



Semi-mechanistic myelosuppression model of docetaxel treatment in liver impaired patients

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Introduction/Objectives

Docetaxel is contraindicated in patients with severe liver function because of the increased risk of neutropenia. As docetaxel is metabolised by CYP3A4 this is likely due to reduced drug clearance. However, the concentration-toxicity relationship is not established in this patient population yet.

Objective: To develop a PKPD model describing the docetaxel induced neutropenia in patients with normal and impaired liver function and to explore patient factors that may explain differences in toxicity.

Material and Methods

Patients and data

- 77 cancer patients with solid tumors
- Single course of docetaxel in monotherapy
- Dose: 40, 50 or 75 mg/m², depending on liver function
- Absolute neutrophil count (ANC) was collected on days 0, 7, 14 and 21

Parameter	Liver function group			
	Group 1 (n=54)	Group 2 (n=11)	Group 3A (n=7)	Group 3B (n=5)
AGE (years)	61 (27-80)	53 (24-71)	54 (36-64)	55 (38-78)
AAG (mg/dl)	138 (60-257)	157 (81-254)	169 (116-271)	115 (80-140)
Liver function tests				
Total Bilirubin (xULN)	0.5 (0.2-1.1)	0.4 (0.2-0.7)	0.7 (0.4-1.0)	2.5 (1.5-5.2)
AST (xULN)	0.9 (0.3-3.2)	2.5 (0.4-4.7)	4.3 (1.7-10.6)	11.4 (0.8-26.7)
ALT (xULN)	0.7 (0.1-2.2)	2.2 (0.3-0.6)	1.7 (0.1-3.1)	2.8 (0.8-4.5)
AP (xULN)	0.9 (0.4-2)	3.0 (1.1-9.9)	5.4 (2.5-15.4)	5.0 (0.9-8.5)
ERMBT - C _{20min} (% dose/min)	0.050 (0.013-0.124)	0.061 (0.041-0.108)	0.031 (0.006-0.050)	0.019 (0.006-0.062)

Population PK-PD modeling

- Individual PK-profiles of unbound docetaxel were predicted using a published population PK-model^[1]
- The semi-mechanistic myelosuppression model^[2] with some modifications,^[3] was used to describe the absolute neutrophil count (ANC) (see Figure 1).
- The following covariates were evaluated:
 - Demographics (age, gender, race, body weight, BSA)
 - α_1 -acid glycoprotein (AAG)
 - Haemoglobin (Hb)
 - Erythromycin breath test (ERMBT)
 - Liver function group (LFG), based on AST, ALT, AP and Bilirubin levels^[1]
- Step-wise covariate analysis (SCM) using $p < 0.05$ in the forward inclusion step and $p < 0.01$ in backward deletion was used.
 - Step 1: Evaluation of LFG
 - Step 2: Evaluation of all covariates
 - AAG and SEX were included on NEU₀ prior to the analysis since they were shown significant on a larger data set with docetaxel.^[4]
 - Statistically non-significant covariate relationships tested in the previous analysis were not evaluated here.^[4]
- Data analysis: NONMEM VI with FOCE

Results

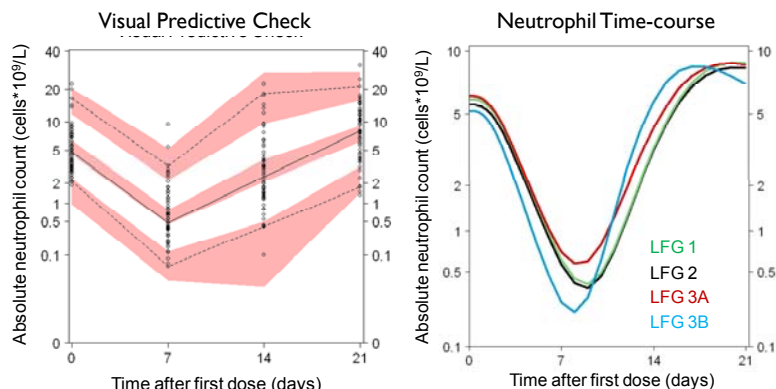


Figure 2. Left: Visual predictive check (90% Prediction Interval) of the final PKPD model with covariates. Observed data (dots) and the 95% confidence interval around the simulated median, 5th and 95th percentiles (pink) are shown. Solid lines are the corresponding percentiles of the observed data. Right: Typical prediction of neutropenia given the same concentration time-profile for all liver function groups and the average covariate value for each of the liver function group.

First Step – Liver function group

- Patients with impaired LFG (3A, 3B) were found to have a higher baseline ($p < 0.05$) and EC₅₀ ($p < 0.01$) compared to patients with normal liver function.

Second Step – all covariates evaluated

- Patients with high levels of AAG were found to have a lower E_{max} and a higher Baseline than patients with low AAG levels, which supports earlier findings [4].
- ERMBT and AAG were equally good predictors for baseline neutrophil count. AAG was chosen in the final model as it is more often routinely measured.
- LFG was no longer significant when AAG was included in the model.
- MMT was reduced with higher levels total Bilirubin.
- SEX on NEU₀ was kept in the model even though it was not significant for this smaller data set.

Conclusions

- The integrated PKPD model showed that when PK is accounted for there are minor differences between patients with impaired liver function (LFG 2, 3A, 3B) and patients with normal liver function (LFG 1) (see Figure 2).
- AAG was the single most important covariate to explain variability in exposure-toxicity relationships between patients.
- The PKPD model described the data well and showed good simulation properties (see Figure 2).

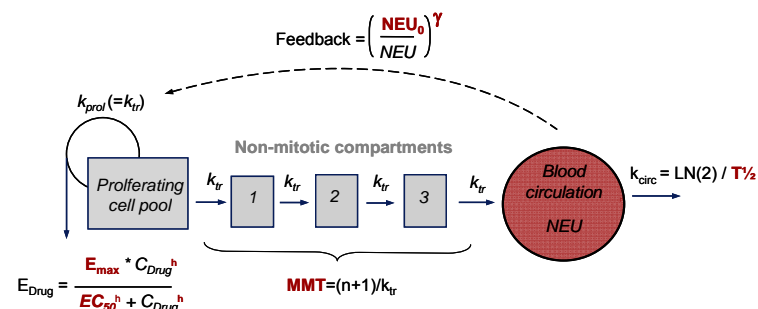


Figure 1: The semi-mechanistic myelosuppression model. The model consists of a proliferation pool with drug sensitive cells, a chain of transit compartments, mimicking the maturation of non-mitotic cells in bone marrow, and a blood circulation compartment. The cells are eliminated from the blood pool by random movement of cells into the tissue (k_{circ}). The feedback mechanism is capturing the effect of e.g. G-CSF on the proliferation rate. The drug effect is modeled as an inhibition of the proliferation rate and a possible kill effect.

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