Title: Lower Inter-occasion Variability than Inter-individual Variability in Chemotherapy-induced Myelosuppression

Authors: Lena E. Friberg*, Emma Hansson, Johan Wallin, Mats O. Karlsson

Institution: Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Objectives: A semi-physiological model of chemotherapy-induced myelosuppression [1] has been applied in numerous projects in drug development and show similar system-related parameter estimates and inter-individual variability (IIV) across drugs. However, there is limited information on the variability in the estimated parameters between courses. For the model to be a valuable tool for individual dose adjustments in the clinic, the inter-occasion variability (IOV) should be relatively low in comparison to IIV. The aim of the present study was to evaluate IOV in the model parameters for neutrophil counts and compare their magnitudes with IIV estimates.

Methods: Four data sets following single or combination chemotherapy with neutrophil counts from several cycles per patient were available (Table 1). One occasion was defined as one treatment cycle and in all investigated data sets the nominal cycle length was 3 weeks. Individual pharmacokinetic (PK) parameters have earlier been determined for the paclitaxel [2], the epirubicin+docetaxel [3] and the 5-fluorouracil+epirubicin+cyclophosphamide [4] data sets. For docetaxel typical population PK parameters were used [5]. In none of the data sets were the PK determined in all cycles and therefore potential IOV in PK will be incorporated in residual error estimates or in IOV of the pharmacodynamic parameters. The semi-physiological myelosuppression model [1] was fit to the neutrophil data (Fig. 1) and analyzed using the FOCE method in NONMEM VI. The model structure was the same as in the original publication except that the half-life of neutrophils ($\ln 2/k_{circ}$) was fixed to the literature value of 7 hours instead of being fixed to a fraction of the mean transit time through the chain of non-mitotic compartments (MTT). In addition, the neutrophil data were Box-Cox transformed with a factor of 0.2, as this transformation resulted in residuals with a symmetrical distribution around zero.

Table 1. Investigated data sets

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

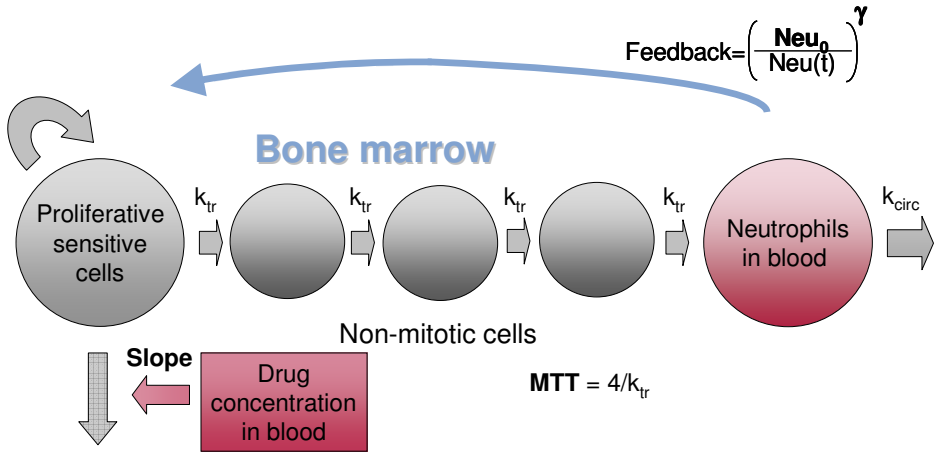

Figure 1. The semi-physiological model of myelosuppression with the estimated system-related parameters Neu_0, MTT and γ and the drug-related parameter Slope. The half-life of neutrophils ($\ln 2/k_{circ}$) was here fixed to 7 hours.

Results: IOV was only significant in MTT and ranged from 8 to 17% in the investigated data sets (Table 2). The estimated IOV values in MTT were approximately of similar magnitudes as IIV in MTT. As observed previously, IIV in the baseline neutrophil counts (Neu_0) and in the drug-effect parameter (Slope) were larger than for IIV in MTT. IIV in Neu_0 was similar across drugs while IIV in Slope was estimated to be larger for the docetaxel and paclitaxel data sets than in the drug combination data sets where a common IIV for Slope was estimated for the component drugs. Inclusion of IOV in MTT reduced the residual errors of approximately 10% for all data sets.

Table 2. Estimated IIV, IOV and residual variability (on Box-Cox transformed scale). Relative standard errors ranged from 6.0 to 22% for IIV parameters, 4.2 to 19 % for IOV and 1.0 to 3.4% for residual errors as determined by $COVARIANCE MATRIX=S.

Data sets	IIV Neu_0 CV%	IIV MTT CV%	IIV Slope CV%	IOV MTT CV%	Residual error
Docetaxel	32	9.0	39	17	0.539
Paclitaxel	36	17	39	16	0.431
Epirubicin + Docetaxel	34	13	20	8.8	0.500
5-Fluorouracil + Epirubicin + Cyclophosphamide	28	17	24	8.4	0.538

Conclusions: The estimated IOV was relatively low and similar across drugs. IOV was only significant for MTT which may reflect that the growth factor levels that regulate the transit time vary from cycle to cycle while drug sensitivity, that has a larger variability between patients, is more consistent within an individual. Alternatively, MTT may be the parameter that has the most influence on all neutrophil observations and therefore inclusion of IOV in MTT results in a significant improvement of the fit. The overall IOV in neutrophil dynamics in relation to overall IIV implies that the semi-physiological model has potential to be useful for dose adjustments based on neutrophil counts and such a tool is under development [6].

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] Henningsson 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.

[5] Bruno R, Vivler N, Vergniol JC, De Phillips SL, Montay G, Sheiner LB. A population pharmacokinetic model for docetaxel (Taxotere): model building and validation. J Pharmacokinet 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]