

SEMI-MECHANISTIC KPD MODEL TO DESCRIBE THE NEUTROPENIA IN CANCER PATIENTS RECEIVING HIGH DOSE OF CHEMOTHERAPY

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OBJECTIVE: The aim is to use using a semi-mechanistic model to describe the time course of the absolute neutrophil count following the administration of high dose of chemotherapy and peripheral blood stem-cells transplantation with haematopoietic growth factors in breast cancer patients.

BACKGROUND:

• High dose of chemotherapy (HDC) and peripheral blood stem-cells transplantation (PBSCT) has been used widely as adjuvant therapy in several types of cancer and it seems to improve disease free survival and overall survival in high risk breast cancer patients.

• Hematological toxicity are major causes of treatment-related complications following HDC and PBSCT. As the infectious complications are directly related to the duration of absolute neutrophil counts (ANC) below $500 \cdot 10^9$ cells/uL, and colony stimulating factors (G-CSF) has been widely used to reduce the duration of neutropenia grade IV. Therefore, a semi-mechanistic model describing the time course of ANC after HDC and PBSCT is of particular clinical interest.

METHODS:

✓ **Patients:** A total of forty-one patients with primary high risk breast cancer receiving an 96-h continuous intravenous infusion of the STAMP-V protocol (6 g/m² cyclophosphamide, 0.5 g/m² thiotepa and 0.8 g/m² carboplatin) were included in this analysis. PBSCT was performed 3 days after the end of the HDC and patients were randomised to received G-CSF on day 1 or day 5 days after the PBSCT. Daily measurements of ANC were available for the analysis.

✓ **Model Development:** In absence of pharmacokinetic data, a 'kinetics of drug action' model (Kpd) was used as a input function of the pharmacodynamic model (figure 1). A five compartments semi-mechanistic model was used to describe the time course of the ANC. One compartment represents the proliferative cells [Prol], such as stem cell and other progenitor cells, which are linked through a three transit compartments representing the maturation process [Transit] with the blood cells in circulation [Circ]. The generation of new cells in [Prol] was dependent on the number of cells in that compartment, which is consistent with the mechanism of self-renewal or mitosis, and is determined by the first-order proliferation rate constant (K_{prol}). The model also includes a feedback mechanism from the circulating cells in order to describe the rebound phenomena. The ratio between the circulating cells at baseline and the circulating cells at each time, $(Circ_0 / Circ)^{\gamma}$, was used to quantify the feedback mechanism and the γ parameter was estimated directly from the data. The transit compartments were linked through the first-order rate constants (K_{tr}). The amount of PBSCT, scaled from the number of CD34+ cells reinfused using the factor F_{CD34+} was incorporated into the first transit compartment following a first-order process determined by K_{in} . According to its mechanism of action, the G-CSF effect was a incorporation into the model as a estimation of the production of proliferative cells and the maturation process. The between subjects variability in the model parameters as well as the residual variability in the ANC were assumed to follow the lognormal distribution. The estimation of model parameters was performed using NONMEM V software.

✓ **Model Validation:** Visual predictive check (VPC) and bootstrap (BS) were used to evaluate the model. One hundred datasets, with the same structure than the original dataset, were simulated from the final model parameters estimates and the median and 95% prediction intervals were compared with the observed data. Two hundred replicates of the original dataset were generated by resampling using WINGS for NONMEM. The final model was fitted to each bootstrap replicate and the mean and the 95% of the parameter estimates from the bootstrap replicates were compared with the estimated parameters from the original dataset.

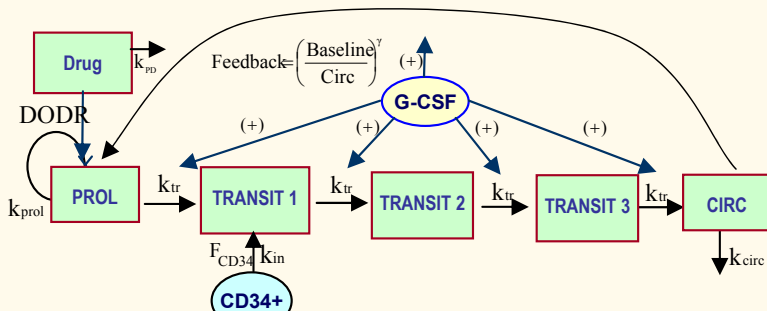


Figure 1. Schematics of the Semi-Mechanistic KPD Model for Neutropenia after HDC and PBSCT

CONCLUSION: The KPD model was suitable to describe the extent and time course of neutropenia following HDC and PBSCT with G-CSF.

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RESULTS:

Model Parameters	Original dataset		Non-Parametric Bootstrap (N = 197 Replicates)	
	Estimate (RSE%)	Mean (RSE%)	95% Confidence Interval	
$CIRC_0$ ($10^9/L$)	5.27 (4.87)	5.23 (5.21)	4.81 – 5.73	
MTT (h)	65.5 (4.99)	63.6 (6.50)	52.6 – 69.5	
K_{RM} (h^{-1})	1.94 (7.42)	1.93 (9.51)	1.62 – 2.31	
K_{EL} ($10^{-3} h^{-1}$)	6.83 (12.7)	6.95 (14.4)	5.35 – 9.33	
γ	0.113 (21.5)	0.113 (25.6)	0.0662 – 0.176	
K_{in} ($10^{-3} h^{-1}$)	4.30 (44.6)	4.52 (48.3)	0.396 – 9.61	
K_{CIRC} (h^{-1})	0.0579 (9.43)	0.0572 (11.8)	0.0475 – 0.0697	
F_{CD34}	352 (30.7)	998 (399)	183.25 – 3185	
Effect G-CSF on MTT (%)	-43.5 (29.6)	-43.5 (32.9)	-10.7 – -65.2	
Effect G-CSF on γ (%)	99.9 (47.6)	114 (49.8)	23.0 – 231	
Interindividual variability (CV %)				
η_{CIRC0}	22.7 (9.65)	21.9 (24.6)	9.81 – 29.9	
η_{MTT}	20.2 (10.0)	21.3 (31.8)	3.78 – 33.9	
η_{KRM}	12.4 (4.46)	11.1 (25.2)	5.60 – 17.1	
η_{KEL}	45.9 (21.57)	47.8 (32.1)	20.3 – 81.4	
η_{KIN}	9.93 (9.58)	8.18 (73.9)	0.01 – 19.4	
η_{FC34}	168 (146)	561 (459)	71.1 – 1550	
η_{KIRC}	117 (113)	521 (494)	41.9 – 1500	
η_{KIRC}	29.4 (34.7)	22.2 (84.8)	0.01 – 55	
Random Effects Correlations (R²)				
$\eta_{KIN} \eta_{FC34}$	0.588 (279)	0.565 (55.3)	0.01 – 1.00	
Residual variability (CV %)				
σ	64.9 (0.649)	64.3 (2.71)	61.1 – 67.7	

Table 1. Parameter Estimates and Bootstrap Analysis of the Final Model.

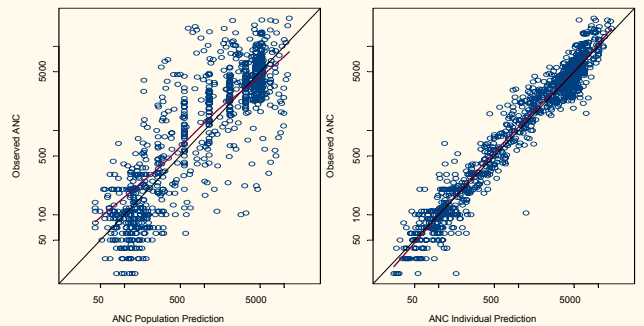


Figure 2. Diagnostic Plots of the Final Model.

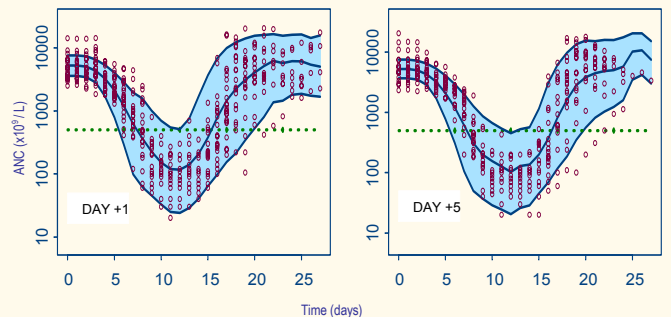


Figure 3. Visual predictive check stratified by the beginning of G-CSF treatment. Black lines represents the 5, 50 and 95th percentiles of the model-based prediction. The observed ANC are represented by red circles, and the dotted green line represents the value of ANC equal to $500 \cdot 10^9/L$.

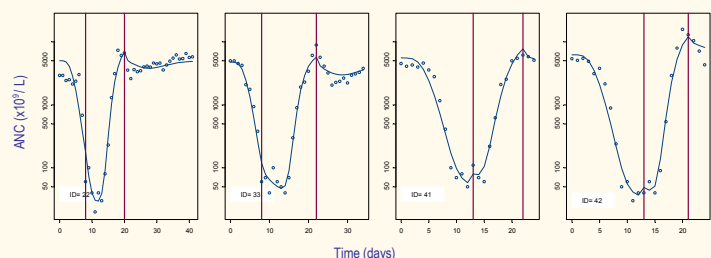


Figure 4. Time Course of the Observed ANC (open circles) and Individual Model Prediction (blue line). Red vertical lines show the duration of the G-CSF treatment, starting on Day 1 (left) and Day 5 (right).