



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

BACKGROUND

- ✗ The semi-mechanistic myelosuppression model by Friberg et al.¹ has successfully described the time-course of both leukocytes and neutrophils following several different anti-cancer drugs.
- ✗ Nonetheless, the model has difficulties in capturing the rapid drop in neutrophil counts following Docetaxel treatment as depicted by VPC (Fig 1b).
- ✗ More information of the haematological system may be gained by a simultaneous analysis of leukocytes (WBC) and neutrophils (NEU) since leukocytes consist mainly of neutrophils (60-70%).

METHODS

Patients

- ✗ 601 cancer patients²
- ✗ Diagnosis: carcinoma, melanoma and sarcoma
- ✗ Single course of docetaxel in monotherapy (no G-CSF)
- ✗ Dose: 75 or 100 mg/m², 1 hour infusion
- ✗ 3549 pairwise observations of WBC and NEU
- ✗ Individual PK-profiles were generated using a population PK-model³

Population PK-PD modeling

- ✗ Data analysis: NONMEM VI with FOCE INTER
- ✗ Data was Box-Cox transformed with a factor of 0.2

Model development

1. A BASIC model describing NEU and WBC simultaneously using a published semi-mechanistic myelosuppression model¹ have been developed⁴
2. An EXTENDED model where each structural component of the BASIC model was optimized to improve the description of the neutrophil time-course.

OBJECTIVES

To improve the predictive capacity of the semi-mechanistic myelosuppression model for neutrophil counts following docetaxel treatment, by refining the model structure and incorporate more knowledge of the hematological system.

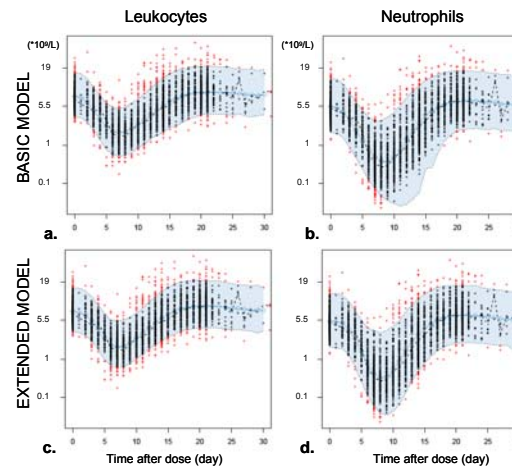


Figure 1 Visual predictive check of the BASIC model and the EXTENDED model for WBC and NEU. Five hundred data sets were simulated from the model and the median (blue solid line) and 95% prediction interval (shadow area) were superimposed on the observed data (dots). The black line is loess smooth of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

RESULTS

Basic Model

- ✗ Two myelosuppression-models¹: one for NEU and one for non-NEU
- ✗ Allowing different parameter values for NEU and non-NEU
- ✗ WBC was modeled as: $Circ_{WBC} = Circ_{NEU} + Circ_{non-NEU}$
- ✗ A linear drug model: $E_{drug} = Slope * C_{drug}$
- ✗ The half-life in blood was fixed to the literature value of NEU (7 h)
- ✗ Residual error: additive on a Box-Cox scale with ETA on EPS

Extended Model

- ✗ The significant ($p < 0.001$) improvements of the model structure:
 - ✗ A sigmoidal E_{max} model for the drug effect was significant for both NEU and non-NEU
 - ✗ A feedback function mimicking the reduction in maturation time in bone-marrow by endogenous growth hormones was significant on NEU but not on non-NEU
 - ✗ The optimal number of transit compartments was six for NEU and one for non-NEU
- ✗ These modifications greatly improved the model's capability to capture the nadir value as determined by a visual predictive check (Fig 1) and resulted in a total drop in OFV by 889.

CONCLUSION

- ✗ A simultaneous analysis of the time-course of neutrophils and leukocytes was successfully performed.
- ✗ The docetaxel data supported a more complex model for the neutrophils which yielded more precise predictions of the time-course of the neutrophil counts
- ✗ The model shows good simulation properties as depicted by the VPC
- ✗ The model can be useful in illustrating the differences between the cell types and allow prediction of neutrophils from leukocyte measurements

Table I. Final parameter estimates from the BASIC and EXTENDED model

Parameter	BASIC model			EXTENDED model		
	Typical value	IIV%	RSE%	Typical value	RSE%	IIV%
Non-Neutrophils						
non-NEU ₀	(¹⁰) / L	2.09	37	2.05	2	37
MMT	h	79.7	11	158	4	9
T _{1/2} blood	h	7 FIX		7 FIX		
Y		0.21		0.97		7
Slope	1/μM	3.36	32			
EC ₅₀	μM			1.1	5	68
E _{max}				93.5	6	
h				9.54	25	
Neutrophils						
NEU ₀	(¹⁰) / L	5.28	39	5.07	2	23
h		101	15	103	1	40
T _{1/2} blood	h	7 FIX		7 FIX		5
Y		0.18		0.178	6	
β				0.082	12	
Slope	1/μM	17.5	47			
EC ₅₀	μM			1.35	4	14
E _{max}				45.8	3	50
h				11.9	17	
Residual error						
non-neutrophils		0.30	14	0.28	2	29
neutrophils		0.46	14	0.44	2	11

IIV, interindividual variability expressed in CV%
RSE%, relative standard error obtained by bootstrap (80 samples)

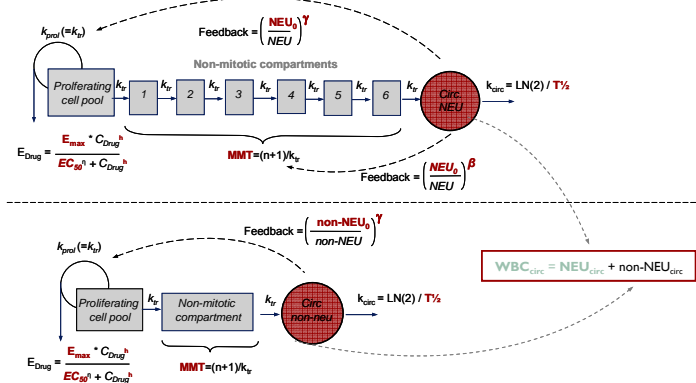


Figure 2: The EXTENDED semi-mechanistic myelosuppression model for neutrophils and non-neutrophils. The model consists of a proliferation pool with drug sensitive cells, a chain of transit compartments, mimicking the maturation of non-mitotic cells in bone marrow, and a blood circulation compartment.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

REFERENCES

1. Friberg LE et al; Model of chemotherapy-induced myelosuppression with parameter consistency across drugs. J. Clin. Oncol. 2002, 20:4713-4721
2. Bruno R et al; population PKPD of docetaxel in phase II studies in patients with cancer. J. Clin. Oncol. 1998, 16:187-96
3. Bruno R et al; A population pharmacokinetic model for docetaxel (Taxotere): Model building and validation. J. Pharmacokinetics Biopharm 1996, 24:153-172
4. Quartino AL et al; A simultaneous analysis of the time course of leukocytes and neutrophils following docetaxel administration using a semi-mechanistic model PAGE 15 (2006) Abstr 1022 [www.page-meeting.org/abstract=1022]