Scaling the Time-Course of Myelosuppression from Rats to Patients with a Semi-Physiological Model

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Background and Objectives:

A model for chemotherapy-induced myelosuppression (Fig.1, [1]), developed from patient data, showed similar system-related parameters (WBC_0, MTT and γ) across drugs but the drug-related parameter estimates (Slope) were drug-dependent, as expected.

The aim of the present study was to explore if the drug-related parameter estimates are of comparable magnitudes in rats and patients and may be used for predictions of the full time-course of myelosuppression in patients.

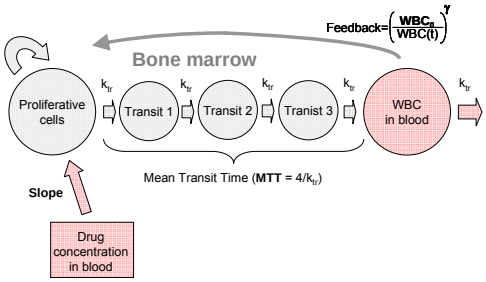

Fig 1. The myelosuppression model with the estimated system-related parameters WBC_0, MTT and γ and the drug-related parameter Slope.

Methods:

5-Fluorouracil (5-FU), epirubicin, cyclophosphamide (CP), docetaxel, paclitaxel or etoposide were administered to rats (n=169).

White blood cell counts (WBC) were measured up to 30 days after drug administration.

Individual or typical population PK parameters were used to predict the drug concentration-time profile in each rat.

The myelosuppression model [1] was applied to all data simultaneously, allowing only the drug-related parameter Slope to differ between drugs.

The analysis was performed using FOCE in NONMEM VI.

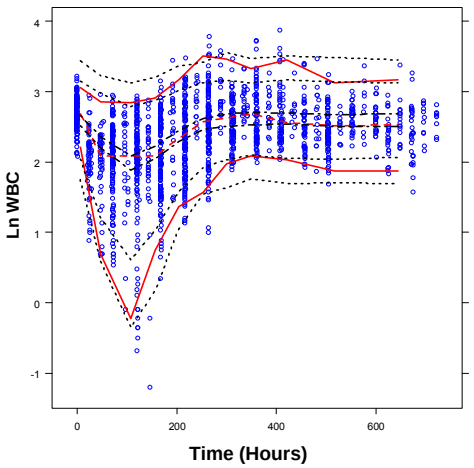

Fig 2. Visual predictive check of the myelosuppression model fit to rat data. Red lines are the 2.5th, 50th and 97.5th percentiles of the observed data, black dashed/dotted lines are the 95% confidence intervals of the corresponding percentiles in 500 simulated data sets.

Table 1. Parameter estimates (Relative Standard Error, RSE%)

	Typical (RSE%)	IIV, CV% (RSE%)
OFV	-1912.0	-
WBC_0 (*10^9/L)	13.3 (2.1)	23 (6.0)
MTT (h)	52.8 (5.3)	20 (15)
γ	0.149 (8.2)	-
$Slope_{5\text{-}FU}$ (L/mg)	0.247 (10)	27 (19)[a]
$Slope_{Epirubicin}$ (L/mg)	12.6 (7.6)	27 (19)[a]
$Slope_{4\text{-}OHCP}$ (L/mg)	2.65 (5.7)	27 (19)[a]
$Slope_{Docetaxel}$ (L/mg)	16.1 (10)	27 (19)[a]
$Slope_{,uPaclitaxel}$ (L/mg)	32.9 (25)	27 (19)[a]
$Slope_{Etoposide}$ (L/mg)	1.08 (15)	27 (19)[a]
Proportional error (%)	28.1 (4.0)	-

a, Same IIV estimated for all Slope values

Results:

The original myelosuppression model fit the rat data adequately (Fig. 2). The fit improved when a fraction of the Slope was allowed to affect also the other cell types, but to be consistent with the model for patients, the original model was used in the comparison with patients.

The MTT was approximately half of the estimate in patients while the feedback parameter was of similar magnitude (Table 1).

The relative difference in Slope estimates for rats and patients [1,2,3] based on total drug concentrations ranged between 28% to 7-fold for the 6 drugs (Fig. 3, left panel).

The relative difference was reduced to ≤37% when correcting for species differences in IC90 ratios in the CFU-GM assay [4] and species difference in protein binding (Fig. 3, right panel).

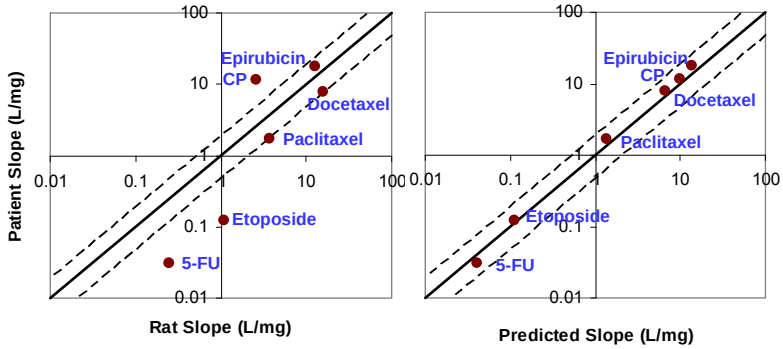

Fig 3. Previously estimated Slope values in patients versus estimated Slope values in rats (left) and versus Predicted Slope values (right), i.e. Rat Slope values adjusted for species differences in protein binding and IC90 ratios in the CFU-GM assay. Solid lines are lines of identity and dashed lines represents a deviation from identity with a factor of 2.

Conclusions:

The estimated drug-related parameters in rats, patient PK models and typical system-related parameters [1] could successfully be used to predict the time-course of myelosuppression in patients (Fig. 4).

Accounting for species differences in protein binding and in *in vitro* sensitivity improved the predictions.

This scaling approach might also be useful to early in development predict combination therapies and schedule dependence of myelosuppression.

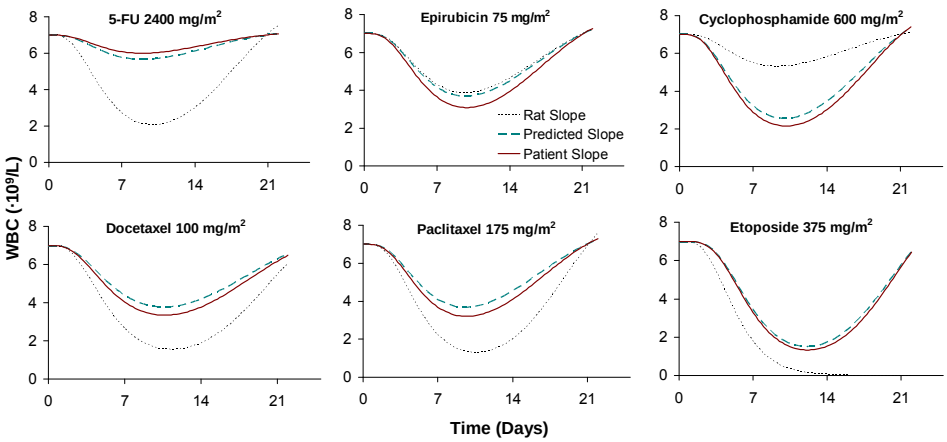

Fig 4. Predicted time-courses of myelosuppression in patients based on Patient Slope estimates, Rat Slope estimates and Rat Slope estimates corrected for species differences in protein binding and in *in vitro* assay sensitivity (Predicted Slope). Typical system-related parameters in patients were used; WBC_0=7·10^9/L, MTT=125 hours and γ=0.17 [1].

References:
[1] Friberg LE, Henningsson A, Maas H, Nguyen L, Karlsson MO. Model of chemotherapy-induced myelosuppression with parameter consistency across drugs. J Clin Oncol; 20:4713-21, 2002.
[2] Sandström M, Lindman H, Nygren P, Lidbrink E, Bergh J, Karlsson, MO. Model describing the relationship between pharmacokinetics and hematologic toxicity of the epirubicin-docetaxel regimen in breast cancer patients. J Clin Oncol; 23:413-21, 2005.
[3] Sandström M, Lindman H, Nygren P, Johansson M, Bergh J, Karlsson MO. Population analysis of the pharmacokinetics and the haematological toxicity of the fluorouracil-epirubicin-cyclophosphamide regimen in breast cancer patients. J Clin Oncol; 58:143-56, 2006.
[4] Pessina A, Albella B, Bueren J, Brantom P, Casati S, Gribaldo L, et al. Prevalidation of a model for predicting acute neutropenia by colony forming unit granulocyte/macrophage (CFU-GM) assay. Toxicol In Vitro;15:729-40; 2001.