

Title: An Extended Semi-Physiological Myelosuppression Model following Docetaxel administration with Improved Simulation Properties

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Objectives: The previously developed semi-mechanistic myelosuppression model⁽¹⁾ was developed based on leukocyte data and with the aim to be applicable across drugs. The model has been successfully applied to both leukocyte and neutrophil counts following numerous different anti-cancer drugs. However, we have seen that the model is over-predicting the nadir value and time to nadir for neutrophils following docetaxel treatment. As neutrophils are a part of the leukocytes (60-70%), a combined analysis may have advantages. The aim of this study was to improve the simulation properties of the myelosuppression model for neutrophils by optimizing the model structure and incorporate more knowledge of the hematological system.

Methods: The analysis included 601 patients with solid tumors treated with a one hour infusion of 75 or 100 mg/m² docetaxel in monotherapy⁽²⁾. Individual concentration time profiles were generated using a population pharmacokinetic model⁽³⁾. A total of 3549 pairwise observations of leukocytes and neutrophils were analyzed using NONMEM (version VI β and VI) and the FOCE method with interaction. The neutrophil and leukocyte data was Box-Cox transformed with a factor of 0.2 before analysis. Model development was guided by mechanistic plausibility, the objective function value (OFV), parameter precision by bootstrap and graphical judgment using PsN toolkit and Xpose 4.0. Models were also evaluated using visual and numerical predictive checks.

The model development for simultaneous analysis of leukocytes and neutrophils was performed in two steps. A BASIC model was developed consisting of a neutrophil and a non-neutrophil model, each with the same structure as previously described⁽¹⁾, but allowing different parameter values for neutrophils and non-neutrophils i.e. all leukocytes except neutrophils. The observed leukocyte count was modeled to be the sum of the predicted neutrophils and non-neutrophils. Subsequently, each part of the cell chain was explored for improvements to obtain the FINAL model.

Results: The BASIC model described the leukocyte data well but over-predicted the nadir value and the time to nadir for neutrophils as shown by a visual predictive check (Figure 1a).

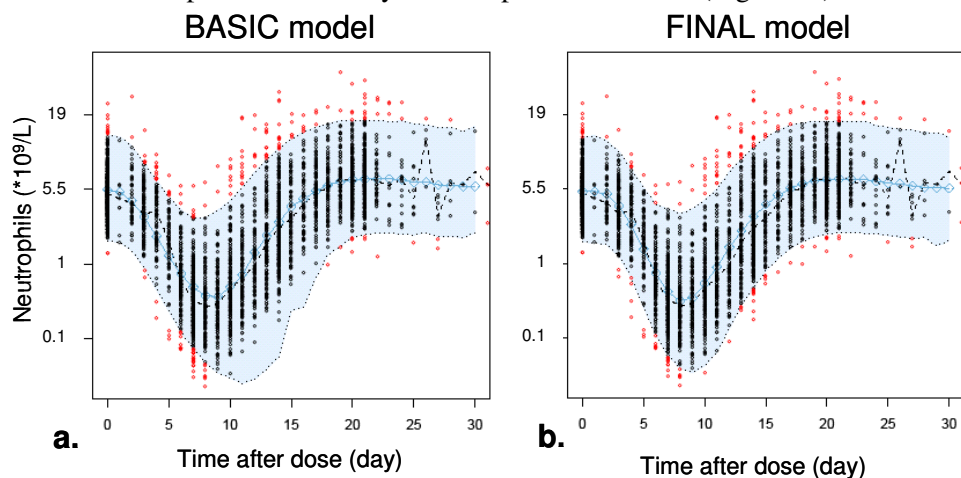


Figure 1 Visual predictive check of the BASIC model (left) and the FINAL model (right) for neutrophils. Five hundred data sets were simulated from the model and the median (blue solid line) and 95% prediction interval (shadow area) were superimposed on the observed data (dots). The black line is loess smooth of the observed data.

The FINAL model is presented in Figure 2. In the original myelosuppression model the drug effect on the proliferation rate was characterized by a linear function for all six investigated drugs although Emax-models were reported to improve the fit for docetaxel and for two of the other drugs⁽¹⁾. We found that a sigmoid Emax-model was significant for both neutrophils and non-neutrophils. Nonetheless, for neutrophils a step function was almost as good as a sigmoid Emax-model ($\Delta\text{OFV}=26$). The original model included a feedback from the circulating neutrophils to the rate of proliferation. An additional feedback function that mimics the reduction of maturation time in bone-marrow by endogenous growth hormones was here introduced on neutrophils, but was not found significant on non-neutrophils. The number of transit compartments was optimized for each of the two cell models. For neutrophils the optimal number of transit compartments was six while one transit compartment for the non-neutrophil model described the data the best. Each improvements of the basic model was significant ($p<0.001$) and greatly improved the model's capability to capture the nadir value as determined by a visual predictive check (Figure 1b). The total difference in OFV between the BASIC simultaneous model and the FINAL model was 889.

Conclusions: In conclusion, a simultaneous analysis of the time-course of neutrophils and leukocytes was performed. The docetaxel data supported a more complex model for the neutrophils compared to the previous model developed by Friberg et al.⁽¹⁾ which yielded more precise predictions of the time-course of the neutrophil counts. The model shows good simulation properties and may be useful in illustrating the differences between the cell types and allow prediction of neutrophil counts from leukocyte measurements.

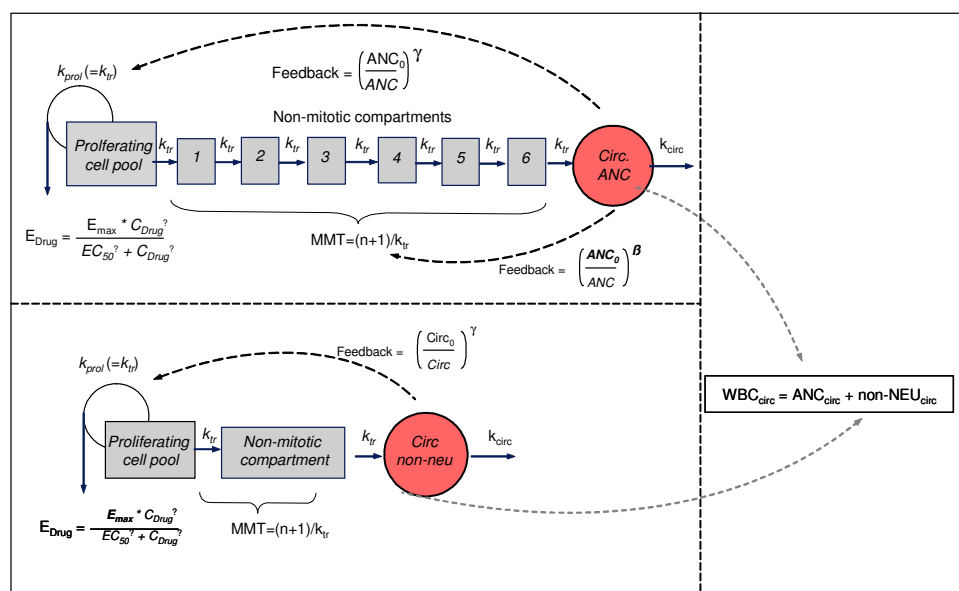


Figure 2: The FINAL myelosuppression model for neutrophils and non-neutrophils. The model consists of a proliferation pool with sensitive cells, a chain of transit compartments with insensitive cells, mimicking the maturation of non-mitotic cells in bone marrow, and a blood circulation compartment, where the observations are made. The cells are eliminated from the blood compartment (k_{circ}) by random movement of cells into the tissue. Feedback mechanisms are incorporated into the model, mimicking the effect of G-CSF on the proliferation rate and MMT. The drug effect is modeled as an inhibition of the proliferation rate. The gray compartments represent the bone marrow and the red compartment corresponds to the blood circulation.

References:

- [1] Friberg, LE, Henningson 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, Vivler N, Vergninol JC, et al: A population pharmacokinetic model for docetaxel (Taxotere): Model building and validation. *J Pharmacokinetics Biopharm* 1996, 24:153-172