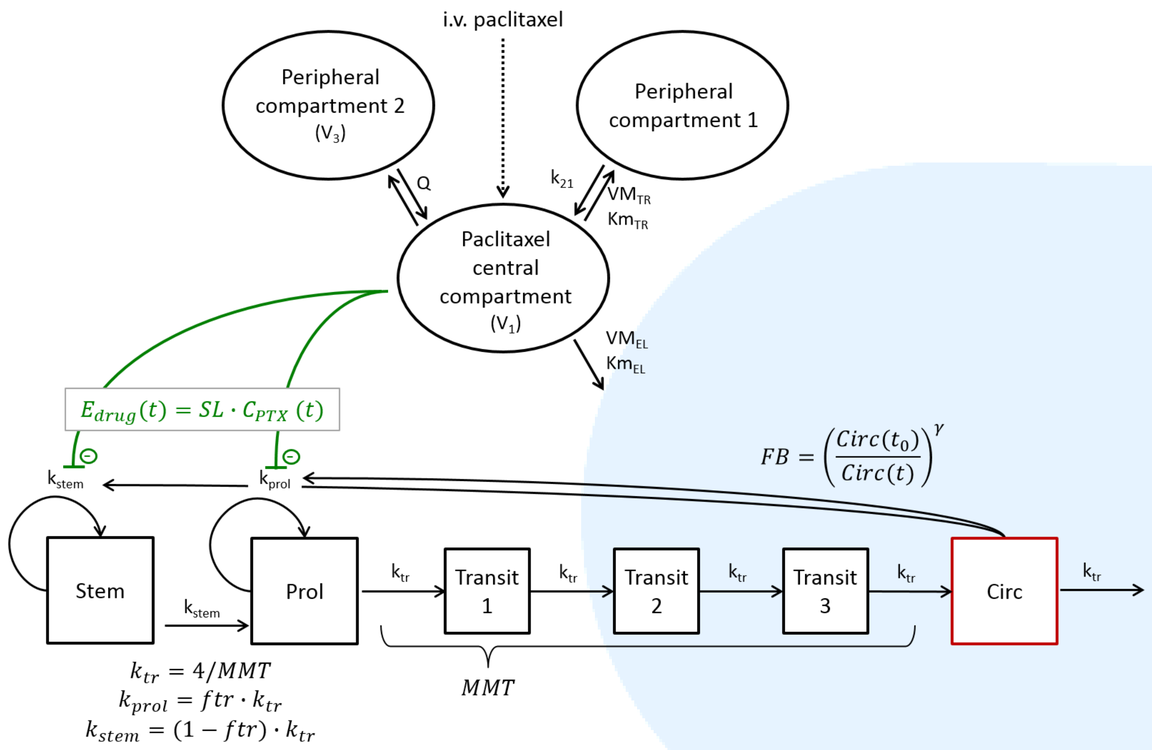

Figure 1: Optimised PK/PD model adapted from Joeger *et al.* [1], describing the PTX plasma concentration- and neutrophil-time profiles.
C_{PTX}: PTX plasma concentration; **V_1**: central volume of distribution; **VM_{TR}**: max. transfer capacity; **Km_{TR}**: C_{PTX} at half VM_{TR}; **k_{21}**: transfer rate constant between central and 1st peripheral compartment; **V_3**: volume of distribution of the 2nd peripheral compartment; **Q**: intercompartmental clearance; **VM_{EL}**: max. elimination capacity; **Km_{EL}**: C_{PTX} at half VM_{EL}
Stem: slowly proliferating stem cells; **Prol**: highly proliferating progenitor cells; **Tranist$_{1-3}$**: transit compartments; **Circ**: circulating neutrophils; **Circ(t)**: neutrophil concentration at time t; **Circ(t_0)**: neutrophil concentration at baseline; **k_{stem}**: proliferation rate constant of Stem; **k_{prol}**: proliferation rate constant of Prol; **k_{tr}**: transition rate constant; **MMT**: mean maturation time; **ftr**: fraction of k_{tr}; **FB**: feedback; **γ**: feedback parameter; **SL**: sensitivity factor linking PTX concentration and drug effect; **E_{drug}**: drug effect.

Results

- Of the re-estimated fixed-effects PK parameters, only Km_{EL} and the covariate bilirubin on VM_{EL} were not within the 95% confidence intervals of the original/prior PK model but the confidence intervals of both (original and optimised) PK parameter sets were overlapping (Table 1).
- VPC (Figure 2A) indicated a better PTX prediction than the original PK model, for which underprediction of concentrations was observed [2].
- The optimised PK/PD model was able to describe the hypothesised BME pattern well over the whole time frame of the study (Figure 2B).
- PD parameters were estimated with high precision (RSE<10%, Table 2).

Results (cont.)

- Inter-individual variability was only implemented on the slope factor. For the other parameters investigated (MMT, γ and ftr), the variability was low (CV% < 10%), while η-shrinkage was high (> 50%).
- The proliferation rate constant of progenitor cells (k_{prol}) was estimated to be 3.69-fold higher than the one of the stem cells (k_{stem}).

Table 2: Parameter estimates of the PK/PD model implementing BME.

Parameter	Estimate (RSE%)
Fixed effects parameters	
MMT [h]	145 (2.65)
SL [L/µmol]	13.1 (4.56)
γ	0.257 (5.53)
ftr	0.787 (2.76)
k_{tr} [h^{-1}]	0.0276
k_{prol} [h^{-1}]	0.0217
k_{stem} [h^{-1}]	0.00588
Inter-individual variability, CV%	
SL	44.8 (6.54)
Residual variability, CV%	
Exponential	51.3 (3.61)

CV%: coefficient of variation; RSE: relative standard error.

Table 1: Parameter estimates of the re-estimated PK model using prior information compared to these original parameters from [1].

Parameter	Estimate (95% confidence interval)	
	Published PK model [1]*	Optimised PK model**
Fixed effects parameters		
V_1 [L]	10.8 (9.99 – 11.6)	10.8 (10.7 – 10.8)
V_3 [L]	275 (245 – 305)	301 (292 – 311)
Km_{EL} [µmol/L]	0.576 (0.49 – 0.662)	0.667 (0.645 – 0.687)
VM_{EL} [µmol/h]	35.8 (32.5 – 39.1)	35.9 (35.1 – 36.6)
Km_{TR} [µmol/L]	1.43 (1.19 – 1.67)	1.44 (1.38 – 1.48)
VM_{TR} [µmol/h]	177 (166 – 188)	175 (174 – 176)
k_{21} [h^{-1}]	1.11 (1.04 – 1.18)	1.12 (1.11 – 1.13)
Q [L/h]	15.6 (14.0 – 17.2)	16.8 (16.5 – 17.1)
BSA on VM_{EL}	1.30 (1.05 – 1.55)	1.14 (1.06 – 1.25)
Sex on VM_{EL}	1.16 (1.07 – 1.25)	1.07 (1.03 – 1.10)
Age on VM_{EL}	-0.449 (-0.630 – -0.268)	-0.447 (-0.525 – -0.367)
BILI on VM_{EL}	-0.160 (-0.223 – -0.0973)	-0.0942 (-0.124 – -0.0648)
Inter-individual variability, CV%		
V_3	46.2% (39.4 – 53.0)	42.2% (41.5 – 43.0)
VM_{EL}	17.8% (14.6 – 21.0)	16.0% (15.1 – 16.9)
Km_{TR}	69.8% (58.2 – 81.4)	68.9% (68.7 – 69.5)
VM_{TR}	28.7% (24.4 – 33.0)	28.3% (28.3 – 28.4)
k_{21}	9.31% (-1.18 – 19.8)	8.94% (8.85 – 9.06)
Q	45.8% (40.4 – 51.2)	42.5% (41.9 – 43.3)
Inter-occasion variability, CV%		
V_1	37.3% (34.0 – 40.6)	37.3% (fixed)
VM_{EL}	15.2% (13.0 – 17.4)	15.2% (fixed)
Residual variability, CV%		
Exponential	18.2% (18.1 – 18.3)	17.8% (17.8 – 17.8)

CV%: coefficient of variation; BSA: body surface area [m²]; BILI: bilirubin concentration [µmol/L].
* Confidence intervals calculated based on relative standard errors.
** Confidence intervals determined by bootstrap analysis (1000 runs, convergence rate 96.5%).

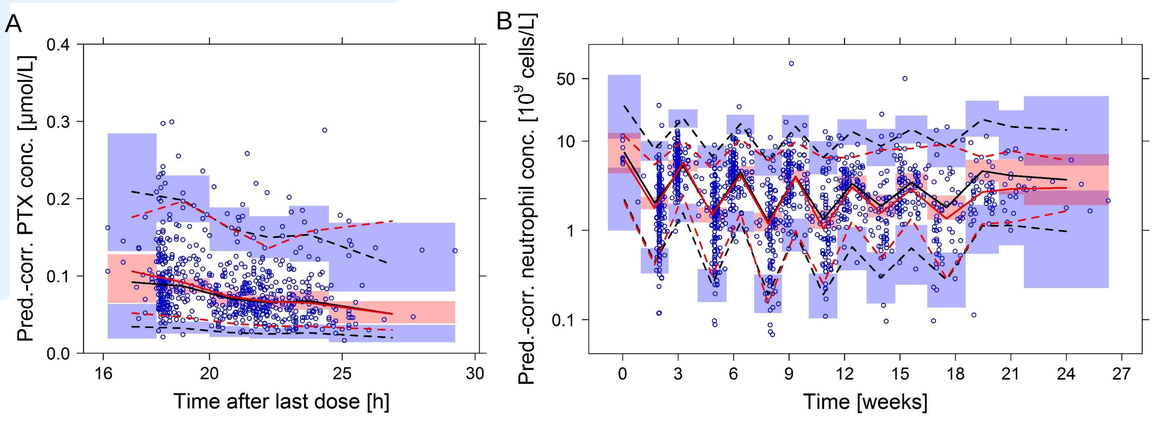

Figure 2: Prediction-corrected visual predictive check (pcVPC) of the optimised A) PK and B) PK/PD model; blue circles: observed PTX/neutrophil concentrations; red line: median (solid), 5th and 95th percentiles (dashed) of observations; black lines: median (solid), 5th and 95th percentiles (dashed) of the simulations; shaded areas: 90% confidence intervals for the prediction lines.

Discussion and Conclusions

- Using the frequentist approach previous knowledge from a model based on former rich data was successfully combined with the sparse CEPAC-TDM study data, enabling an adequate description of PTX PK.
- A mechanistically plausible PK/PD model was developed to describe the hypothesised bone marrow exhaustion.
- The developed PD model structure provides a framework to predict toxicity of long-term chemotherapy, not only for PTX but potentially also for other cytotoxic drugs.
- In a next step the model can be used for simulations in order to enhance mechanistically motivated individualised dosing recommendations.

References:

[1] M. Joerger et al. *Clin Pharmacokinet.* 51:607–17 (2012).
[2] A. Henrich et al. *PAGE 24* Abstr. 3460 (2015).
[3] L.E. Friberg, et al. *J. Clin. Oncol.* 20: 4713–21 (2002).

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