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Lower Inter-occasion variability than Inter-individual variability in Chemotherapy-induced Myelosuppression

Background and Objectives:

For individual dose-adjustments based on neutrophil counts to be beneficial inter-occasion variability (IOV) should be relatively low in relation to inter-individual variability (IIV).

A semi-physiological model of chemotherapy-induced myelosuppression [1] has shown similar system-related parameters and IIV parameters across drugs. The IOV magnitude has however not been investigated similarly.

The aim of the present study was to evaluate IOV in myelosuppression model parameters and compare IOV magnitudes across drugs and with corresponding IIV estimates.

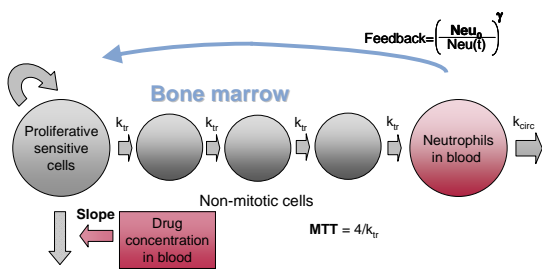


Figure 1. The myelosuppression model with the estimated system-related parameters Neu_0 , MTT and γ and the drug-related parameter Slope. k_{circ} was set to $\ln(2) / 7$ hours.

Methods:

Four data sets with neutrophil counts following single or combination chemotherapy from several cycles per patient were analyzed (Table 1).

Individual or population PK parameters were taken from previous studies [2,3,4,5]. IOV in PK was not included.

The myelosuppression model (Fig. 1, [1]) was fit to the neutrophil data and analyzed using the FOCE method in NONMEM VI.

IOV in baseline (Neu_0), mean transit time (MTT) and the drug-effect parameter Slope were evaluated for statistical significance ($p < 0.001$).

The neutrophil data were Box-Cox transformed with a factor of 0.2 to obtain residuals symmetrically distributed to around zero.

Table 1. Investigated data sets

Data sets	# of patients	# of cycles/patient Median (range)	# of neutrophil samples
Docetaxel	244	4 (1-16)	2262
Paclitaxel	45	3 (1-11)	523
Epirubicin + Docetaxel	41	4 (1-9)	659
5-FU + Epirubicin + Cyclophosphamide	60	7 (2-10)	1196

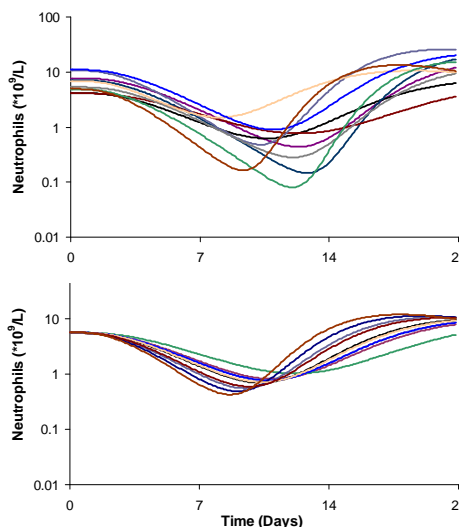


Figure 2. Ten simulated time-courses of myelosuppression following paclitaxel administration including IIV only (top) or IOV only (bottom).

Results:

IOV was significant in MTT for all data sets and ranged from 8 to 17% (Table 2) and was of similar magnitude as IIV in MTT.

For the docetaxel data set IOV was also significant in Slope with an estimated CV of 19%.

In all data sets were the overall IOV clearly lower than IIV. The relative impact of the estimated IIV and IOV variability is illustrated in Fig. 2.

Inclusion of IOV reduced the residual error variability (SD) by approximately 10%.

Conclusions:

IOV in myelosuppression was low and similar across drugs.

IOV was most important for MTT and may reflect that growth factor levels regulating the transit time vary from cycle to cycle while drug sensitivity is more consistent within an individual.

The limited overall IOV in neutrophil dynamics in relation to overall IIV implies that the semi-physiological model has potential for individual dose adjustments based on neutrophil counts and such a tool is under development [6].

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Table 2. Estimated IIV (CV%), IOV (CV%) and residual variability (SD on Box-Cox transformed scale). Relative standard errors (RSE) were derived from \$COV MATRIX=S.

Data sets	IIV Neu_0 (RSE%)	IIV MTT (RSE%)	IIV Slope (RSE%)	IOV MTT (RSE%)	Residual error (RSE%)
Docetaxel	33 (5.9)	8.6 (21)	38 (6.5)	17 (4.6)	0.539 (1.1)
Paclitaxel	36 (13)	17 (22)	39 (20)	16 (8.5)	0.431 (2.6)
Epirubicin + Docetaxel	37 (15)	13 (21)	22 (23)	8.4 (2.0)	0.499 (3.4)
5-FU + Epirubicin + Cyclophosphamide	28 (15)	16 (13)	23 (14)	8.4 (11)	0.535 (1.9)

References:

- [1] Friberg LE, Henningson 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] Henningson A, Sparreboom A, Sandström M, Freijs A, Larsson R, Bergh J, Nygren P, Karlsson MO. Population pharmacokinetic modeling of unbound and total concentrations of paclitaxel in cancer patients. *Eur J Cancer*; 39:1105-1114, 2003.
- [3] 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.
- [4] 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.
- [5] Bruno R, Vivier N, Vergniol JC, De Phillips SL, Montay G, Sheiner LB. A population pharmacokinetic model for docetaxel (Taxotere): model building and validation. *J Pharmacokinetic Biopharm*; 24:153-72, 1996
- [6] Wallin J, Friberg LE, Karlsson MO. An adaptive dosing tool for etoposide using neutrophil counts based on a semi-physiological model. *PAGE 15 (2006) Abstr 966 [www.page-meeting.org/?abstract=966]*