A simultaneous analysis of the time course of leukocytes and neutrophils following docetaxel administration using a semi-mechanistic model

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Introduction

- Neutropenia is a life-threatning adverse event in anti-cancer treatment and the dose-limiting toxicity of docetaxel.
- Earlier developed semi-mechanistic PK-PD models for myelosuppression have been applied separately to measurements of total leukocyte counts and absolute neutrophil counts.
- More information of the haematological system may be gained by a simultaneous analysis of leukocytes and neutrophils since leukocytes consist mainly of neutrophils (60-70%).

Objectives

1. To model the time course of neutrophils (NEU) and leukocytes (WBC) simultaneously using a previously developed myelosuppression-model [1].
2. To compare neutrophils and non-neutrophils (non-NEU) with respect to system related parameters and drug effect.
3. To build a model that allows predictions of individual neutrophil profiles from only measurements of leukocytes and vice versa.

Material and Methods

Patients

- 637 cancer patients
- Single course of docetaxel in monotherapy (no G-CSF)
- Dose: 75 or 100 mg/m^2, 1 hour infusion
- 9771 measurements of total plasma drug concentration
- 3549 pairwise observations of WBC and NEU
- Individual PK-profiles were created using a population PK-model [2]

Population PK-PD modeling

- Data analysis: NONMEM (ver VIβ) with FOCE interaction
- Data transformation: no transformation, log-transformation and Box-Cox transformation were evaluated

Model structure

- Two myelosuppression-models [1]: one for NEU and one for non-NEU (Fig. 1)
- WBC was modeled as: $Circ_{WBC} = Circ_{NEU} + Circ_{non\text{-}NEU}$
- k_{circ} was either equal to k_{tr}, estimated or fixed to literature value ($T_{1/2}$ for NEU is 7 hr)
- An L2-data item was used to force the residuals for NEU to be the same for the observation of WBC and NEU at the same time point
- Residual error structure: additative, proportional or combined with and without ETA on EPS were evaluated for NEU and non-NEU
- ETA structure and correlations between parameters was explored

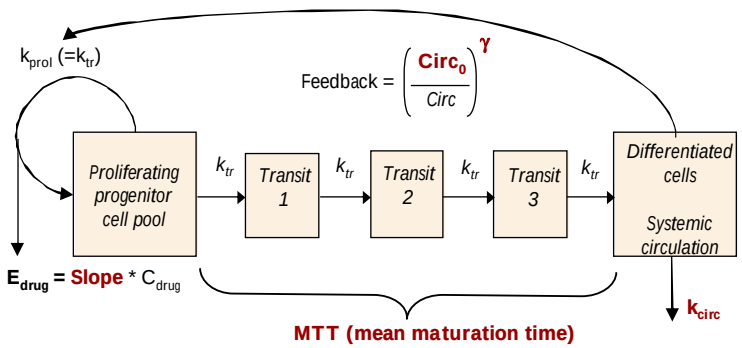

Figure 1. *The figure shows one hemtox-model, which consist of a proliferating cell pool connected to three transit compartments, mimicking the maturation of the non-proliferative cells, and a blood circulation compartment where the observations were made. A feedback loop from the circulation compartment stimulates the proliferation rate while the drug effect suppresses it. The drug effect is modeled as proportional to the drug concentration in plasma. The estimated parameters are in red.*

Results

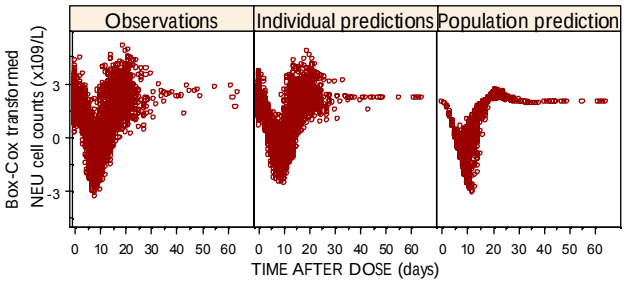

Figure 2. The figure shows the observed, individual predicted and population predicted time-course of NEU after a single dose of docetaxel.

Parameter (IIV%)	NEU	non-NEU	Correlation between the two cell types (%)
$Circ_0$ (x 10^9/L)	5.35 (38)	2.11 (37)	47
MTT (hours)	100 (14)	79.7 (7.5)	72
Slope (μM^{-1})	17.3 (46)	3.43 (30)	76
Power	0.173 (12)	0.202 (15)	89
$T_{1/2}$ blood (hours)	7 FIX	7 FIX	-
Residual error	0.453 (10)	0.286 (19)	100
Corr: MTT – Slope (%)	69	40	

Table 1. Left side: the pharmacodynamic population parameter estimates with the interindividual variability (IIV). Right side: correlations between the interindividual parameters of the two celltypes.

- Data transformation: Box-Cox with a factor of 0.2 improved both the model stability and the fit, especially at low cell counts.
- Residual error model: an additative residual error on a Box-Cox scale was applied.
- k_{circ} fixed to litterature value increased the parameters MTT and slope but did not affect the model prediction for neither cell type, compared to k_{circ} equal to k_{tr}.
- The model was able to predict the individual time-course of NEU based on individual WBC measurements and vice versa (Figure 3).

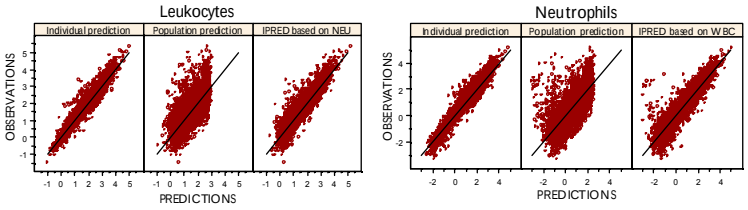

Figure 3. The two left panels shows the individual predictions and the population predictions from the final model and the right panel is the individual predictions of NEU based on WBC and WBC based on NEU respectively.

Conclusions

- A joint model describing the time course of both neutrophils and leukocytes following docetaxel treatment described the data well
- The model shows differences between the NEU and non-NEU:
  - NEU mature more slowly
  - NEU have a weaker feedback mechanism
  - NEU are more sensitive to docetaxel
- The model may be useful to get a good prediction of the neutrophil profile when only leukocyte measurements are available.

References

[1] Friberg, LE, Henningsson A, Maas H, Nguyen L, and Karlsson MO: Model of chemotherapy-induced myelosuppression with parameter consistency across drugs. J. Clin. Oncol. 2002, 20:4713-4721

[2] Bruno R, Vivier N, Vergniol JC, et al: A population pharmacokinetic model for docetaxel (Taxotere): Model building and validation. J Pharmacokinetics Biopharm 1996, 24:153-172