A new population PK/PD model to assess the myelotoxicity of candidate drugs in preclinical and in clinical studies

F. Del Bene[1], N. Terranova[2], F. Fiorentini[1], M. Germani[1], P. Magni[2]

[1] Accelera Srl – Viale Pasteur 10, 20014 Nerviano, Milan - Italy
[2] Dipartimento di Informatica e Sistemistica, Università degli Studi di Pavia, Italy

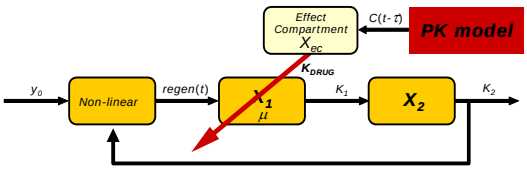
www.accelera.org

About 50% of oncology drugs, including those with target-specific mechanism of action, induce myelosuppression as a dose limiting toxicity in patients. The benefits of these drugs, such as a reduction of the solid tumor mass, are achieved at the expense of serious injury to the immune system, as the decrease of multipotent cells in the bone marrow can lead to infections and fever.
A new population PK/PD approach can be adopted during the different phases of drug development to test and select new candidate compounds devoid of myelosuppression effects preserving the therapeutic efficacy. The aim is to describe the peripheral concentrations of leukocytes and/or neutrophils during and after treatment to predict the minimum concentration (nadir), and the time necessary to reach that concentration (time-to-nadir). The proposed model was implemented in NONMEM and successfully applied to analyzed different datasets in rats and in humans.

MATERIALS AND METHODS

A semi-mechanistic PK/PD model, characterized by a dynamical system with non-linear feedback was formulated for describing leukocytes/neutrophils peripheral concentrations during and after the treatment in rats and humans. An effect compartment was introduced to describe the non-instantaneous relationship between drug toxicity on bone marrow and its plasma concentration(1).

NONMEM (v. VI, Globomax) was used for PK/PD data fitting of both rats and humans data.



$$\begin{cases} \dfrac{dX_1(t)}{dt} = -(K_1 + K_{DRUG}\cdot X_{ec}(t))\cdot X_1(t) + \mu\cdot K_1\cdot regen(t) \\ \dfrac{dX_2(t)}{dt} = K_1\cdot X_1(t) - K_2\cdot X_2(t) \\ \dfrac{dX_{ec}(t)}{dt} = K_{e0}\cdot\left(C(t-\tau) - X_{ec}(t)\right) \end{cases}$$

$$\bar{X}_1 = \frac{K_2}{K_1} C_{base} \qquad \bar{X}_2 = C_{base} \qquad \bar{X}_{ec} = 0$$

$$regen(t) = \begin{cases} y_0 - X_2(t) & X_2(t) \le y_0 \\ 0 & X_2(t) > y_0 \end{cases}$$

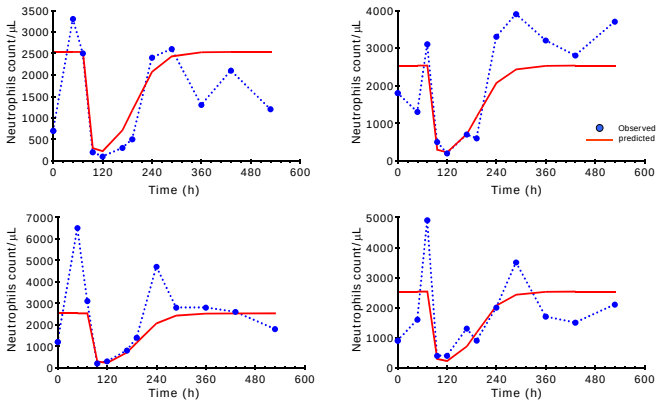
$$y_0 = \frac{(K_2 + \mu\cdot K_1)\cdot c_{base}}{\mu\cdot K_1}$$

K_1 is the rate constant describing the cell maturation process [h^{-1}];
K_2 is the rate constants related with the natural cell death [h^{-1}];
K_{DRUG} is the parameter quantifying the drug toxicity [concentration expressed as μM, $h^{-1}\cdot\mu M^{-1}$];
μ is the parameter describing the feedback mechanism of the circulating cells;
K_{e0} is the first-order constant for the effect compartment model [h^{-1}];
τ is the lag-time between the administration and the decrease of neutrophils concentration in blood;
C_{base} in the set point y_0 is the baseline value of mature leukocytes [counts/μL)];
regen(t) describe the bone marrow stimulation.

RESULTS

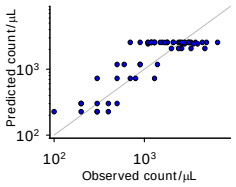
In RATS Myelotoxicity assessment

60 mg/kg single IV dose was administered at t=0 to 5 animals.
The PK/PD model adequately fitted the experimental data, and the drug X potency was quantified in parameter k_{drug}.
Nadir and Time To Nadir were 92% and 110 h, respectively.



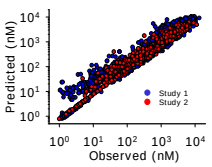
Population parameters are reported in the table. Predicted vs. Observed counts/μL are shown for the 5 treated rats.

Parameter	estimate	CV
K_1 [1/h]	0.0378	22.30
K_2 [1/h]	0.105	11.90
K_{drug} [1/(h×μM)]	19.2	4.21
μ	68.7	11.62
K_{e0} [1/h]	0.0312	6.86
τ [h]	72	0.02
C_{base} [counts/μL]	2540	9.29

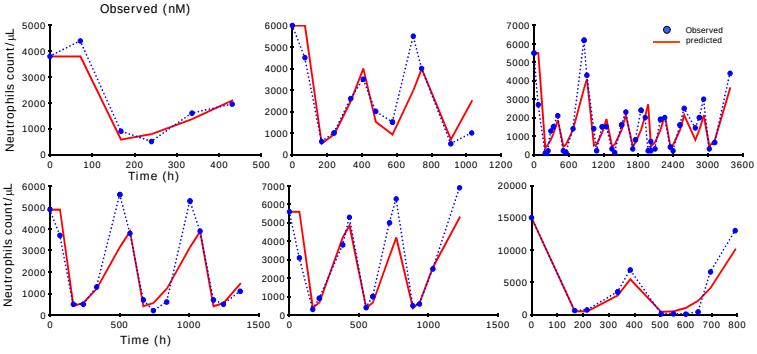


In HUMANS Myelotoxicity assessment

Drug X was also investigated in two phase I studies:
(1) 45, 90, 135, 190, 250, 330 and 400 mg/m² 3, 6 h IV infusion weekly for 3 consecutive weeks in a 28-day cycle (52 patients);

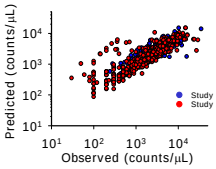


(2) 45, 90, 180, 360, 500, 580 and 650 mg/m² 24 h IV infusion in a 14-day cycle (47 patients).
A population PK analysis was performed using a standard three compartment model.
In the figure on the left, concentrations Observed vs. Predicted are shown. PK results were linked to the PD model for estimating individual neutrophils level.



PD population parameters are reported in the table. Predicted vs. Observed counts/μL are shown considering patients from both study 1 and 2.

Parameter	estimate	intra-subject variability (η)
K_1 [1/h]	0.0206	-
K_2 [1/h]	0.0995	-
K_{drug} [1/(h×μM)]	2.03	89%
μ	37	-
K_{e0} [1/h]	0.0133	<1%
τ [h]	125	54%
C_{base} [counts/μL]	fixed at pre-dose level	-
inter-individual variability (σ^2)	0.289	



CONCLUSIONS

Table and figures on the right show how the PK/PD model can predict the outcome of different doses/schedules during clinical studies and from preclinical data.

Interestingly, this *in vivo* PK/PD approach seems to be able to assist at various stages of drug development to predict human neutropenia grade from rat PK/PD. Moreover, the use of the human PK/PD model can help to save resources and time during dose escalation.

(1) N. Politi *et al.* "Modeling Myelosuppression In Patients Treated With Anticancer Drugs" GNB 2010.

Percentage predicted Nadir based on typical human PK/PD parameters.												
Clinical dose (mg/m²)	45	90	135	180	190	250	330	360	400	500	580	650
3 h IV infusion	43 (19)	58 (31)	67 (40)		73 (47)	78 (53)	82 (59)		84 (63)			
6 h IV infusion	43 (19)	58 (31)	67 (40)		73 (47)	78 (53)	82 (59)		84 (63)			
24 h IV infusion	39 (17)	54 (28)		69 (44)				81 (60)		85 (67)	87 (70)	88 (72)
between brackets prediction based on typical rat PK/PD parameters, using human PK data.